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BEST ABSTRACTS

SOFTWARE-ASSISTED RESPONSE ASSESSMENT PREDICTS SURVIVAL IN 258 NEWLY DIAGNOSED CGVHD PATIENTS: A PROSPECTIVE MULTICENTER GITMO STUDY

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Background. Standardized response assessment in chronic graft-versus-host disease (cGVHD) remains an unmet clinical need, with documented inter-rater discordances when applying NIH criteria. Software-assisted (SA) tools may reduce operator-dependent variability and improve prognostic accuracy.

Methods. We prospectively enrolled 258 patients with newly diagnosed cGVHD across 23 Italian GITMO centers (NCT02991846, 2017-2022). The primary endpoint was failure-free survival (FFS) after first-line systemic therapy (ST); a pre-specified secondary endpoint was the comparison between SA and clinician-based (CB) response assessment at 6 and 12 months, both applying NIH criteria. SA evaluation used Crosy, a web-based platform that records organ-specific NIH scores at baseline and follow-up and automatically computes the overall response per NIH consensus criteria.

Results. At enrollment, baseline NIH severity was moderate in 60% (n=155), severe in 22% (n=58) and mild in 17% (n=45); two-year OS (85.3%) significantly differed across severity groups. Among 177 patients receiving first-line ST, 167 were evaluable at 6 months: SA ORR was 62% (CR 19%; PR 43%) versus 65% by CB (CR 23%; PR 42%); overall agreement was 66% (kappa 0.53). Within response categories, relevant discordances emerged predominantly around mixed response (MR): SA captured MR in 23% of cases versus only 7% by CB, with CB tending to misclassify MR as either PR or progression. In an exploratory landmark multivariate analysis from 6 months, SA response independently predicted OS (HR 0.37; 95%CI 0.17-0.81; p=0.013), together with baseline ECOG PS and NIH skin score, whereas CB did not (HR 0.52; p=0.09). As the SA vs CB comparison was pre-specified, we further tested their prognostic accuracy in a parsimonious Cox model adjusted for ECOG PS and NIH severity, with 1000-replication bootstrap validation: SA retained significance (p=0.046) while CB did not (p=0.120). At 12 months, 23% of patients had discontinued IST, with significantly higher rates among those who maintained first-line ST (39% vs 9.5%; p<0.001). Two-year FFS and OS in patients receiving ST were 67% and 85%.

Conclusions. SA evaluation of cGVHD response with Crosy is feasible in a multicenter real-world setting, captures mixed responses more accurately than CB assessment, and independently predicts OS. These findings support the implementation of IT-assisted tools in cGVHD management and future drug development trials.

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A Response category agreement at 6 months

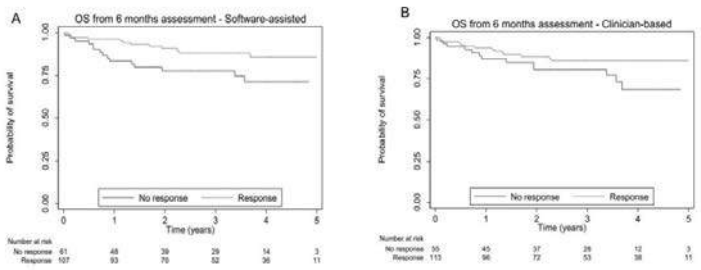
Clinician-based (CB) evaluation

Software-assisted (SA) evaluation	CR	PR	SD	MR	PD	Total SA
CR	**30**	3	0	0	0	33 (18.6%)
PR	10	**56**	7	0	3	76 (42.9%)
SD	0	3	**3**	0	1	7 (4.0%)
MR	1	12	6	**12**	9	40 (22.6%)
PD	0	0	2	0	**9**	11 (6.2%)
Total CB	41 (23.2%)	74 (41.8%)	18 (10.2%)	12 (6.8%)	22 (12.4%)	

Overall agreement: 110/167 (65.9%) • kappa = 0.53 (moderate)

Percentages calculated over 177 patients receiving first-line systemic therapy; 10 patients with exitus or missing 6-month evaluation are not shown.

B Overall survival from 6-month landmark assessment



SA: HR 0.37 (95% CI 0.17-0.81), p = 0.013 **CB: HR 0.52 (95% CI 0.24-1.11), p = 0.09**

Stampa pp. 2-3

IMPACT OF ANTIBIOTIC-EXPOSURE AND LEVOFLOXACIN-PROPHYLAXIS ON OUTCOMES FOLLOWING CART IN LARGE B-CELL LYMPHOMAS

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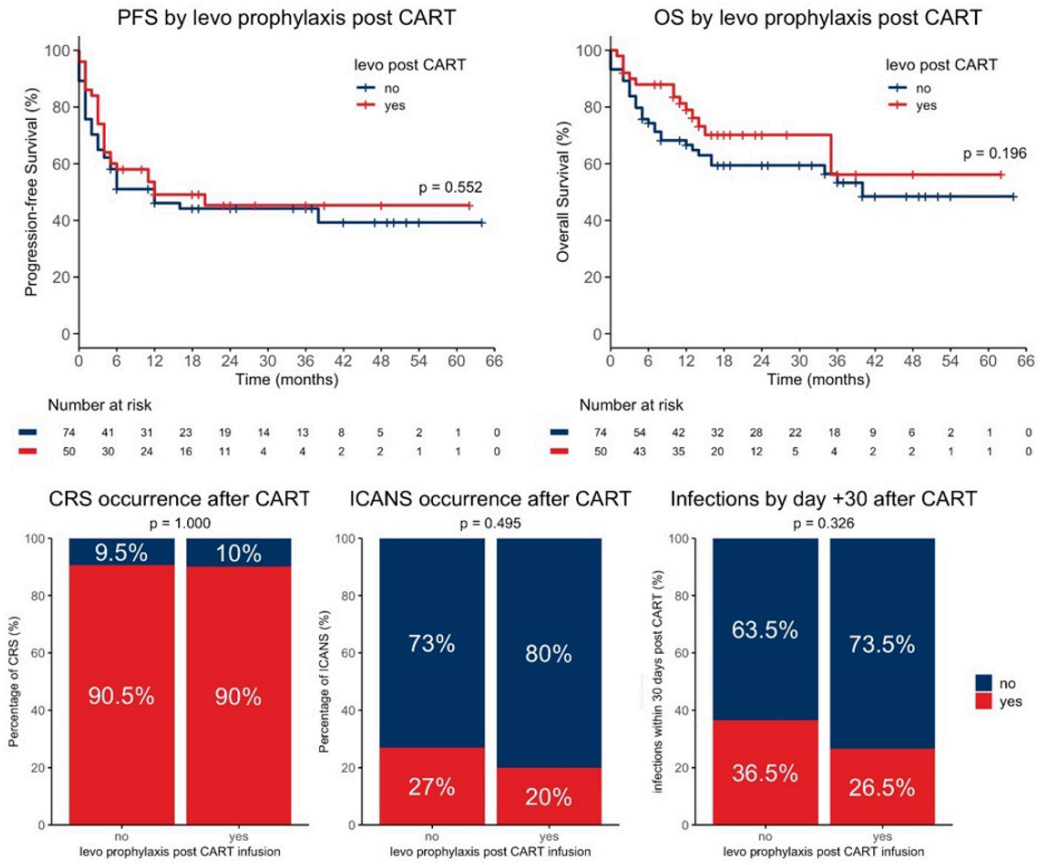
Antibiotics (AB) profoundly alter the microbiota composition, which is recognized as a critical modulator of responses to immunotherapies, including chimeric antigen receptor T-cell (CART) therapy. They are widely used in hematology, for both therapeutic and prophylactic purposes. Levofloxacin (levo) is a generally well-tolerated and effective strategy for the prevention of febrile episodes; however, it has also been associated with adverse outcomes in allogeneic transplant recipients, making its role controversial. The emergence of multidrug-resistant pathogens has further raised concerns regarding its widespread use. In this study, we evaluated the effects of AB-exposure and levo-prophylaxis in a cohort of large B-cell lymphoma (LBCL) patients treated with anti-CD19 CART at the Institute of Hematology in Bologna. Considering the effect on dysbiosis, we retrospectively collected AB-exposure within 30 days before CART, levo-prophylaxis (500 mg/day) within 30 days after CART and analyzed the effects on responses and toxicities after CART. Analyses were performed using R. Among 124 LBCL patients, 94 (75.8%) received axi-cel and 30 (24.2%) tisa-cel; median age was 59 years. At leukapheresis, most patients had stage III/IV disease (71.0%), were primary refractory (89.5%), and received bridging therapy (83.1%). After a median follow-up of 24.0 months, median progression-free survival (mPFS) was 12.0 months, and median overall survival (mOS) was not reached. Baseline characteristics were balanced between AB- and levo-exposed versus -naïve groups, respectively. Three-month responses and mPFS were similar between AB-naïve and AB-exposed patients, whereas mOS was longer in the naïve (not reached vs 35.0 months, p=0.003). Pre-CART AB-exposure was associated with higher neurotoxicity rate (20.4% vs 50.0%; p=0.010), but not with cytokine release syndrome, and remained independently associated with inferior OS on multivariable analysis. Levo-prophylaxis did not impact survivals or toxicities, and rates of infection within 30 days after comparable were comparable between groups (fig 1). Our study confirms the detrimental impact of AB-exposure on survival and neurotoxicity after CART, consistent with prior reports. To our knowledge, this is the first analysis of levo-prophylaxis after CART, showing no significant effect on outcomes or reduction in early post-CART infections. Further studies are needed to clarify its long-term impact and interactions with the microbiome.

Fig1. Effects of levo-exposure on survivals and toxicities after CART.



NEW IMS/IMWG RISK CRITERIA BY NEXT-GENERATION SEQUENCING: ANALYSIS OF DARATUMUMAB BENEFIT IN BOTH HIGH- AND STANDARD-RISK PATIENTS IN THE PERSEUS STUDY

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Introduction. IMS/IMWG proposed Consensus Genomic Staging (CGS) high-risk criteria for newly diagnosed multiple myeloma (NDMM), including genetic alterations identifiable by NGS. PERSEUS/EMN017 (NCT03710603) evaluated adding daratumumab to VRd induction/consolidation and to R maintenance (DVRd) vs VRd+R (VRd) in transplant-eligible (TE) pts; DVRd significantly improved progression-free survival (PFS) regardless of cytogenetic risk (classic criteria).

Methods. 709 pts with NDMM were randomized 1:1 to DVRd or VRd. 434 pts had DNA samples for NGS testing by unique molecular assay (UMA)-NGS target panel. CGS high risk was defined post-hoc as having del17p/TP53 mutations; t(4;14) or t(14;16) or t(14;20) with additional amp1q or del1p; amp1q and del1p; biallelic del1p; and high β2 microglobulin with normal renal function. Classic high risk was defined per-protocol as having del17p, t(14;16), and/or t(4;14). Minimal residual disease negativity (MRD neg) was assessed by NGS (Adaptive) in pts with ≥complete response.

Results. 152/434 (35%) pts were high risk by CGS. Most common genetic lesions were del17p/*TP53* (n=59,14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% had biallelic focal del1p. Using CGS criteria, 17% of pts were reclassified from standard risk to high risk; 4% of pts were reclassified from high risk to standard risk. DVRd was associated with increased MRD neg rates (10^{-6}) vs VRd in both CGS standard-risk (67% vs 39%, p=0.0001) and high-risk pts (56% vs 26%, p=0.0003). Sustained MRD neg (10^{-6}) rates for ≥12 mos (+/-1 mo) were higher with DVRd vs VRd for CGS standard-risk (57% vs 24%; p<0.0001) and high-risk pts (41% vs 19%; p<0.0001). Regardless of CGS risk status, pts who achieved sustained MRD neg (10^{-6}) had superior PFS outcomes vs those who did not (p<0.0001). DVRd led to improved PFS in CGS standard-risk (HR 0.38, [95% CI 0.20–0.73]; p=0.001) and high-risk pts (0.54, [0.31–0.95]; p=0.039), adjusting for ISS, lactate dehydrogenase, and age (>65 yrs).

Conclusions. DVRd improved MRD negativity and PFS over VRd in IMS/IMWG CGS high-risk and standard-risk subgroups. UMA-NGS panel identified nearly twice as many high-risk pts in the PERSEUS study per the CGS criteria. Results support DVRd induction/consolidation and DR maintenance as standard of care for TE-NDMM, regardless of cytogenetic risk. © *American Society of Clinical Oncology (2026). Reused with permission.*

R-NAT SCORE: A NOVEL TOOL TO PREDICT THROMBOSIS IN MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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Background. Thrombosis is a major complication in myelofibrosis (MF), yet MF specific prognostic models are lacking. Risk scores developed for polycythemia vera (PV) and essential thrombocythemia (ET) are therefore sometimes applied, although their performance, particularly during ruxolitinib (RUX), remains uncertain. The neutrophil to lymphocyte ratio (NLR) is an inflammatory marker with prognostic relevance in MPNs. We assessed whether PV/ET derived risk scores, baseline NLR and early NLR changes predict thrombosis during RUX.

Methods. RUX MF (NCT06516406) is a multicenter real world study including 1150 RUX treated MF patients (pts). Thrombotic risk was assessed by IPSET T and conventional PV criteria. Baseline NLR≤3.53 was considered low. Thrombosis free survival (TFS) was estimated by KM; only G≥2 thromboses were recorded.

Results. At RUX start, 78.1% of pts were >60 yrs, 61.0% had ≥1 cardiovascular risk factor, 75.2% were JAK2 mut and 16.2% had prior thrombosis. Mean baseline NLR was 7.4. JAK2 VAF>50% (52.1%) and NLR>3.53 (70.6%) showed significant collinearity (p=.001). By IPSET T, 69.9% were high risk, whereas 17.7% were low risk by PV criteria.During RUX, 85 thrombotic events occurred in 78 pts (6.8%), with an incidence rate (IR) of 2.19%patient years (%py), predominantly venous. 5-year TFS was 89.6%. IPSET T failed to stratify thrombotic risk, while PV criteria did (IR 0.87 vs 2.69%py, p=.004). Patients developing thrombosis were older and had higher mean plt and WBC and NLR. NLR >3.53 was associated with higher thrombotic risk (HR 1.91, p=.04), particularly among high risk pts.In a 3-month landmark analysis, NLR increase (>3.53) was linked with higher thrombotic risk (HR 4.21, p=.04). NLR decrease to ≤3.53 was associated with lower thrombotic risk vs stable high NLR (HR 2.63; p=.02).Multivariable analysis identified age >60, prior thrombosis, and NLR >3.53 as independent predictors. These factors informed the R NAT (Ruxolitinib NLR, Age, Thrombosis) score, stratifying pts into three risk groups (low: 0–1 points, intermediate: 2–3, high risk: 4) with 5 year TFS of 96.6%, 88.5%, and 79.7%, outperforming IPSET T and PV criteria (C index 0.61 vs 0.56 vs 0.53).

Conclusions. Inflammation is key to thrombotic vulnerability during RUX. The R-NAT Score may improve discrimination of MF thrombotic risk compared with existing models. Baseline NLR and its dynamic evaluation are reliable biomarkers linking inflammatory control to thrombotic risk.

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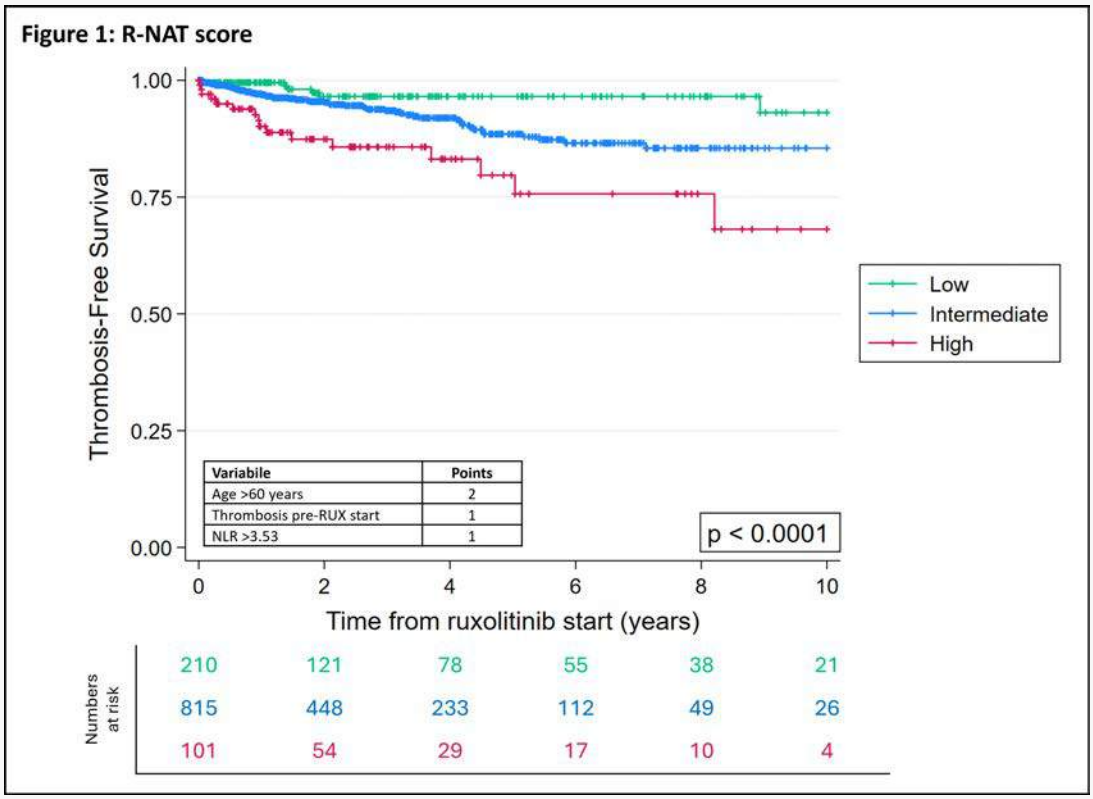
Figure 1: R-NAT score



ADVANCE IV+: LONG-TERM SAFETY AND EFFICACY OF EFGARTIGIMOD IN PRIMARY IMMUNE THROMBOCYTOPENIA

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Efgartigimod (EFG) is a human IgG1 antibody Fc fragment which blocks the neonatal Fc receptor and increases degradation of IgG antibodies, including pathogenic autoantibodies that contribute to primary immune thrombocytopenia (ITP). The phase 3 ADVANCE IV trial evaluated EFG in 131 adults with chronic or persistent ITP. Participants completing ADVANCE IV could roll over to the ongoing open-label extension trial, ADVANCE IV+ (NCT04225156), to evaluate the long-term safety and efficacy of EFG.At the time of data cut-off (01 September 2023), of the 101 participants enrolled in ADVANCE IV+, 7.9% had completed the study and 57.4% had discontinued; 34.7% were ongoing. Most (51.5%) participants discontinued treatment in the first 52 weeks, mainly due to per-protocol lack of efficacy (27.7%). During weeks 0–24, 33.7% of participants received every-other-week (Q2W) EFG (stable platelet count [PC] ≥100×109/L). One-third (32.7%) had sustained PC responses (≥50×109/L at ≥4 visits between weeks 19–24); 29.7% achieved PC of ≥50×109/L in ≥4 visits between weeks 0–6, and the mean (standard error) percentage of weeks with PC of ≥50×109/L was 39.2% (3.9%). Median (Q1, Q3) time-to-response (two consecutive PC ≥50×109/L) was 122.0 (50.0, 213.0) days. The majority of participants (92.1%) reported one or more treatment-emergent adverse event (TEAE), most of which were mild or moderate in severity (serious adverse events [AEs]: 15.8% pts; severe [grade ≥3] AEs:18.8% pts). There were no treatment-related deaths.ADVANCE IV+ demonstrated long-term safety and efficacy of EFG in participants with chronic or persistent ITP, highlighting its value as a treatment in this patient group

DECISION-MAKING PREFERENCES AND PERCEPTIONS OF HEALTH STATUS AMONG PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: AGREEMENT BETWEEN PATIENTS AND PHYSICIANS

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Clinical decision-making in relapsed/refractory multiple myeloma (RRMM) is challenging due to the wide range of available treatment options, making effective patient–physician communication essential. The aim of this study was to evaluate: (1) patients' preferred role in treatment decisions and agreement with physicians' perception; (2) agreement between patients and physicians in the assessment of patients' global health status.This was a cross-sectional analysis of baseline data from an international observational GIMEMA study of RRMM patients. At baseline, patients' preferred role in decision-making was assessed with the 5-level Control Preference Scale (CPS), and global health status with the EORTC QLQ-C30. For descriptive purposes, CPS responses were categorized into three groups: active, collaborative, passive. For patients receiving treatment at study entry, physicians provided corresponding assessments. Agreement was evaluated using frequencies, percentages, and weighted kappa (κ), with disagreement classified as minor or major based on the magnitude of difference between ratings.Analysis included 348 patients receiving treatment at study entry with available CPS data, of whom 45 (13%) preferred an active role, 84 (24%) a collaborative role, and 219 (63%) a passive role in decision-making. Of 312 available patient–physician paired assessments, agreement on decision--making preferences occurred in 119 (38.1%) cases, with minor and major disagreements in 129 (41.4%) and 64 (20.5%) cases, respectively (κ=0.23). In discordant cases (n=193), physicians more frequently rated patients as preferring a more active role than that reported by patients themselves (64.8% vs 35.2%).Agreement on global health status was limited (97/312, 31.0%), with minor and major disagreement in 121 (38.8%) and 94 (30.2%) cases, respectively (κ=0.29). Physicians overestimated patients' health status in 132/215 cases (61.4%), corresponding to 42.3% of the overall cohort.-Most patients preferred a passive role in decision-making, leaving treatment choices to physicians. Discordance between patients and physicians was observed for both decision-making preferences and perceived global health status. Physicians tended to indicate higher levels of patient involvement and better global health status. These findings underscore the importance of ongoing efforts to enhance communication strategies and strengthen patient-centered care in hematology.

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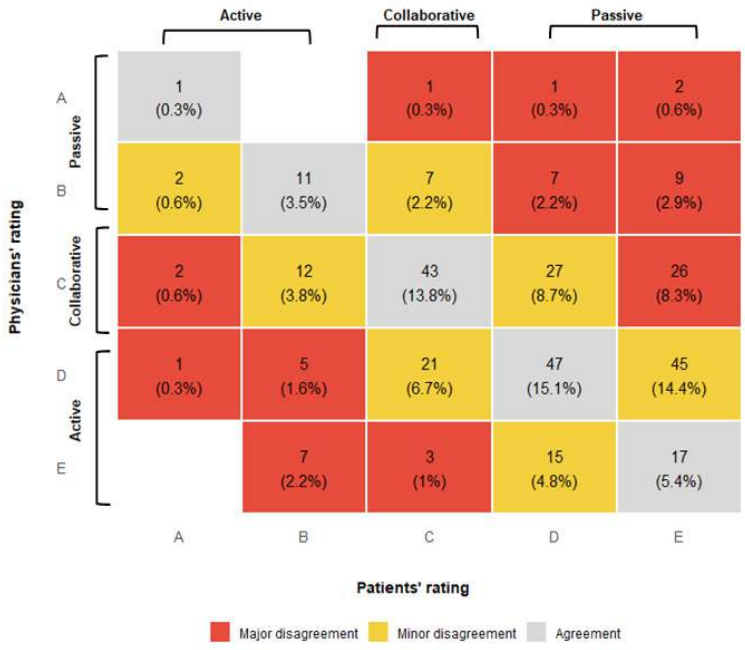
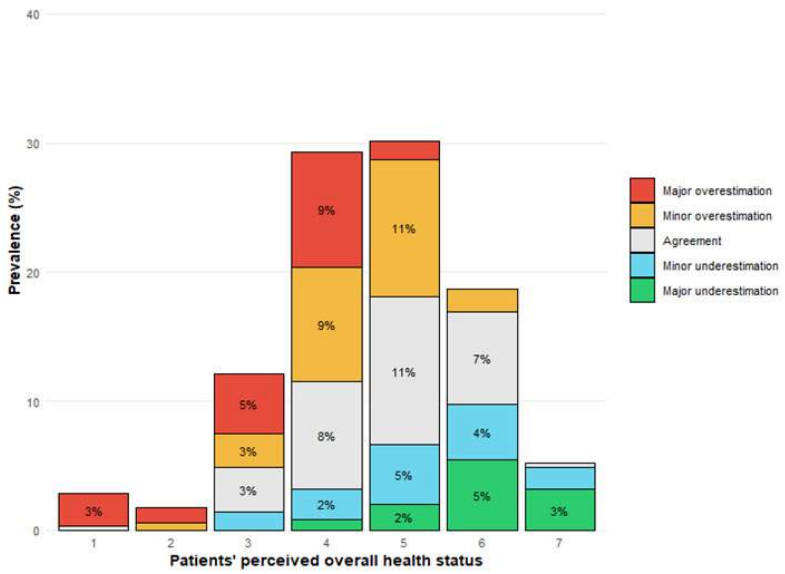
Figure 1. Agreement/disagreement patterns between physicians and patients regarding (A) patients' preference for involvement in treatment decisions and (B) patients' perceived global health status.

(A)



(B)



LUSPATERCEPT INITIATED AT THE MAXIMUM-APPROVED DOSE IN PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES WHO REQUIRE TRANSFUSIONS: PRIMARY ANALYSIS FROM MAXILUS

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Background. MAXILUS is an open-label, global, ph 3b study (NCT06045689) evaluating LUSPA at the maximum-approved dose (1.75 mg/kg) in pts with LR-MDS who are erythropoiesis-stimulating agent (ESA)–naive or –relapsed/refractory or intolerant (R/R/I) and require transfusions. We report efficacy and safety from the primary analysis (Wks 1–24).

Methods. Pts (≥18 y; non-del[5q] LR-MDS; ≥1 unit packed RBCs ≤8 wks before tx) received LUSPA (1.75 mg/kg; SC Q3W). Primary endpoint (PE): RBC-transfusion independence (RBC-TI) ≥8 wks with concurrent mean Hb increase ≥1 g/dL (Wks 1–24). Secondary endpoints included RBC-TI ≥8 and ≥12 wks (Wks 1–24), modified erythroid hematologic improvement (mHI-E; Wks 1–24), and safety.

Results. ESA-naive: At cutoff (Oct 1, 2025), 53 pts received ≥1 LUSPA dose. PE was achieved in 81.1% of pts; RBC-TI ≥8 wks in 83.0% and ≥12 wks in 75.5% (Figure 1); RBC-TI ≥12 wks in 72.7% of ring sideroblast–negative (RS–) pts and 85.7% of baseline serum erythropoietin (BL sEPO) ≤200 IU/L pts; mHI-E in 86.8%. Overall, 69.8% of pts remained on tx, 1.9% completed, and 28.3% discontinued. Median tx duration was 47.4 (range, 10.7–71.1) wks; 22.6% of pts had ≥1 dose reduction; 52.8% had ≥1 dose delay. Tx-emergent adverse events (TEAEs) occurred in 94.3% of pts (30.2% tx-related); 20.8% led to tx interruption; grade 3/4 TEAEs occurred in 66.0% (11.3% tx-related). HR-MDS progression occurred in 3.8% of pts; none progressed to AML.ESA-R/R/I: At cutoff, 53 pts received ≥1 LUSPA dose. PE was achieved in 62.3% of pts; RBC-TI ≥8 wks in 67.9% and ≥12 wks in 50.9% (Figure 1); RBC-TI ≥12 wks in 40.0% of RS– pts and 58.3% of BL sEPO ≤200 IU/L pts; mHI-E in 77.4%. Overall, 39.6% of pts remained on tx, 1.9% completed, and 58.5% discontinued. Median tx duration was 41.0 (range, 2.1–97.1) wks; 11.3% of pts had ≥1 dose reduction; 43.4% had ≥1 dose delay. TEAEs occurred in all pts (45.3% tx-related); 20.8% led to tx interruption; grade 3/4 TEAEs occurred in 54.7% (7.5% tx-related). HR-MDS progression occurred in 3.8% of pts; none progressed to AML.

Conclusions. From Wks 1–24, LUSPA initiated at 1.75 mg/kg led to high, sustained PE achievement in both cohorts and sustained RBC-TI ≥12 wks in RS– and low BL sEPO pts. RBC-TI and mHI-E were notable in both cohorts. Tx was well tolerated; few pts progressed to HR-MDS, in line with known rates, and none to AML. This primary analysis reinforces the favorable efficacy and safety profile of LUSPA at the maximum-approved dose in LR MDS.

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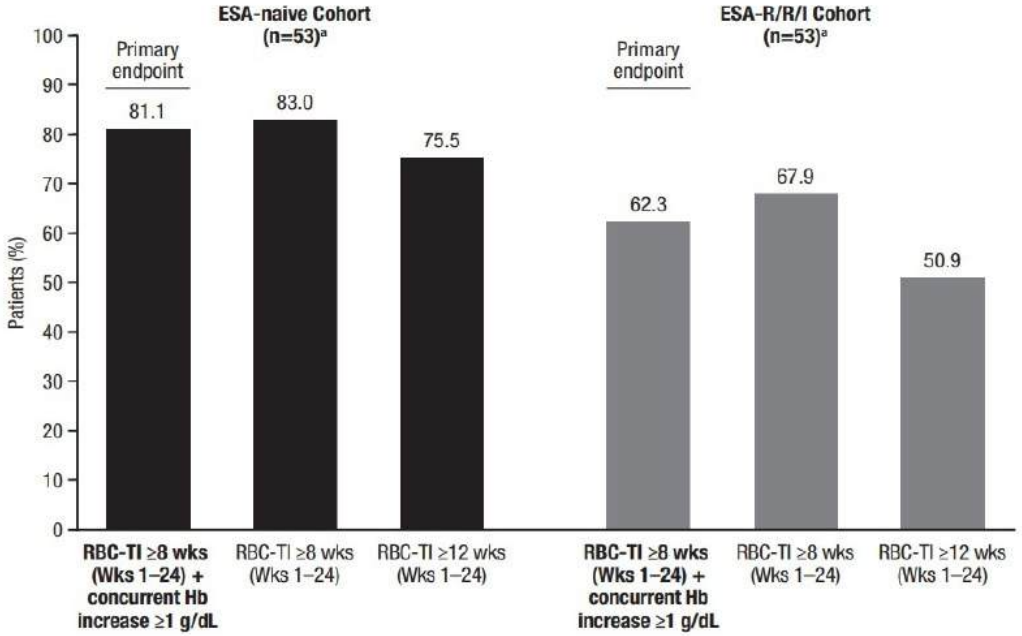
Figure 1: Primary Analysis of RBC-TI ± Hb Increase ≥8 Wks and RBC-TI ≥12 Wks for LUSPA Tx in the MAXILUS Study Among the ESA-naive Cohort and the ESA-R/R/I Cohort



Data cutoff: October 1, 2025.
ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; R/R/I, relapsed/refractory or intolerant; RBC-TI, red blood cell-transfusion independence; wks, weeks; tx, treatment.
[a]Efficacy-evaluable population (patients who received first tx ≥24 wks prior to data cutoff).

DEEP TRANSCRIPTOMIC PROFILING OF NPM1-MUTATED/FLT3-ITD-NEGATIVE AML IDENTIFIES A CLINICALLY RELEVANT FLT3^{LIKE} SUBGROUP

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Background. Acute Myeloid Leukemia (AML) with Nucleophosmin (*NPM1*) mutations without *FLT3*-ITD (*NPM1*^{mut} / *FLT3*-ITD^{neg}) defines a subgroup with favorable outcomes when treated with chemotherapy alone. However, up to 40% of these patients relapse. We analyzed the biological landscape of this subgroup using an integrated RNA-seq dataset, aiming to identify clinically relevant subgroups.

Methods. We created the "Gu" algorithm (EHA2025 - PS1463) to generate a unified RNA-seq dataset of n = 894 samples with strong biological coherence (Fig. 1a), also reproducing the ELN 2022 risk stratification (Fig. 1b). Several bioinformatic analyses were performed, using multiple microarray- and RNA-seq-based gene expression profiles as validation cohorts.

Results. Transcriptomic dissection of *NPM1*^{mut} / *FLT3*-ITD^{neg} AML revealed two subgroups (Fig. 1c): a "*FLT3*^{LIKE}" cluster resembling *FLT3*-ITD AML, and a "*NPM1*^{PURE}" cluster enriched in inflammatory/immune genes. These subgroups display distinct genomic profiles (with *RAS* mutations prevailing in *NPM1*^{PURE} cases and *FLT3*^{LIKE} cases enriched for *IDH2* mutations), together with different FAB subtype distributions and immune microenvironments: a markedly "hotter" immune signature profile was highlighted within *NPM1*^{PURE} samples, whereas *FLT3*^{LIKE} samples appeared relatively "cold". Consistent with a transcriptional program partially overlapping with *FLT3*-ITD AML, *FLT3*^{LIKE} AML samples showed predicted drug sensitivity to *FLT3*-directed agents (including quizartinib, midostaurin, and sorafenib) compared with *NPM1*^{PURE} AML. These results were confirmed in the independent validation cohorts. Preliminary data supported the generation of a prognostic score able to refine risk stratification within this otherwise favorable-risk AML subgroup (Fig. 1d). To further strengthen this approach, an expanded survival-modeling pipeline combining several machine learning algorithms is being validated across independent microarray and RNA-seq cohorts.

Conclusions. Our work has opened an innovative window into the clinic and biology of *NPM1*^{mut} / *FLT3*-ITD^{neg} AML, revealing a distinctive transcriptomic signature correlated with different molecular profiles, immune environments, and drug sensitivity. Deep machine learning analyses are ongoing to identify potential biomarkers for further prognostic stratification, and new therapeutic targets have emerged, with biological validations ongoing in our lab.

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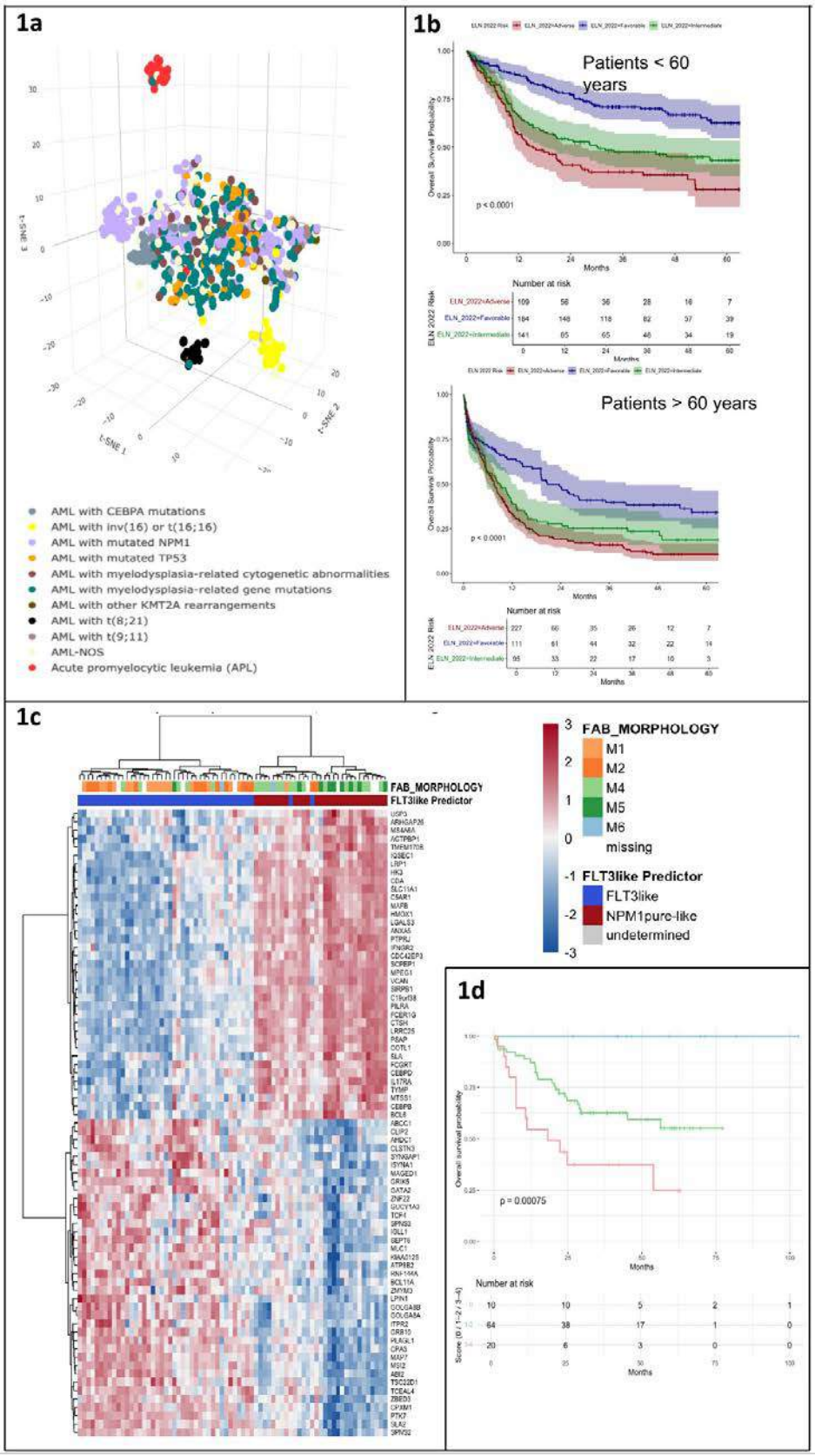
1a
AML with CEBPA mutations
AML with inv(16) or t(16;16)
AML with mutated NPM1
AML with mutated TP53
AML with myelodysplasia-related cytogenetic abnormalities
AML with myelodysplasia-related gene mutations
AML with other KMT2A rearrangements
AML with t(8;21)
AML with t(9;11)
AML-NOS
Acute promyelocytic leukemia (APL)
1b
Patients < 60 years
Patients > 60 years
Number at risk
1c
FAB_MORPHOLOGY
FLT3like Predictor
M1
M2
M4
M5
M6
missing
FLT3like
NPM1pure-like
undetermined
1d
p = 0.00075
Number at risk

IMPROVED RISK STRATIFICATION IN PHILADELPHIA-NEGATIVE B-ACUTE LYMPHOBLASTIC LEUKEMIA THROUGH MOLECULAR CHARACTERIZATION RETROSPECTIVE ANALYSIS OF THE GIMEMA LAL2317 TRIAL

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Background. Definition of risk features in B-adult lymphoblastic leukemia (B-ALL) is pivotal for optimal disease management and early transplant allocation. The GIMEMA LAL2317 phase II trial for newly diagnosed Ph- B-ALL (18-65 years) is based on a pediatric-inspired regimen plus blinatumomab. Baseline clinical and biological features at diagnosis defining very high and high-risk (VHR, HR) B-ALL were age, white blood cell (WBC) count, cytogenetic or molecular abnormalities (*KMT2A*-r, adverse karyotype , pro-B phenotype) according to the literature (Gökbuget N., Blood 2024). To improve this prognostic stratification, we retrospectively re-allocated patients on the basis of a refined molecular characterization of the latter ICC criteria.

Methods. A total of 127 adults with Ph- B-ALL enrolled in the GIMEMA LAL2317 trial were included. At diagnosis, the BCR/ABL1-like predictor (Chiaretti S., BJH, 2018) was performed in 109 patients, negative for recurrent fusion transcripts (*KMT2A*-r and *TCF3::PBX1*). RNA/DNA sequencing was carried out in 105 and 75, respectively.

Results. The median age was 41 years (18-65) and the median WBC count 5.3×10^9/L (0.1-474). Cytogenetics identified an adverse karyotype in 7 cases (5 complex, 1 del(6), 1 low-hypodiploid); 13 were *KMT2A*-r, 5 *TCF3::PBX1*+. As per trial risk criteria, 34 patients (27%) were classified as VHR, 25 (20%) as HR and 68 (54%) as standard risk (SR). Thirty-one patients proved Ph-like. DNA/RNA-seq allowed to identify a set of prognostically relevant aberrations: *ZNF384*-r (10), *PAX5 P80R* (4), *PAX5*-altered (6), *MEF2D*-r (4) and *TP53* mut/del (11). Re-stratifying patients according to molecular features, 61 were classified as SR (*PAX5*-altered/*P80R*, *ZNF384*-r and B-neg) and 66 as HR (Ph-like, adverse karyotype, *TP53* mut/del, *MEF2D*-r). While the initial risk stratification did not show differences in 3-year overall survival (OS) and disease-free survival (DFS), after risk reallocation HR patients showed a 3-year OS of 56% vs 84% for SR (p=0.0062); likewise, the 3-year DFS was 48% vs 85%, respectively (p<0.0001) [Figure 1].

Conclusions. A comprehensive genomic profiling of Ph- B-ALL patients led to the identification of additional HR categories, including *MEF2D*-r cases and *TP53* mut/del. It also confirmed previously recognized HR groups (adverse karyotype, *KMT2A*-r and Ph-like ALL). Conversely, *ZNF384*-r and *PAX5* alt/*P80R* patients were confirmed as a favorable subset. Further data will be provided at the congress.

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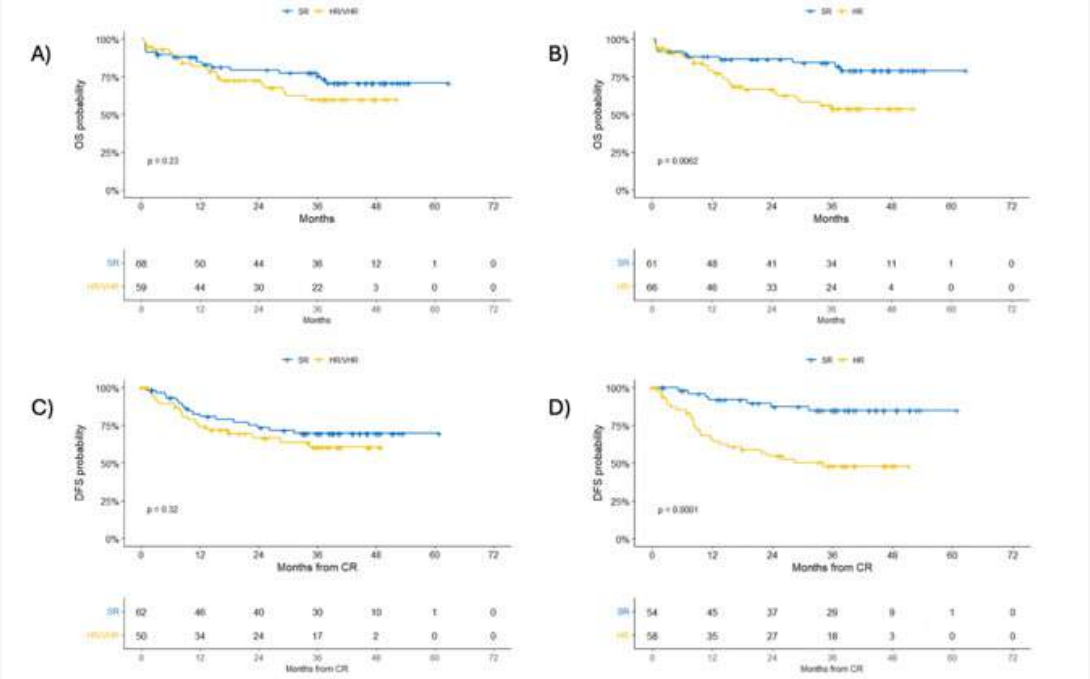
Figure 1. OS and DFS based on the initial risk stratification (A, C) and on the molecularly based stratification (B, D).



BGB-16673, A BRUTON TYROSINE KINASE DEGRADER, IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: A PHASE 1 CADANCE-101 STUDY UPDATE

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Background. BTK inhibitors (BTKis) are effective treatments (tx) for CLL/SLL; but, resistance and intolerance remain challenges. BGB-16673 is a novel BTK degrader that induces proteasomal degradation of BTK, inhibiting signaling and promoting tumor regression. The ongoing phase 1/2 CaDAnCe-101 study (NCT05006716) is evaluating BGB-16673 monotherapy in patients (pts) with B-cell malignancies.

Aims. To report updated safety and efficacy results for phase 1 of CaDAnCe-101 in pts with relapsed/refractory (R/R) CLL/SLL.

Methods. Eligible pts had R/R CLL/SLL, ≥2 prior therapies, ECOG performance status 0-2 (0-1 in the EU), and adequate organ function. Pts in the US, EU, and Australia had prior tx with a covalent BTKi. BGB-16673 was administered orally once daily. Primary objectives were safety/tolerability and dose determination. Secondary objectives included overall response rate (ORR) per iwCLL 2018 criteria (with PR-L modification) and 2014 Lugano criteria.

Results. As of Dec 15, 2025, 67 pts received BGB-16673 (50 mg, n=1; 100 mg, n=22; 200 mg, n=17; 350 mg, n=15; 500 mg, n=12). Median age was 70 years, and pts received a median of 4 prior lines of therapy. 94% had prior covalent BTKi, 82.1% BCL2 inhibitor, and 20.9% noncovalent BTKis. Baseline mutations are shown (Table). Median study follow-up was 24.1 months, and 52.2% remained on tx.Any-grade tx-emergent adverse events (TEAEs) occurred in 97.0% of pts; the most common were fatigue (37.3%), contusion (32.8%), diarrhea (29.9%), and neutropenia (29.9%). Grade ≥3 TEAEs occurred in 61.2% of pts, most commonly infections (34.3%) and neutropenia (25.4%), and thrombocytopenia (7.5%). TEAEs led to dose reduction in 13.4% and tx discontinuation in 17.9% of pts; 5 pts died due to infection (one in the context of disease progression, PD).The ORR (≥PR-L) was 85.1%, with a PR or better rate of 77.6%; the complete response (CR)/CR with incomplete marrow recovery rate (CRi) of 3.0%. At 200-mg, the ORR was 94.1% (16/17). Median time to first response was 2.8 months, and median duration of response was 20.7 months. Responses were seen in pts with high-risk features (Table). The 18-month PFS rate was 65.2% (95% CI, 50.9%-76.2%); 21 pts (31.3%) had PD, and 5 (7.5%) died.

Conclusions. BGB-16673 demonstrated a manageable safety profile and durable responses in heavily pretreated pts with R/R CLL/SLL, including those with high-risk disease. The 200 mg-dose is being further evaluated in ongoing phase 2 and 3 studies.

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Table. ORR (defined as PR-L or better) according to prior therapy and mutation status

Characteristic	Patients, n/N (%)	ORR, n/N (%)
Prior therapy		
cBTKi and BCL2i	43/67 (64.2)	40/43 (93.0)
cBTKi, BCL2i, and ncBTKi	12/67 (17.9)	9/12 (75.0)
Mutation status		
BTK mutation	25/66 (37.9)	19/25 (76.0)
del(17p)/*TP53* mutation	44/67 (65.7)	35/44 (79.5)
PLCG2 mutation	10/66 (15.2)	9/10 (90.0)
IGHV unmutated	37/48 (77.1)	32/37 (86.5)
Complex karyotype (≥3 abnormalities)	23/43 (53.5)	17/23 (73.9)

BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; IGHV, immunoglobulin heavy-chain variable region; ncBTKi, noncovalent BTK inhibitor; PR-L, partial response with lymphocytosis.

LONG-TERM SAFETY AND EFFICACY OF IPTACOPAN IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: 4- AND 5-YEAR FOLLOW-UP OF PATIENTS FROM PHASE 2 STUDIES WHO ENTERED THE ROLL-OVER

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Introduction Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis and anemia. Despite anti-C5 therapy, many patients remain anemic, with ongoing symptoms and extravascular hemolysis. Iptacopan is an oral factor B inhibitor targeting the alternative complement pathway, showing rapid and sustained hemolysis control in Phase 2/3 studies. We report 4 and 5-year follow-up data from patients who entered the roll-over extension program (REP) from Phase 2 studies.

Methods. PNH-REP (NCT04747613) is an ongoing, open-label, single-arm, multicenter, Phase 3 study of patients with PNH who completed prior iptacopan studies. This analysis includes 26 patients from two Phase 2 trials (NCT03439839, NCT03896152)[1,2]. Baseline was first dose of iptacopan 200 mg BID. Efficacy at 4 and 5 years includes hemoglobin (Hb) levels, Hb ≥12.0 g/dL (irrespective of red blood cells transfusions), transfusion avoidance, lactate dehydrogenase (LDH) levels, absolute reticulocyte count (ARC). Safety assesses breakthrough hemolysis (BTH), major adverse vascular events (MAVEs), adverse events (AEs), serious AEs (SAEs).

Results. Of 26 patients, 22 entered REP. Among the 26 patients, 61.5% and 30.8% received iptacopan for ≥4 and ≥5 years, respectively. Mean Hb was 12.1 and 12.9 g/dL; 63.6% and 66.7% achieved Hb ≥12.0 g/dL; mean LDH was 315.8 and 292.2 U/L; 81.8% and 83.3% achieved LDH <1.5× the upper limit of normal (ULN) at 4 and 5 years, respectively. Transfusion independence was achieved by 96.2% at 5-year follow-up. Mean ARC levels were 81.4×109/L and 84.6×109/L at 4 and 5 years, respectively; all patients achieved ARC normalization. Four BTH events occurred in 3 patients; 1 MAVE (unstable angina) was reported. AEs occurred in 84.6% (COVID-19 and pyrexia 30.8% each, headache 15.4%); SAEs in 38.5%. Three deaths (11.5%) occurred, none considered treatment related (Table 1).

Conclusions. Iptacopan provides durable hematological response with sustained Hb levels, transfusion independence, LDH control, and ARC normalization, confirming the long-term control of intravascular andextravascular hemolysis. BTH and MAVEs were rare and no new safety signals were observed. These results support iptacopan as a potentially practice-changing oral therapy for PNH[3].

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Table 1. Long-term efficacy and safety outcomes with iptacopan in patients with PNH (4- and 5-year follow-up)

Study population	
Patients, n	26
Patients entering the PNH-REP extension study, n	22
Treatment with iptacopan ≥4 years, n (%)	16 (61.5%)
Treatment with iptacopan ≥5 years, n (%)	8 (30.8%)
Hematologic efficacy	
Mean Hb at 4 years, g/dL (SD)	12.1 (2.0)
Mean Hb at 5 years, g/dL (SD)	12.9 (2.0)
Patients with Hb ≥12 g/dL at 4 years, %	63.6
Patients with Hb ≥12 g/dL at 5 years, %	66.7
Transfusion independence at 5 years, %	96.2
Mean LDH at 4 years, U/L (SD)	315.8 (123.7)
Mean LDH at 5 years, U/L (SD)	292.2 (71.9)
Patients with LDH <1.5× ULN at 4 years, %	81.8
Patients with LDH <1.5× ULN at 5 years, %	83.3
Mean ARC at 4 years, $\times 10^9$/L (SD)	81.4 (31.3)
Mean ARC at 5 years, $\times 10^9$/L (SD)	84.6 (15.7)
ARC normalization, %	100
Safety	
Breakthrough hemolysis, n# (%)	3 (11.5%)
Breakthrough hemolysis OccR (95% CI)	3.7 (1.2, 11.6)
MAVE, n# (%)	1 (3.8%)
MAVE OccR (95% CI)	0.9 (0.1, 6.6)
≥1 AEs, n# (%)	22 (84.6%)
SAEs*, n# (%)	10 (38.5%)
Deaths**, n (%)	3 (11.5%)

#n (%) refers to patients with ≥1 event

* Treatment-emergent infection-related SAEs were reported in 3 patients (11.5%), including pneumonia (considered treatment-related by the investigator), bacterial pneumonia, pneumococcal pneumonia, sepsis, and urinary tract infection.

** None considered treatment-related by investigator.

AEs: adverse events; ARC: absolute reticulocyte count; CI: confidence interval; Hb: hemoglobin; LDH: lactate dehydrogenase; MAVE: major adverse vascular events; OccR: occurrence rate (exposure-adjusted OccR expressed as total number of episodes per 100 patient-years); SAEs: serious adverse events.

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COMBINATION TREATMENT WITH NOVEL BCL2 INHIBITOR SONROTOCLAX (BGB-11417) AND ZANUBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: RESULTS FROM A PHASE 1/1B STUDY

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Background. Although venetoclax + ibrutinib are efficacious in R/R MCL, durable treatments (tx) with improved tolerability are needed. Sonrotoclax (sonro), a next-generation BCL2 inhibitor, is more selective and pharmacologically potent than venetoclax. Zanubrutinib (zanu) is a 2nd-generation BTK inhibitor approved for R/R MCL in the US. Here, we report safety and efficacy of combination sonro+zanu (SZ) in patients (pts) with R/R MCL in a phase 1/1b study (NCT04277637).

Methods. Study tx started with zanu lead-in (320mg QD or 160mg BID) for 8-12 wk, after which sonro was added with ramp-up to target dose (80, 160, 320, or 640mg QD). Treatment continued until progression, unacceptable toxicity, or elective discontinuation after 96 wk. Primary endpoint was safety; secondary endpoints included overall response rate (ORR).

Results. As of Dec 6, 2025, 51 pts were enrolled in sonro dose cohorts: 80mg (n=6), 160mg (n=13), 320mg (n=27), and 640mg (n=5). At data cutoff, 46/51 (90.2%) had initiated SZ, with 25 (49.0%) remaining on tx. Pts had a median of 1 prior tx (range, 1-4; stem cell transplant, n=15 [1 allogeneic, 14 autologous]; CAR-T, n=1; BTK inhibitor, n=4). Maximum tolerated dose was not reached; the recommended phase 2 dose of sonrotoclax was determined to be 320mg QD.Twenty-one pts (41.2%) discontinued SZ and 6 (11.8%) discontinued zanu only. TEAEs led to discontinuation of SZ in 4 pts (7.8%) and zanu in 2 (3.9%); none led to discontinuation of sonro only. TEAEs led to death in 2 pts (3.9%; pneumonia; abdominal sepsis). The most common any-grade TEAE was diarrhea (37.3%). Grade ≥3 TEAEs occurred in 66.7% of pts (most common: neutropenia [21.6%]). Serious TEAEs occurred in 41.2% of pts (most common: pneumonia [15.7%]).For sonro 320mg+zanu, the most common any-grade TEAE was diarrhea (51.9%; most grade 1-2) and grade ≥3 TEAE was neutropenia (22.2%). No laboratory or clinical TLS occurred.In sonro 320mg+zanu pts (median follow-up, 21.3 mo), ORR was 81.5% (22/27); CR rate was 59.3% (16/27). Median duration of response (DOR) was not reached; 30-mo DOR rate was 77.7% (95% CI, 50.2%-91.2%). Of 4 pts with prior BTK inhibitor therapy, 2 achieved PR. All 6 pts who elected to discontinue tx achieved CR and remain in complete remission (median time off tx, 9.6 mo; range, 2.9-12.1).

Conclusions. SZ was well tolerated with promising antitumor activity. A phase 3 trial of sonro 320mg+zanu is ongoing (NCT06742996).

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CONGRESSO NAZIONALE SIE

Società Italiana di Ematologia

ROMA, 21-23 Settembre 2026

Roma Convention Center La Nuvola

ORAL COMMUNICATIONS

Non-Hodgkin's Lymphoma

THE GUT MICROBIOME MATTERS: DEFINING THE ROLE OF GUT MICROBIAL COMPOSITION AND ITS DYNAMICS IN MODULATING THE CAR T-CELL RESPONSE IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B-CELL LYMHPHOMA: A PROSPECTIVE, SINGLE-CENTRE STUDY

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Prognosis for relapsed/refractory large B-cell lymphoma (rrLBCL) has significantly improved with CAR T-cell, but outcomes considerably vary. Given the gut microbiome (GM) key role on immune regulation, we designed a prospective study on its role in the outcome of rrLBCL patients undergoing CAR-T, monitoring its longitudinal changes from apheresis (T0) to follow-up (fup) (AIRCIG202227350). Fecal samples of 59 rrLBCL patients treated with CAR-T (55 axicel, 4 lisocel) were collected at T0, the day before and after lymphodepletion (LD), the day of infusion, and during fup. 16S rRNA sequencing was performed to obtain genus-level insights into GM, while shotgun metagenomic (MTG) analysis was carried out to have high-resolution compositional information. Responders (R) were defined as those who obtained at least a partial response. Median age was 58 years (range 29-74), 76% had stage III/IV, 93% were refractory to last treatment and 95% received bridging therapy. Best overall response rate was 76%, median progression-free survival was 6.2 months, and median overall survival was not reached (median follow-up 18.2 months). Alpha diversity, assessed by both 16S and MTG, remained stable in R but significantly decreased in non-responders (NR), with a marked reduction observed from the acute post-LD phase to the last fup. Beta diversity analysis revealed a clear divergence in microbial community structure between R and NR over time, results confirmed by taxonomic evaluation. At genus level, NR exhibited a progressive decrease in the relative abundance of Ruminococcus, Christensenellaceae R-7 group, Prevotella and Monoglobus, with significant differences compared to R emerging from day 30. Species-level analysis showed a reduction of Faecalibacterium prausnitzii, Anaerostipes hadrus and Blautia wexlerae in NR, alongside an increase in Enterocloster clostridioformis and Enterocloster bolteae (Fig.1). Notably, taxa depleted in NR are commonly associated with short-chain fatty acid production and maintenance of gut homeostasis, whereas taxa enriched in NR have been linked to dysbiotic and pro-inflammatory states. Our findings highlight the potential of integrating the microbiome profile into patient assessments not only to predict response to therapy but also to guide personalised treatment strategies.

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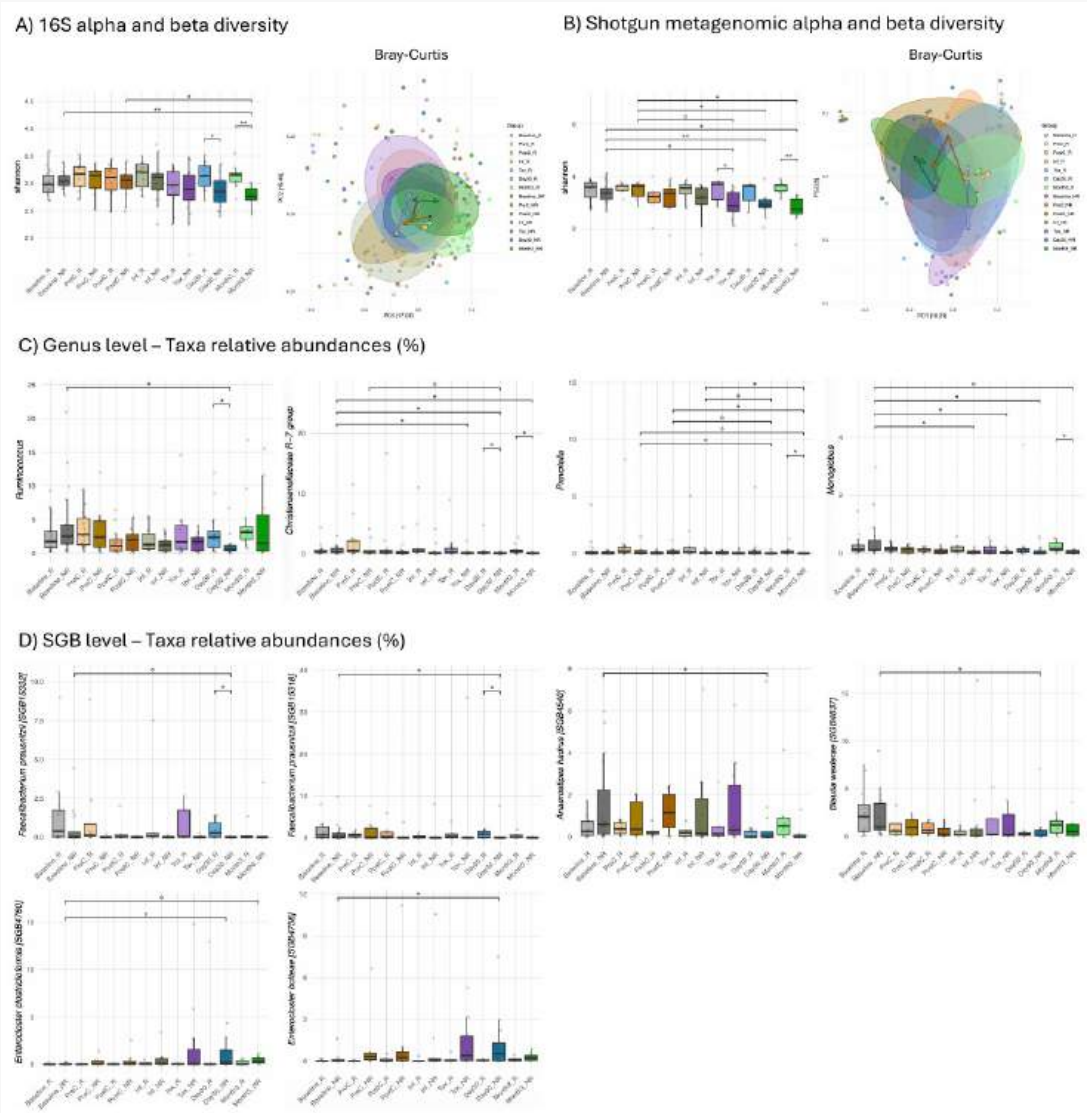

Figure 1. Alpha and beta diversity of the fecal microbiome in responder and non responder patients, assessed in both 16S rRNA gene sequencing (A) and shotgun metagenomic (B) analysis, using Shannon diversity index and Bray-Curtis dissimilarity. Boxplots showing differences in the relative abundance of bacterial genera (C) and species-level genome bins (SGB, D) assessed by 16S and shotgun metagenomic analyses, respectively. Statistical significance (Wilcoxon test, FDR correction): * $p < 0.1$, * $p < 0.05$, ** $p < 0.01$.

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Non-Hodgkin's Lymphoma

CTDNA MRD ASSESSMENT AND CLINICAL OUTCOMES IN HIGH-RISK ABC-DLBCL: UPDATED RESULTS FROM THE FIL_RI-CHOP TRIAL

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Background. The FIL_RI-CHOP trial evaluated R-CHOP plus ibrutinib (I) with I maintenance in young, untreated high-risk ABC-DLBCL, integrating molecular genotyping and ctDNA-based MRD analysis.

Methods. Prospective, multicenter, single-arm phase II trial enrolling newly diagnosed ABC-DLBCL aged 18-65 and IPI ≥2. COO was centrally assessed by Nanostring. After one R--CHOP cycle, confirmed ABC-DLBCL received R-CHOP+I (560 mg/day) from cycle 2-6, followed by 2 rituximab+I cycles and 18-month I maintenance for patients achieving ≥PR. Primary endpoint was 2-year PFS. Baseline genotyping and serial ctDNA MRD were assessed by CAPP-Seq.

Results. Among 279 registered patients, 75 (35%) were classified as ABC and received experimental treatment. Median age was 57 years (IQR 50-60), 58 (77.3%) patients presented elevated LDH levels, 34 (46%) IPI > 2 and 8 (10.7%) elevated CNS-IPI. At baseline ctDNA was evaluated in 66 patients and the DLBClass showed enrichment of clusters typical of ABC DLBCL, namely C5 (48.3%) and C1 (25.0%) (Fig 1A). Baseline ctDNA levels correlated with IPI >2 (p=0.039) and with high LDH (p<0.001) but did not associate with poor outcomes, potentially suggesting that ibrutinib may overcome the prognostic impact of baseline ctDNA levels. At EOI, assessed by PET-CT, ORR was 85.33% with a metabolic CR of 72%. A total of 64 patients initiated I maintenance; after 6 months, 6 of 10 patients with PR at EOI converted into CR. After a median FU time of 39 months, the 2 year-PFS rate was 77.9% IQR (68.9-88.1) (Fig 1B) and, notably, no patient developed CNS relapse. EOI ctDNA-based MRD was evaluated in 52 patients. MRD positivity significantly predicted shorter PFS (p<0.001) and presented a strong negative predictive value (90.9%) (Fig 1C). MRD independently associated with PFS also when adjusted for IPI>2 (HR 12.1, p<0.001) (Fig. 1D). Treatment was generally well tolerated; grade 3-4 neutropenia occurred in 13% of patients, febrile neutropenia in ≤2%, and three grade 1–2 cardiac events were recorded.

Conclusions. FIL_RI-CHOP is the first Italian academic lymphoma trial integrating central COO classification, molecular genotyping, and ctDNA MRD in a prospective design. The regimen was safe and highly effective with favorable PFS and no CNS relapses, despite the high-risk ABC-DLBCL population. ctDNA MRD retained independent prognostic value and should guide treatment stratification in future trials.

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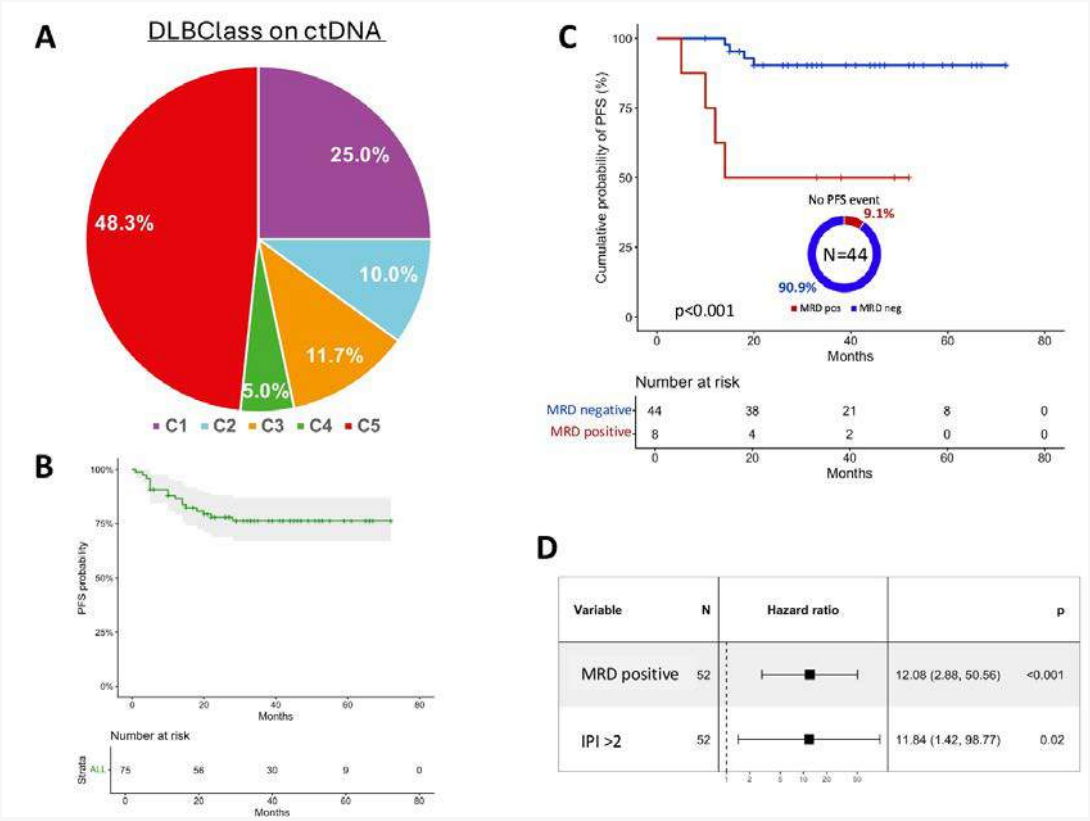
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5.0%
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C1 C2 C3 C4 C5
B
PFS probability
Months
Number at risk
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C
Cumulative probability of PFS (%)
No PFS event
9.1%
N=44
90.9%
MRD pos MRD neg
p<0.001
Months
Number at risk
MRD negative 44 38 21 8 0
MRD positive 8 4 2 0 0
D
Variable N Hazard ratio p
MRD positive 52 12.08 (2.88, 50.56) <0.001
IPI >2 52 11.84 (1.42, 98.77) 0.02

Non-Hodgkin's Lymphoma

CLINICAL FEATURES, TREATMENTS AND OUTCOME OF PLASMABLASTIC LYMPHOMA: RESULTS FROM A PRELIMINARY ANALYSIS OF THE RETROSPECTIVE MULTICENTER INTERNATIONAL PLALY STUDY ON BEHALF OF FIL, LEO/MER REGISTRY AND PLRG

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Plasmablastic Lymphoma (PBL) is a rare and aggressive B--cell malignancy with unique clinicopathological features, correlated with immunosuppression. Standard therapy is not established yet and few prognostic factors are known. We are carrying an international multicenter retrospective study (PlaLy) on PBL patients, diagnosed in 37 centers across three countries (Italy, Poland, USA), to describe clinical and pathological characteristics, treatments, outcome and prognostic factors. All patients locally diagnosed with PBL between 2000 and 2022, with available histopathological samples, are included. We present a preliminary analysis on the first 50 patients. A comprehensive histopathological central review is ongoing. At the time of analysis, 50 patients were enrolled: median age 56 (35-87), with 46% older than 60 years, 82% male, B symptoms in 13 (28%), advanced stage in 28 (62%), ECOG PS > 1 in 11 (23%), more than 1 extranodal site in 19 (40%) cases. R-IPI was low in 11%, intermediate in 39%, high in 50%. HIV was positive in 20 (44%) patients: all but one were already under antiretroviral treatment at the time of lymphoma diagnosis, but in 52% of cases it was started less than 12 months earlier. Median CD4+ count was 99 (70-280) cells/ uL and 4 patients had a concomitant opportunistic infection. EBV viremia was positive in 57% of cases, while EBER was positive in 72% of histological samples. Front line treatment regimens were: CHOP-like in 25, EPOCH in 15, MAGRATH/GMALL in 2, others in 3 cases. 20% patients received bortezomib in association to chemotherapy, 20% radiotherapy (RT) and 14% autologous stem cell transplantation (ASCT) consolidation. Response was evaluated in 45 cases, with ORR 71%, CR 60%. At a median follow-up of 134 months, 10-year PFS and OS were 42% (95% CI, 26–56) and 55% (95% CI, 38–69), respectively. On univariate analysis, ECOG PS >1, >1 extranodal site correlated with worse outcomes. IPI, R-IPI, and CNS-IPI strongly retained their prognostic role (p=0.016). We recorded 10 relapses, one in CNS. Patients receiving upfront consolidation therapy (RT or ASCT) showed better outcomes than those treated with CT alone (Figure 1); the trend remained favorable for ASCT alone (p=0.09). 21 deaths occurred (71% for lymphoma). In this preliminary analysis new risk factors have been identified; patients treated with upfront consolidation therapy showed better survival, which needs to be confirmed in the whole cohort we expected to enroll in the study.

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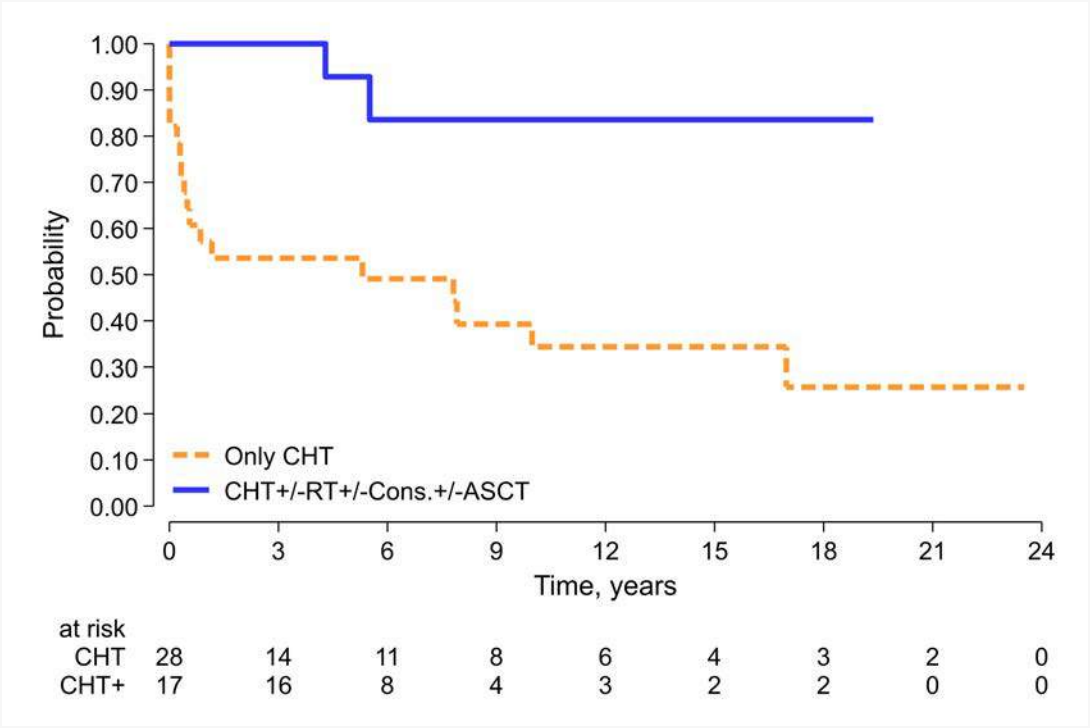
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Time, years
at risk
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CHT+ 17 16 8 4 3 2 2 0 0

Non-Hodgkin's Lymphoma

EFFICACY AND SAFETY OF GLOFITAMAB IN RELAPSED/REFRACTORY B-CELL NON HODGKIN LYMPHOMA: RESULTS FROM THE RETROSPECTIVE OBSERVATIONAL GIMEMA-FIL IMM0123 STUDY

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Background. Glofitamab, a T-cell bispecific antibody targeting CD20 and CD3, has demonstrated clinically meaningful activity with a good safety profile in patients with relapsed and refractory (R/R) aggressive B Cell Non Hodgkin Lymphoma (NHL).

Aims. To evaluate real-world effectiveness and safety of Glofitamab in patients with R/R B-cell lymphoma.

Methods. IMM0123 is a multicenter, retrospective observational study promoted by GIMEMA-FIL. Adult patients who received at least one dose of Glofitamab in the context of the compassionate use program in Italy between March 2022 and March 2024 were included.

Results. Fifty-eight patients with a median age of 64 years (range, 29-85) were included. Most patients had advanced-stage disease with stage III-IV in 83% (48/58) and high-intermediate/high IPI in 49% (26/58). Histology was diffuse large B-cell lymphoma (DLBCL) in 47 patients (81%), high grade lymphoma in 6 (10%) and other histologies in 5 (8.6%). Patients have received a median of 4 previous line of therapy (range, 2 – 9). Forty-five patients (78%) were refractory at last therapy and 32 (55%) had failed CAR T-cell therapy. The median number of Glofitamab cycles administered was 4 (range, 1-12). The best ORR was 48% (28/58) including CR in 29% (17/58) and PR in 19% (11/58). With a median follow-up of 24 months (range, 0.29 –33.04), the estimated 2-years OS was 40% (95% CI:28.7-56) and 2-years PFS was 32% (95% CI:21.8-47.6). Patients who achieved CR showed significantly improved 2-years OS (80.1% vs 21.5%, p<0.0001) and PFS (81.4% vs 10.3%, p< 0.0001) compared to those who did not achieve CR (Figure 1). Twenty-five patients died due to lymphoma (44%) and 5 (9%) due to infections. Adverse events occurred in 66% of patients (37/56), mainly grade 1-2 cytokine release syndrome (26 events) and infections (28 events), 8 patients presented a grade > 3 infection. Following Glofitamab, 3 patients underwent CAR T--cell therapy and 5 underwent allogeneic stem cell transplantation.

Conclusions. In this real-world compassionate-use setting, Glofitamab demonstrated a meaningful clinical activity and a manageable safety profile in heavily pretreated patients with R/R B cell NHL with results consistent with findings from other real-world studies. Among patients who achieved CR, sustained OS and PFS at 2 years of follow-up further support these promising results, showing Glofitamab as an effective salvage treatment option for R/R NHL patients.

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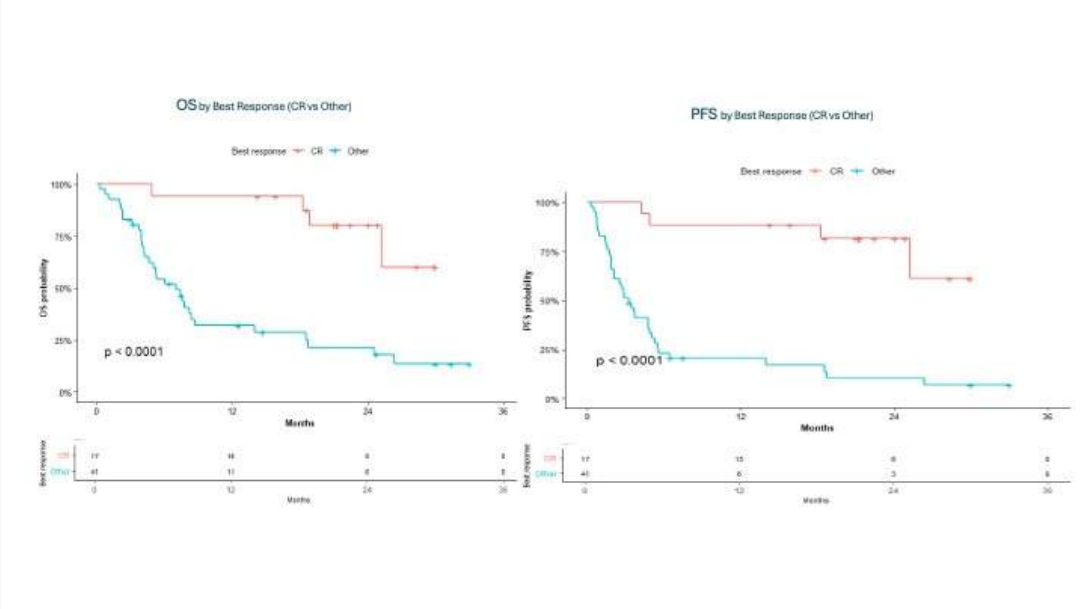
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Months
PFS by Best Response (CR vs Other)
Best response CR Other
p < 0.0001
PFS probability
Months

Myeloma and other monoclonal gammopathies

PHASE 3, RANDOMIZED STUDY OF TALQUETAMAB PLUS DARATUMUMAB ± POMALIDOMIDE *VS.* DARA PLUS POM AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: MONUMENTAL-3

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Introduction. Talquetamab (Tal), an anti-GPRC5D bispecific antibody, has shown deep and durable responses in late line relapsed/refractory (RRMM) with a favorable infection profile. A B-cell sparing mechanism facilitates Dara and Pom combinations, enabling synergistic efficacy in earlier lines. We report efficacy and safety from the Monumental-3 interim analysis (NCT05455320).

Methods. Phase 3 study randomizing pts with RRMM and ≥1 prior LOT including lenalidomide and a proteasome inhibitor 1:1:1 to Tal+Dara+Pom (Tal-DP), Tal+Dara (Tal-D) or DPd. Primary endpoint was progression-free survival (PFS).

Results. 864 pts were randomized (Tal-DP, n=287; Tal-D, n=287; DPd, n=290). Median prior LOT was 2 (range 1–8). At 24.6 months median follow-up, Tal-DP and Tal-D significantly improved PFS vs DPd (HRs [95% CI]: 0.28 [0.20–0.40], P<0.0001 and 0.33 [0.24–0.46], P<0.0001; Figure A+B). 24-month PFS (95% CI) favored Tal-DP (81.3% [75.8–85.7]) and Tal-D (77.6% [71.7–82.5]) vs DPd (51.2% [44.8–57.1]). ORRs (88.2%, 88.5%, 77.6%) and ≥CR rates (71.1%, 69.0%, 34.5%) were significantly higher for Tal-DP and Tal-D vs DPd, respectively. OS HRs (95% CI) vs DPd were 0.47 (0.30–0.73; P=0.0006) for Tal-DP and 0.51 (0.33–0.78; P=0.0015) for Tal-D. AEs were manageable and consistent with expectations. AEs leading to discontinuation (d/c): 10.5% (Tal-DP), 8.0% (Tal-D), 6.7% (DPd). Grade (gr) 5 AEs: Tal-DP (1.8%), Tal-D (4.0%), DPd (4.6%). Infection rates (gr 3–4, gr 5): Tal-DP (37.0%, 0.7%), Tal-D (27.7%, 1.5%), DPd (41.0%, 1.8%). CRS (mostly gr 1-2): Tal-DP (67.8%) and Tal-D (58.4%). GPRC5D-related AEs (mostly gr 1-2) with Tal-DP, Tal-D, DPd, respectively: taste changes (72.8%; 74.8%; 3.9%), weight decrease (45.7%; 38.3%; 7.4%). Ataxia (gr 1-2, gr 3): Tal-DP (11.6%, 2.9%), Tal-D (10.2%, 2.2%), DPd (0.4%, 0%).

Conclusions. Tal-DP and Tal-D had a significant PFS benefit vs DPd, clinically meaningful OS improvements, and similar gr ≥3 infection rates to DPd. Tal was combinable, with low treatment d/c. Tal-D ± Pom represents a new RRMM standard of care as early as 2L across all practice settings.*Accepted and presented at the European Hematology Association (EHA) Annual Congress 2026.*

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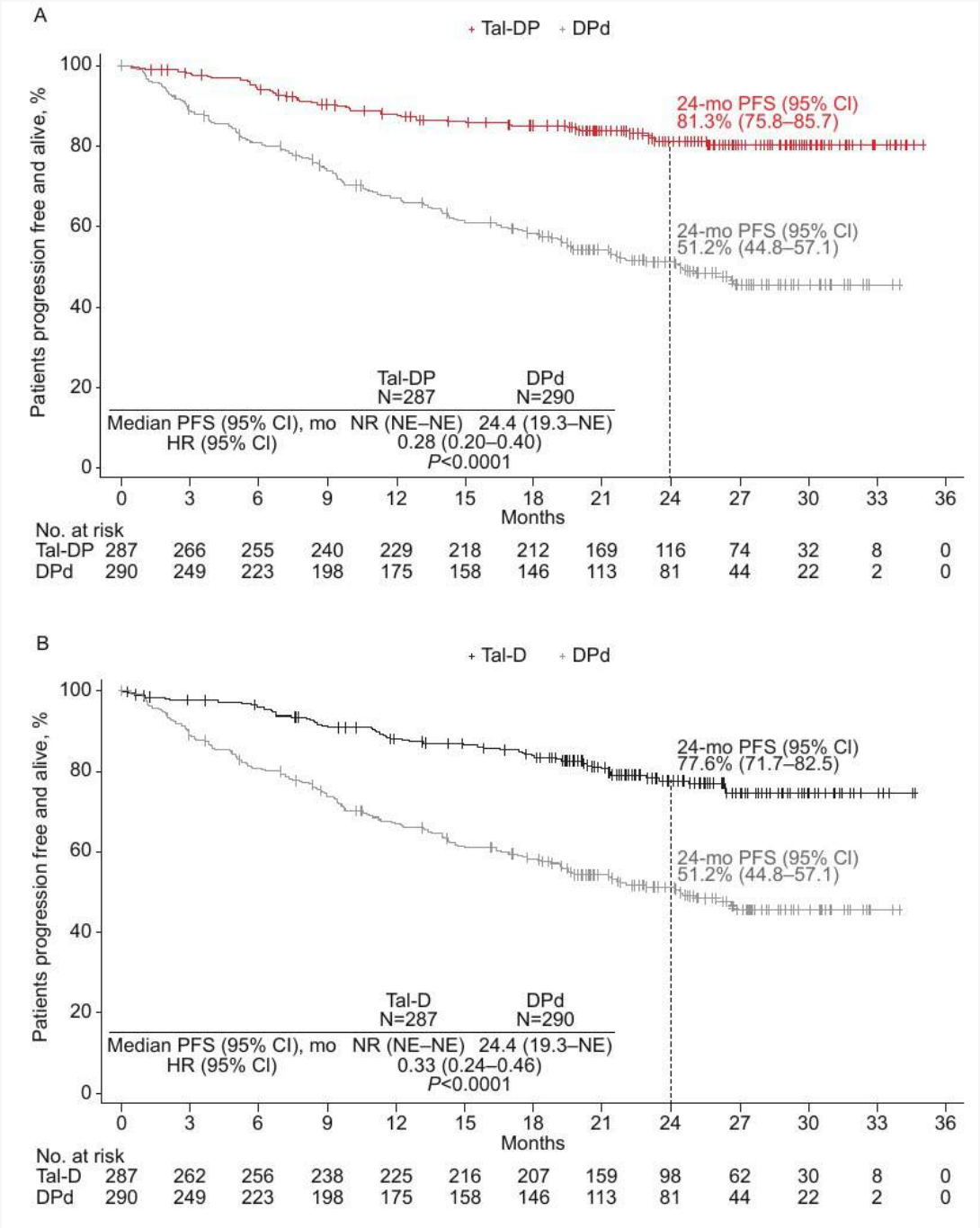

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Myeloma and other monoclonal gammopathies

TECLISTAMAB PLUS DARATUMUMAB IN PATIENTS WITH RELAPSED REFRACTORY MULTIPLE MYELOMA: ANALYSIS OF MAJESTEC-3 BASED ON CYTOGENETIC AND FUNCTIONAL RISK

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Introduction. Tec-Dara showed significant improvement in progression-free survival (PFS) and all key secondary endpoints vs Dara + dexamethasone + pomalidomide or bortezomib (DPd/DVd) in the phase 3 MajesTEC-3 trial (NCT05083169) in early-line RRMM. PFS/overall survival (OS) favored Tec-Dara across all subgroups, with a well-managed safety profile. We report post-hoc subgroup analyses of MajesTEC-3 by high-risk cytogenetic abnormalities (HRCAs) and functional high-risk (FHR) status.

Methods. Pts had 1-3 prior lines of therapy (pLOT), including a proteasome inhibitor and lenalidomide with progressive disease (PD) on/after last LOT. Pts were randomized 1:1 to Tec-Dara or DPd/DVd. Tec and Dara dosing were aligned with the approved Dara schedule. DPd/DVd were administered per approved schedules.HRCAs were defined as: t(4;14), t(14;16), or del(17p); a revised definition included gain(1q21) or amp(1q21). Risk subgroups were: standard (std.) or high, revised std. or high, and 1 or ≥2 HRCAs. FHR was defined as 1 pLOT with PD ≤18 mo post-ASCT or start of initial therapy. Minimal residual disease negativity (MRD-neg) complete response or better (≥CR) rates (10^{-5} or 10^{-6}) were assessed by next-generation sequencing.

Results. 587 pts were randomized (Tec-Dara, n=291; DPd/DVd, n=296). At 34.5 mo median follow-up, PFS favored Tec-Dara vs DPd/DVd across all cytogenetic subgroups (Figure). Estimated 36-mo PFS rates were higher with Tec-Dara vs DPd/DVd in std. (87.4% vs 37.1%) and high-risk cytogenetics (77.7% vs 11.5%). Among pts with 1 pLOT, PFS also favored Tec-Dara vs DPd/DVd in pts with (77.3% vs 0%) and without FHR (89.9% vs 35.9%).MRD-neg CR (10^{-5} and 10^{-6}) rates were higher with Tec-Dara vs DPd/DVd across all risk subgroups (all P<0.0001). MRD-neg CR rates were also higher with Tec-Dara in pts with FHR MM (10^{-5} P=0.0106; 10^{-6} P=0.0040).

Conclusions. Tec-Dara improved PFS and MRD-neg CR rates vs DPd/DVd regardless of cytogenetic or functional risk, supporting its use as a steroid-sparing standard-of-care option from second line of therapy. *Accepted and presented at the European Hematology Association (EHA) Annual Congress 2026.*

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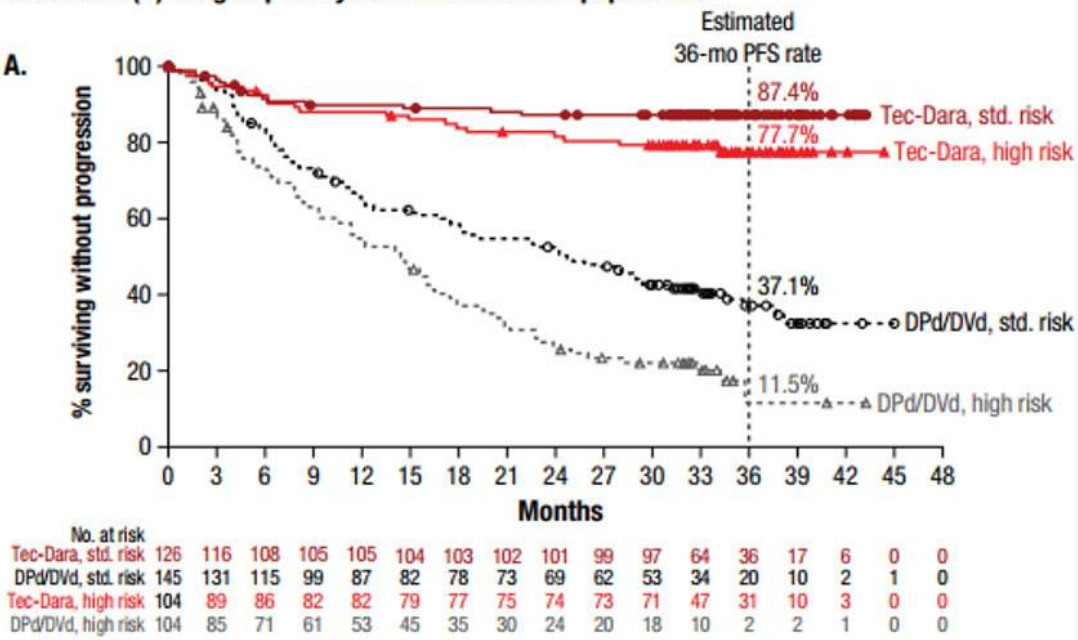
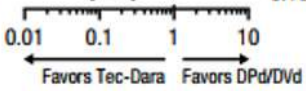
Figure. (A) Subgroup analysis of PFS based on the prespecified definition for cytogenetic risk status and (B) subgroup analysis of PFS in the ITT population.



B.

	Tec-Dara Events n/N	Tec-Dara Median PFS (mo)	DPd/DVd Events n/N	DPd/DVd Median PFS (mo)	HR (95% CI)	*P* value
Functional high risk	5/26	NE	14/20	23.2	0.22 (0.08-0.62)	0.0019
Not functional high risk	8/82	NE	57/94	20.8	0.11 (0.05-0.23)	<0.0001
Std. risk	15/126	NE	84/145	24.7	0.16 (0.19-0.27)	<0.0001
High risk	20/104	NE	78/104	14.4	0.15 (0.09-0.25)	<0.0001
Revised std. risk	5/52	NE	34/55	24.2	0.12 (0.04-0.30)	<0.0001
Revised high risk	30/169	NE	122/180	15.8	0.18 (0.12-0.26)	<0.0001
1 HRCA	17/105	NE	69/111	17.9	0.19 (0.11-0.32)	<0.0001
≥2 HRCAs	13/64	NE	53/69	14.4	0.16 (0.08-0.29)	<0.0001



PFS, progression-free survival; ITT, intent-to-treat; Tec-Dara, teclistamab in combination with daratumumab; DPd/DVd, daratumumab with pomalidomide and dexamethasone/daratumumab with bortezomib and dexamethasone; std., standard; HR, hazard ratio; CI, confidence interval; NE, not estimable; HRCA, high-risk cytogenetic abnormality; FISH, fluorescence in situ hybridization; ASCT, autologous stem cell transplantation.
NOTE that cytogenetic risk was centrally assessed by FISH. Functional high-risk status included only those patients with 1 prior line of therapy and disease progression ≤18 mo after receiving ASCT or starting initial therapy.

Myeloma and other monoclonal gammopathies

MAJESTEC-9: A PHASE 3 RANDOMIZED STUDY OF TECLISTAMAB MONOTHERAPY VS INVESTIGATOR'S CHOICE OF POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE OR CARFILZOMIB AND DEXAMETHASONE IN PATIENTS WITH RELAPSED REFRACTORY MULTIPLE MYELOMA

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Introduction. Teclistamab (Tec) is a BCMA×CD3 BsAb used in heavily pretreated RRMM, with improved outcomes in earlier lines of therapy (LOTs). In MajesTEC-3, the Tec-daratumumab combination significantly improved progression-free and overall survival (PFS/OS) as early as first relapse. MajesTEC-9 (NCT05572515) is the first phase 3 study of Tec monotherapy in pts with 1–3 prior LOTs (pLOTs).

Methods. Pts with RRMM and 1–3 pLOTs including anti-CD38 and lenalidomide (Len) were randomized 1:1 to receive 28-day cycles (C) of Tec or investigator's choice of PVd/Kd (21/28-day cycle). Primary endpoint was PFS; secondary endpoints included OS, complete response or better (≥CR), and safety.

Results. 593 pts were randomized (Tec, n=296; PVd/Kd, n=297). Median age was 70 yrs; median (range) pLOTs, 2 (1–3); Len refractory, 80%; anti-CD38 refractory, 85%; refractory to last LOT, 92%. At 17.3-mo median follow-up, Tec significantly improved PFS vs PVd/Kd (HR, 0.29; 95% CI, 0.23–0.38; p<0.0001); mPFS: NR vs 8.2 mo; 18-mo PFS rate: 69.8% vs 26.9%. OS was significantly improved with Tec vs PVd/Kd (HR, 0.60; 95% CI, 0.43–0.83; p=0.0020). PFS favored Tec across all prespecified subgroups, including anti-CD38-refractory pts and Len-refractory pts. BsAb or CAR-T was received by 68.4% of 174 PVd/Kd pts on subsequent treatment. ≥CR rate was significantly higher with Tec vs PVd/Kd (65.9% vs 16.8%; OR, 10.42; 95% CI, 6.89–15.76; p<0.0001).At data cutoff, 65.3% of pts remained on Tec vs 24.0% on PVd/Kd. For Tec vs PVd/Kd, TEAEs were 99.7% vs 97.9%; grade (G) 3/4 TEAEs were 84.9% vs 76.3% and G5 TEAEs were 6.5% vs 3.5%, with a longer median treatment duration for Tec (13.1 vs 7.0 mo). Treatment discontinuation due to TEAEs was lower with Tec vs PVd/Kd (10.7% vs 13.1%). G3/4 infections were higher with Tec vs PVd/Kd (41.6% vs 29.0%). Any-onset G≥3 infections decreased over time. CRS occurred in 66.0% of pts with Tec (G1/2: 48.8%/16.5%) and ICANS in 4.1% (G1/2: 2.4%/1.4%).

Conclusions. Tec monotherapy significantly improved PFS/OS vs standard of care (SoC) in this high unmet need population. CRS and infections were managed with established protocols. Phase 3 results support Tec-based regimens as a SoC as early as second line, across all treatment settings and regardless of prior anti-CD38/Len exposure. © *American Society of Clinical Oncology (2026). Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting.*

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Myeloma and other monoclonal gammopathies

IMPACT OF SUSTAINED MRD-NEGATIVITY ON LONG-TERM OUTCOME OF TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS ENROLLED IN THE RANDOMIZED PHASE 2 FORTE TRIAL

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Background. Novel combinations achieve high rates of minimal residual disease (MRD) negativity in multiple myeloma (MM), but the optimal duration to predict long-term outcomes remains unclear.

Methods. Patients (pts) enrolled in the FORTE trial who received maintenance with carfilzomib plus lenalidomide (KR) or lenalidomide alone (R) were included. MRD was assessed by flow cytometry (10^-5 sensitivity) at pre-maintenance and every 6 months up to 60 months. SustMRD-neg was defined as consecutive MRD-negative results for ≥1 to 5 years. Subgroup analyses by modified Consensus Genomic Staging (mCGS) and MGUS-like profile were performed.

Results. 356 pts were randomized to maintenance according to study protocol. At pre-maintenance, 232 patients (65%) were negative, and 124 patients (35%) were positive or not evaluable. Median follow-up from maintenance randomization was of 85.9 months and 80% of pts had at least one MRD-neg sample within 60 months. The rate of at least 1, 2, 3, 4, 5-years sustMRD neg was 53%, 42%, 36%, 28% and 20% respectively, while 24% of pts lost MRD-neg during the first year. Compared to MRD-positive patients, MRD-neg lasting <1 year (HR 0.72; p=0.12), 1 year (HR 0.04; p=0.003), 2 years (HR 0.36; p<0.001), 3 years (HR 0.17; p<0.001), 4 years (HR 0.15; p<0.001) and 5 years (HR 0.06; p<0.001) significantly and progressively improved pts' PFS. In pts with at least 5-year SustMRD neg, a 7-year PFS rate of 91% and OS rate of 98% was observed.In pts with ≥ 3-years sustMRD neg vs < 3-year sustMRD, 7-years PFS rates were 85% vs 35% (HR 0.16; p<0.001) and 7-years OS rates were 97% vs 69% (HR 0.08; p<0.001).Among patients with ≥ 3-years sustMRD neg, 7-years PFS rates were 84% for mCGS standard risk and 83% for mCGS high risk (HR 0.9; p=0.9); among patients with < 3-y sustMRD, mCGS classification retain its prognostic role (7-years PFS high vs. standard: 23% vs 43%, HR 10.5, p<0.001).Among patients with < 3-years sustMRD neg, the presence of an MGUS-like profile predicted a significantly better PFS to non MGUS-like pts (7-years PFS 67% vs 33%, HR 0.33; p=0.009).

Conclusions. Duration of MRD negativity, particularly sustMRD neg for more than 3 years, was associated with significantly improved PFS and OS in NDMM pts. Achieving ≥3-year sustained MRD negativity had a strong impact on outcomes also in high-risk patients, whereas MGUS-like patients may experience favourable outcomes even without achieving ≥ 3-y sustMRD neg.

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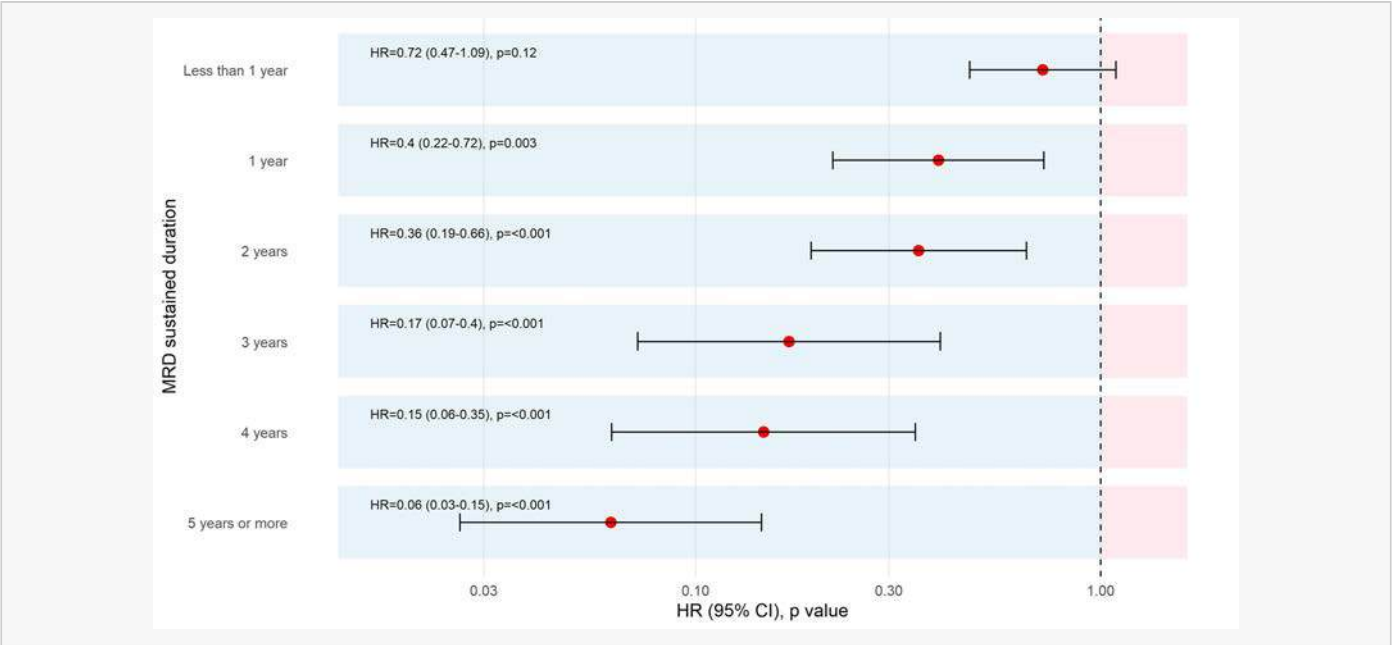

Myeloma and other monoclonal gammopathies

DARATUMUMAB PLUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: FINAL ANALYSIS OF TRANSPLANT-INELIGIBLE PATIENTS IN THE PHASE 3 CEPHEUS STUDY

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Introduction. First analysis of the phase 3 CEPHEUS study established DVRd improved overall minimal residual disease (MRD)-negativity (neg) rates and progression-free survival (PFS) vs VRd in TIE pts: at a median follow-up of 58.7 months (mo), 80.6% had a complete response or better (≥CR), and 60.4% had MRD neg, with ~70% alive and progression free. We present the final analysis at a median follow-up of 76.0 mo in the TIE subpopulation.

Methods. The primary endpoint of overall MRD neg rate (10^{-5} and ≥CR), and secondary endpoints, including investigator-assessed PFS, ≥CR rate, and sustained MRD neg (confirmed MRD neg ≥12 months +/- 1 mo apart without MRD positivity in between and ≥CR) were assessed in the TIE population.

Results. Of 395 pts enrolled, 289 pts with TIE NDMM received either DVRd (n=144) or VRd (n=145). The overall MRD neg rate at 10^{-5} was 61.1% for DVRd and 40.0% for VRd (odds ratio [OR] 2.35; 95% CI 1.47–3.77; P=0.0004) and at 10^{-6} was 46.5% for DVRd vs 27.6% for VRd (OR 2.27; 95% CI 1.39–3.71; P=0.0010). Sustained MRD neg rate at 10^{-5} was 49.3% for DVRd and 29.0% for VRd (OR 2.40; 95% CI 1.47–3.91; P=0.0005) and at 10^{-6} was 37.5% for DVRd and 16.6% for VRd (OR 3.01; 95% CI 1.73–5.24; P<0.0001). Overall ≥CR rate was 80.6% for DVRd and 61.4% for VRd (OR 2.64; 95% CI 1.54–4.51; P=0.0003). Median PFS was not estimable (NE; 95% CI 74.81–NE) for DVRd and was 50.20 mo (95% CI 41.95–62.95) for VRd (HR 0.55; 95% CI 0.39–0.78; P=0.0007), with 59.3% for DVRd vs 38.3% for VRd alive and progression free at 72 mo. OS favored DVRd over VRd (HR 0.84; 95% CI 0.57–1.24), particularly when censoring for COVID-19 (HR 0.74; 95% CI 0.49–1.12). The treatment effect was consistent across most subgroups (Table).

Conclusions. After median follow-up of over 6 years, final analysis of CEPHEUS demonstrated that TIE pts treated with DVRd continue to have deep and durable responses compared with those on VRd, reinforcing the role of DVRd as a standard of care in this subpopulation. *©2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting. All rights reserved.*

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Table: MRD negativity and PFS subgroup analyses for DVRd vs VRd in CEPHEUS

	MRD neg (10^{-5}) rate, %				Median PFS, mo			
BL characteristic	**DVRd**	**VRd**	**OR**	**95% CI**	**DVRd**	**VRd**	**HR**	**95% CI**
ISS stage I	66.0	41.7	2.72	1.20–6.17	NE	60.5	0.52	0.28–0.97
ISS stage II	59.3	45.6	1.73	0.82–3.68	NE	49.4	0.50	0.28–0.88
ISS stage III	57.5	30.0	3.16	1.26–7.94	66.4	43.8	0.66	0.35–1.24
High cytogenetic risk	50.0	50.0	1.00	0.28–3.57	58.0	31.7	0.82	0.36–1.87
Standard cytogenetic risk	63.8	39.6	2.68	1.55–4.66	NE	61.6	0.58	0.38–0.89
ECOG PS 0	57.7	45.6	1.63	0.76–3.47	NE	59.9	0.33	0.17–0.64
ECOG PS ≥1	63.0	36.4	2.99	1.63–5.48	74.8	47.2	0.70	0.46–1.06

BL, baseline; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

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Acute myeloid leukemia

GEMTUZUMAB OZOGAMICIN IMPROVES MRD CLEARANCE IN LOW/INTERMEDIATE-RISK AML: FIRST CO-PRIMARY ENDPOINT ANALYSIS OF THE GIMEMA AML1819 TRIAL

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Background. Measurable residual disease (MRD) is a key prognostic factor in acute myeloid leukemia (AML) and represents a cornerstone for risk-adapted post-remission strategies. The GIMEMA AML1819 (EudraCT 2019-003871-20) is an ongoing phase III trial evaluating whether the addition of gemtuzumab ozogamicin (GO) to standard chemotherapy improves MRD clearance and survival outcomes in adult patients with newly diagnosed favorable/intermediate-risk AML.

Aims. To report the results of a pre-established analysis of the first co-primary endpoint, defined as MRD negativity after consolidation.

Methods. Patients aged 18–60 years with de novo AML (ELN 2017 favorable/intermediate risk) received GO combined with standard "7+3" induction and consolidation. According to the study design, 199 evaluable patients were required to assess the MRD endpoint. This target was reached within the first 281 consecutively treated patients, allowing the planned analysis to be performed while enrolment is ongoing for the second co-primary and secondary endpoints. MRD was assessed after consolidation by RQ-PCR or multiparametric flow cytometry (MFC). The threshold for MFC MRD negativity was set at 0.035% (10-4) leukemic residual cells.

Results. Median age was 53 years, with 145 (52%) males; 148 (53%) and 133 (47%) patients were classified as low and intermediate risk, respectively. After induction, 224/281 patients (80%) achieved CR/Cri (cCR), including 194 (69%) CR and 30 (11%) CRi, while 57 (20%) did not achieve remission. Among favorable-risk patients cCR was 58% (131/224) whereas 42% (93/224) intermediate-risk patients achieved cCR ($p<0.001$). After consolidation, 73% (146/199) achieved MRD negativity, 24% (47/199) were MRD positive, while 3% (6/199) had no leukemia-associated immunophenotype suitable for MRD monitoring. Entering a MRD negative status was significantly associated with baseline risk, being MRD negativity observed in 82% (98/120) favorable- and 61% (48/79) intermediate-risk patients ($p=0.002$).At a median follow-up of 17 months, 18-months overall survival (OS) and disease-free survival (DFS) were 79% (95% CI: 74%, 85%) and 67% (95% CI: 60%, 75%), respectively (Figure 1). OS showed a trend toward improvement in favorable- compared with intermediate-risk patients and in MRD-negative versus MRD-positive patients, whereas no significant differences were observed for DFS across these subgroups.

Conclusions. In this interim analysis of the AML1819 trial, GO combined with standard chemotherapy was associated with high rates of cCR (80%) and MRD negativity (73%), exceeding the predefined activity threshold of at least 114 patients becoming MRD negative after consolidation, as set by the statistical study design. MRD status remained strongly associated with baseline risk and clinical outcome, reinforcing the clinical relevance of MRD-driven therapeutic strategies in frontline AML.

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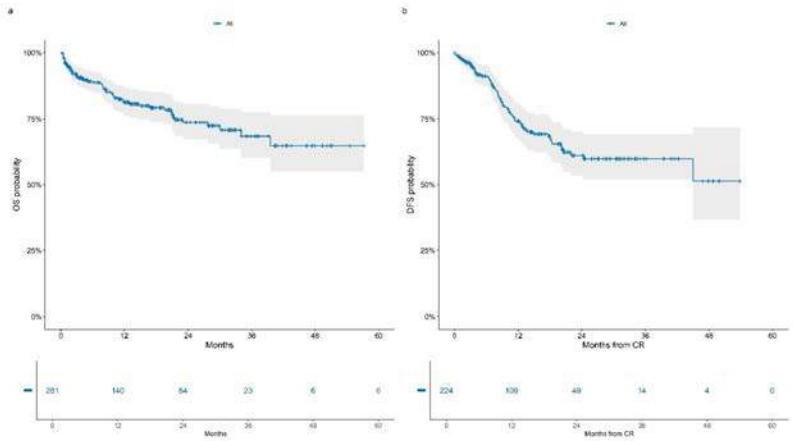

Figure 1: Kaplan-Meier survival curves. With a median follow-up of 17 months, 18-months OS (a) and DFS (b) were 79% (95% CI: 74%, 85%) and 67% (95% CI: 60%, 75%), respectively

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Acute myeloid leukemia

DDX41-ASSOCIATED MYELOID NEOPLASMS: CLINICAL SPECTRUM AND VARIANT PATHOGENICITY WITHIN A GERMLINE–SOMATIC MODEL

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DDX41-mutated myeloid neoplasms (DDX41-MN) represent the most frequent germline (GL) predisposition to adult MDS/AML. Interpretation of DDX41 variants remains challenging, as pathogenicity may depend on the interaction between GL and somatic milieu. To characterize the clinical and genomic spectrum of DDX41-MN and assess variant pathogenicity, we performed a retrospective single-center study (King's College Hospital, 2020–2025) including all patients with at least one DDX41 variant identified by NGS. Variants were classified as pathogenic/likely pathogenic (P/LP) or variants of unknown significance (VUS); GL origin was defined by VAF >40% and confirmatory testing if available. Among 12.044 NGS analyses, DDX41 variants were identified in 2% of cases (n=235), including 57% P/LP and 34% VUS; GL origin was confirmed or presumed in 92%. We identified "hot VUS" (n=13) as GL VUS co-occurring with somatic DDX41 mutations: these cases were clinically indistinguishable from P/LP variants, supporting reclassification as likely pathogenic. The final cohort included 148 patients (135 GL P/LP and 13 hot VUS) with median age 70.6y, male predominance (69.6%), and diagnoses of MDS (44%) or AML (43%), with mostly normal karyotype (77%), hypocellular BM (38%) and median 15% BM blasts. A clear divergence emerged between biallelic and monoallelic state. Biallelic DDX41-MN (GL + somatic DDX41 hit) defined a homogeneous entity with hypocellular BM, normal karyotype, high response to HMA and favorable survival (mOS 90.2m). In contrast, monoallelic carriers frequently lacked a myeloid phenotype; when present, MN was driven by alternative mutations (SF3B1, NPM1, FLT3), with lower HMA response (28% vs 75%, p=0.05) and shorter survival (39m). Within biallelic cases, genomic configuration further refined risk: somatic p.Arg525His DDX41 identified a higher-risk subgroup enriched in AML (63 vs 27%, p<0.001), higher BM blasts (25 vs 5%, p<0.001), lower PLTs (68 vs 137×10^3/mmc, p<0.001) and reduced survival (57.6m). This study provides the largest monocentric analysis of DDX41-MN to date and proposes a dynamic GL–somatic model. First, the acquisition of somatic DDX41 mutations provides in vivo evidence for VUS reclassification. Secondly, biallelic alterations define the classical DDX41-driven MN, while monoallelic GL DDX41 reflect either silent carriers or MN driven by alternative mutations. These findings support context-dependent variant interpretation with direct clinical implications.

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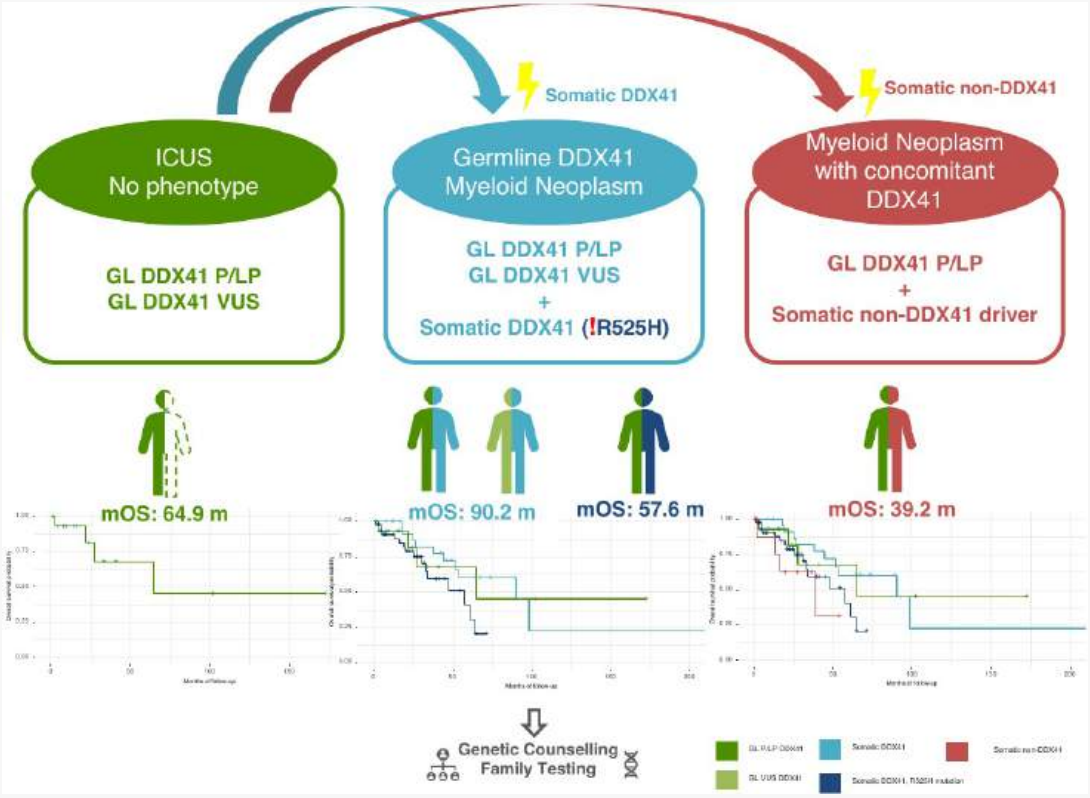

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Acute myeloid leukemia

CLINICAL AND MOLECULAR CHARACTERIZATION OF THERAPY-RELATED AML: INSIGHTS FROM THE HARMONY PLATFORM

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Background. Therapy-related acute myeloid leukemias (t-AML) are characterized by high-risk biological features and dismal prognosis. However, the role of "therapy-related" status has not been completely elucidated.

Methods. We leveraged the HARMONY Platform, including data from public and private sources, and examined genetic characteristics and outcomes of a large cohort of patients with t-AML as compared to de novo AML (dn-AML).

Results. We selected 4335 patients, 4103 dn-AML and 232 t-AML, with available information on previous cytotoxic treatment, and treated with intensive chemotherapy. Compared to dn-AML, t-AML patients were older (median 57y vs 51y, p<0.001), and more frequently female (63% vs 49%, p<0.001). t-AML showed higher prevalence (p<0.05) of high-risk genetic abnormalities, including trisomy 8, del(5q), del(7), t(9;11), and TP53, RUNX1 and ASXL1 mutations (Fig 1A). Patients with t-AML had inferior OS and EFS when compared to dn-AML (both p<0.001). ELN2022 risk classification correctly stratified both dn- and t-AML (p<0.001 for OS and EFS for both). Notably, OS was similar in the favourable risk group, while it was inferior for patients with t-AML in the intermediate (p=0.008), and in the adverse groups (p<0.001; Fig. 1B-D). When investigating ELN2022 model performance, there was no difference in dn vs t-AML (c-index: 0.6 vs 0.61 for OS, and 0.6 vs 0.6 for EFS). We then built a multivariable model including age, ELN2022 stratification, allogenic transplantation and AML type (dn vs t-AML). All these variables independently correlated with OS (HR for therapy-related status: 1.3308, 95% CI: 1.1216-1.5790, p=0.001). When investigating the role of specific mutations, we found that TP53 mutations conferred an inferior prognosis in all patients (p<0.001 for OS and EFS), with no differences between dn and t-AML. In AML with MDS-related gene mutations t-AML had inferior OS and EFS as compared to dn-AML (both p<0.001). Karyotype abnormalities including del(7), del(5q) and t(9;11) were prognostically unfavourable in dn-AML (p<0.001, p<0.001, p=0.006, respectively), but not in t-AML. Trisomy 8 did not play a prognostic role in both.

Conclusions. In intensively-treated AML, therapy-related status conferred an independent, inferior prognosis, especially in high-risk subsets, including the ELN2022 adverse-risk subgroup and cases with mutations in MDS-related genes. TP53 mutations were prognostically unfavourable, regardless of AML subtype.

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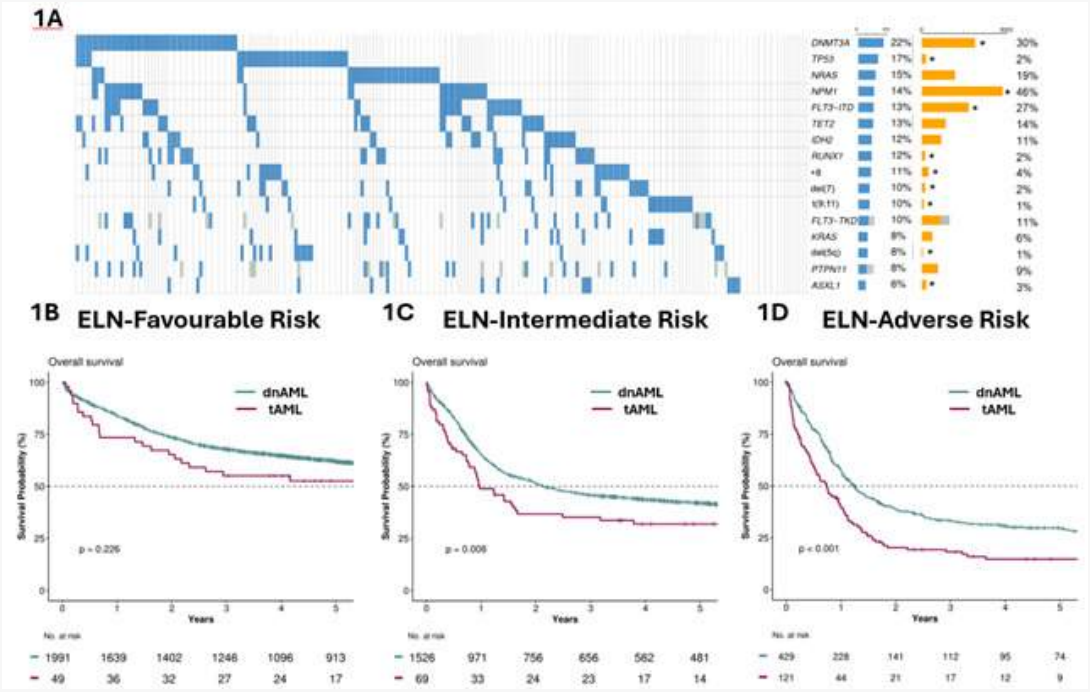
1A
DNMT3A 22% 30%
TP53 17% 2%
NRAS 15% 19%
NPM1 14% 46%
FLT3-ITD 13% 27%
TET2 13% 14%
IDH2 12% 11%
RUNX1 12% 2%
+8 11% 4%
del(7) 10% 2%
t(9;11) 10% 1%
FLT3-TKD 10% 11%
KRAS 8% 6%
del(5q) 8% 1%
PTPN11 8% 9%
ASXL1 6% 3%
1B ELN-Favourable Risk
1C ELN-Intermediate Risk
1D ELN-Adverse Risk
Overall survival
dnAML
tAML
Survival Probability (%)
Years
p = 0.226
p = 0.006
p < 0.001
No. at risk
1991 1639 1402 1246 1096 913
49 36 32 27 24 17
1526 971 756 656 562 481
69 33 24 23 17 14
429 228 141 112 95 74
121 44 21 17 12 9

Acute myeloid leukemia

REVUMENIB + INTENSIVE CHEMOTHERAPY FOR NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA HARBORING GENETIC ALTERATIONS IN *KMT2A*, *NPM1*, OR *NUP98*: UPDATED PHASE 1 RESULTS FROM SNDX-5613-0708

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Background. Acute leukemias (AL) with *KMT2A* or *NUP98* rearrangements (*KMT2A*r or *NUP98*r) are associated with poor clinical outcomes. Revumenib, a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction, is used for the treatment (tx) of relapsed/refractory (R/R) AL harboring a *KMT2A* translocation or R/R AML with *NPM1* mutation (*NPM1*m) in adult and pediatric patients (pts) ≥1 year (y). Here, we report data from the dose-escalation phase 1 study of revumenib+intensive chemotherapy (IC) in newly diagnosed (ND) AML with a *KMT2A*r, *NPM1*m, or *NUP98*r.

Methods. SNDX-5613-0708 (NCT06226571) is a multicenter, open-label, dose-escalation/expansion study enrolling pts 18–75 y with ND AML harboring *KMT2A*r, *NPM1*m, or *NUP98*r eligible for IC. Two dose levels (DL) of revumenib were evaluated (DL1: 110mg/220mg±strong CYP3A4 inhibitor [CYP3A4i]; DL2: 160mg/270 mg±strong CYP3A4i) with cytarabine plus daunorubicin or idarubicin. Pts achieving complete remission (CR) or CR with incomplete hematologic recovery received consolidation therapy (revumenib+high-dose cytarabine), then optional hematopoietic stem cell transplant (HSCT) and revumenib maintenance. Primary endpoints are dose-limiting toxicities (DLTs) and safety.

Results. As of 02Oct2025, 13 pts were treated at DL1 and 18 at DL2; 12 and 13, respectively, were evaluable for DLTs per protocol criteria (received ≥75% planned dosing or experienced a DLT during the evaluation period). *KMT2A*r was detected in 92% (12/13) of pts in DL1 and 39% (7/18) in DL2; *NPM1*m was detected in 8% (1/13) of pts in DL1 and 56% (10/18) in DL2. Median (range) tx duration was 73.0 days (1.0–170.0) for DL1 and 34.0 days (1.0–156.0) for DL2. One DLT occurred (grade 3 QTcF prolongation) in DL1. Tx-emergent adverse events are shown in the table. Among response-evaluable pts, overall response rate was 100% (12/12) in DL1 and 92.9% (13/14) in DL2; composite CR rate was 100% (12/12) and 85.7% (12/14); and CR rate was 91.7% (11/12) and 78.6% (11/14), respectively. Measurable residual disease–negative CR was achieved in 100% (8/8) of tested pts in DL1 and 70.0% (7/10) in DL2. Seven DL1 pts proceeded to HSCT, and 5 resumed revumenib post HSCT.

Conclusions. Revumenib+IC showed manageable safety, comparable to IC alone, with no new safety signals. Preliminary efficacy data suggest deep responses. Revumenib+IC will be investigated in the phase 3 REVEAL-ND NPM1 trial in fit pts with *NPM1*m AML (NCT07211958). Updated results to be presented.

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Table. Summary of TEAEs

Parameter, n (%)	DL1 (n=13)	DL2 (n=18)	Total (N=31)
Any TEAE	**13 (100)**	**18 (100)**	**31 (100)**
Revumenib-related	9 (69)	10 (56)	19 (61)
Grade ≥3 TEAEs[a]	**11 (85)**	**16 (89)**	**27 (87)**
Febrile neutropenia	6 (46)	10 (56)	16 (52)
Platelet count decreased	5 (38)	4 (22)	9 (29)
Anemia	3 (23)	6 (33)	9 (29)
White blood cell count decreased	4 (31)	4 (22)	8 (26)
Neutrophil count decreased	4 (31)	3 (17)	7 (23)
Thrombocytopenia	1 (8)	5 (28)	6 (19)
Neutropenia	1 (8)	4 (22)	5 (16)
Grade ≥3 revumenib-related TEAEs[b]	**5 (38)**	**8 (44)**	**13 (42)**
Anemia	3 (23)	3 (17)	6 (19)
Neutrophil count decreased	3 (23)	1 (6)	4 (13)
Serious TEAEs	**6 (46)**	**8 (44)**	**14 (45)**
TEAEs of special interest			
QTcF prolongation	2 (15)	0	2 (6)
Differentiation syndrome	0	0	0
TEAEs leading to dose modifications			
Reduction	2 (15)	0	2 (6)
Discontinuation	3 (23)	1 (6)	4 (13)
TEAEs leading to death	**0**	**1 (6)**	**1 (3)**

[a]Events that occurred in ≥15% of total population. [b]Events that occurred in ≥10% of total population. DL1, dose level 1; DL2, dose level 2; TEAE, treatment-emergent adverse event.

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Acute myeloid leukemia

ATRA/ATO FOR HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA: FINAL ANALYSIS OF THE APOLLO TRIAL

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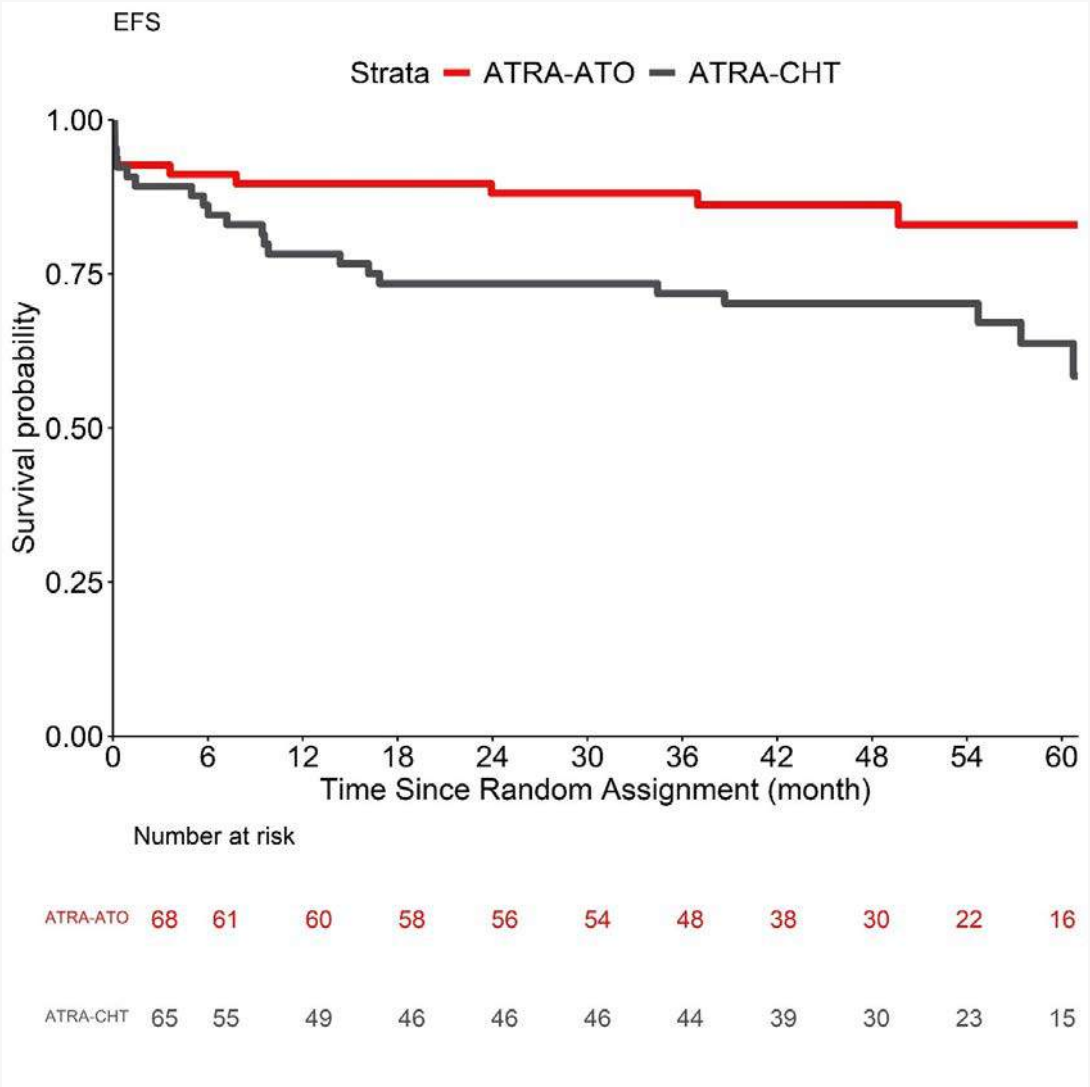
Background. The APOLLO trial, a phase III European academic trial for high-risk APL, defined by WBC >10 x10^9 /L, showed superiority of all-trans retinoic acid and arsenic trioxide (ATRA/ATO) preceded by 2 doses of idarubicin, and followed by 4 ATRA/ATO consolidation cycles (arm A), compared with the classical AIDA regimen (arm B, 2 year EFS: 88% vs 71%, p=0.02).Aims The present analysis aimed to evaluate long-term outcomes and to assess additional prognostic factors for EFS, including short-term management measures and long-term adverse events (AEs), with a median follow-up of 50 months (range, 1.4-101.8).Methods The trial included 133 patients randomized to ATRA/ATO (n= 68) or AIDA (n= 65). Median age was 46 years (range, 18-65), with 52% males.

Results. The rate of early death during induction was similar between treatment arms (7.4% in Arm A vs 9.2% in arm B). A total of 111 bleeding events were reported in Arm A and 124 in arm B (8 vs 6 CTCAE grade ≥ 3, p=0.4), while thrombosis was rarely reported (1 and 4 cases, p=0.2). Cytoreduction with hydroxyurea (HU) was administered in 67.7% of pts in arm A and 64% in arm B (p=0.4). Median HU duration was 3 days in both arms (IQ range, 0-6 d for both), corresponding to a median cumulative dose of 11,500 mg and 12,000 mg, respectively (p=0.1).5-year EFS was 83% (95% CI, 73-94) in arm A vs 64% (95% CI, 52-79) in arm B (Log-rank p=0.0089; Figure 1), while 5-year OS was 88% (95% CI, 79-97) vs 83% (95% CI, 74-93), respectively (p=0.16). The Cox regression analysis for EFS showed that age and white blood cell count (logWBC), but not BMI, were independent predictors for inferior EFS (age: HR:1.03, CI:1.00-1.07, p=0.045; logWBC: HR:1.75, CI: 1.16-2.64, p=0.007).The 5-year cumulative incidence of relapse (CIR) was 3.4% in arm A (1 molecular and 1 hematologic relapse) versus 16% arm B (7 molecular and 2 hematologic relapses), occurring at a median of 11 months (range, 6.4-33.1) from CR (HR 0.20, 95% CI: 0.04-0.9, p=0.036). Two cases of secondary acute myeloid leukemia occurred in Arm B at a median of 55 months from randomization.Conclusions The final analysis of the APOLLO trial confirms the superiority of the nearly chemotherapy-free ATRA/ATO regimen over AIDA chemotherapy in high-risk APL. In this setting, ATRA-ATO was able to early control leukocytosis similar to AIDA, as

shown by similar HU total dose and duration in the two arms.



Red blood cell pathologies

ORAL IPTACOPAN MONOTHERAPY DEMONSTRATES CLINICALLY MEANINGFUL HEMOGLOBIN INCREASES IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA WITH BASELINE HEMOGLOBIN LEVELS 10 TO <12 G/DL ON ANTI-C5 THERAPY: SUBGROUP ANALYSIS OF THE APPULSE-PNH PHASE 3B TRIAL

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Introduction. Despite achieving a good response with anti-C5 therapy (hemoglobin [Hb] ≥10 to <12 g/dL), some patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) remain anemic and symptomatic due to extravascular hemolysis. The oral selective factor B inhibitor iptacopan showed superior efficacy vs anti-C5 therapy in APPLY-PNH (NCT04558918)[1]. APPULSE-PNH (NCT05630001)[2] evaluated iptacopan in pts with Hb ≥10 g/dL who had received anti-C5 therapy. We present subgroup analyses in pts with baseline (BL) Hb ≥10 to <12 g/dL.

Methods. APPULSE-PNH is a Phase 3b, open-label study in adults with PNH and mean Hb ≥10 g/dL on stable anti-C5 therapy, who had not received red blood cell (RBC) transfusions for 6 months, switched to iptacopan monotherapy 200 mg twice daily for 24 weeks. The primary endpoint was change from BL in Hb, tested for noninferiority and superiority vs anti-C5 therapy using predefined thresholds (95% confidence interval [CI] lower bound > –1 and 0 g/dL, respectively).

Results. Of 52 pts enrolled, 32 (61.5%) had BL Hb ≥ 10 to <12 g/dL. Overall, 93.8% switched from ravulizumab and 6.3% from eculizumab. Mean (standard deviation [SD]) BL Hb and lactate dehydrogenase (LDH) were 11.1 (0.5) g/dL and 236.6 (75.5) U/L, respectively. Adjusted mean Hb change from BL was +2.0 g/dL (P<0.0001) overall, and +2.4 g/dL in the subgroup, meeting noninferiority and superiority criteria. No pts required RBC transfusions. Absolute reticulocyte count was reduced by −101.9 $\times 10^9$/L, and LDH remained stable (ratio vs BL was 1.0). Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue improved (+6.4) as well as Treatment Satisfaction Questionnaire for Medication – 9 items (TSQM-9) scores. In the overall population, the most common treatment-emergent adverse events were headache (17.3%), diarrhea, nausea, and nasopharyngitis (11.5% each) (Table 1). No clinical breakthrough hemolysis, major adverse vascular events, treatment related serious adverse events, or deaths occurred.

Conclusions. Switching to iptacopan led to clinically meaningful Hb increases in pts with PNH and Hb ≥10 g/dL. Results in pts with BL Hb ≥10 to <12 g/dL were consistent with the overall study findings. Iptacopan was well tolerated, representing a potentially practice-changing, outpatient treatment option for pts with PNH[3].

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Table 1. Baseline characteristics and outcomes in the Hb 10–<12 g/dL subgroup (APPULSE-PNH)

Population	
Patients, n	52
Hb 10–<12 g/dL subgroup, n (%)	32 (61.5%)
Mean age, years	47.0
Female, %	43.8%
Time since diagnosis, years (SD)	9.4 (6.8)
Duration of anti-C5 therapy, years, mean (SD)	3.0 (2.2)
Efficacy vs baseline*	
Hb change (overall), g/dL (95% CI)	+2.0 (1.7, 2.3)
Hb change (subgroup), g/dL (95% CI)	+2.4 (2.0, 2.7)
RBC transfusions#	–
ARC change, $\times 10^9$/L (95% CI)	−101.9 (−107.9, −95.9)
LDH ratio vs baseline (95% CI)	1.0 (0.9, 1.1)
Patient-Reported Outcomes vs baseline**	
FACIT-Fatigue change (95% CI)	+6.4 (3.2, 9.5)
TSQM-9 effectiveness (95% CI)	+11.1 (0.7, 21.6)
TSQM-9 convenience (95% CI)	+25.1 (16.4, 33.9)
TSQM-9 global satisfaction (95% CI)	+20.6 (12.3, 28.8)

ARC: absolute reticulocyte count; TSQM-9: treatment satisfaction questionnaire for medication–9 items

*Endpoints reported as adjusted mean change from BL, or ratio vs BL, used the mean of four visits between Days 126 and 168

** Endpoints used day 168 only

#Endpoint between day 1 and 168

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Red blood cell pathologies

EFFICIENCY AND RELIABILITY OF CELOCENTESIS FOR EARLY PRENATAL DIAGNOSIS OF HEMOGLOBINOPATHIES: A STUDY OF 825 CASES

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Currently, prenatal diagnosis of hemoglobinopathies is performed via chorionic villus sampling or amniocentesis. Although these procedures are highly reliable, they are performed only after the 11th and 16th weeks of gestation, respectively. The main limitation of these methods lies in the advanced gestational age at which they are performed, which places a considerable emotional and psychological burden on couples, particularly those with a history of pregnancy termination due to a affected fetus. Celiocentesis is an early prenatal diagnostic technique that can be performed as early as the 7th week of gestation. The procedure involves the transvaginal aspiration of approximately 1 ml of celomic fluid. Within the coelomic cavity lies the secondary yolk sac, where the first embryo-fetal erythroid cells are produced immediately after embryo implantation. These cells can be identified morphologically and isolated individually using a micromanipulator. This study involved 825 women, partners of healthy carriers of hemoglobinopathies, who voluntarily underwent celocentesis. The cohort consisted primarily of patients of Sicilian origin (64.5%), followed by residents of other Italian regions (35.0%) and those living abroad (0.5%). The median gestational age at the time of the procedure was 8.4 weeks. The diagnosis identified 220 affected fetuses (26.7%). Among the remaining 605 unaffected fetuses (73.3%), 197 (23.9%) were found to be healthy and 408 (49.4%) were healthy carriers. Validation of the results, performed by comparing them with samples of aborted tissue (following voluntary termination of pregnancy), amniotic fluid, or neonatal blood, confirmed the correct classification of all cases, demonstrating 100% sensitivity and specificity. The findings support the clinical efficacy of celocentesis as an early and reliable diagnostic procedure for hemoglobinopathies. It constitutes a valid alternative to conventional techniques, allowing for diagnosis at a stage of pregnancy that was previously inaccessible. Although further studies are needed to monitor long-term outcomes, current evidence supports its integration into standard clinical practice for high-risk couples.

Red blood cell pathologies

MITAPIVAT IN PYRUVATE KINASE DEFICIENCY: AN ITALIAN REAL-WORLD EXPERIENCE

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Pyruvate kinase deficiency (PKD) is a rare congenital hemolytic anemia characterized by chronic hemolysis, ineffective erythropoiesis, and serious long-term complications. Mitapivat, an oral allosteric pyruvate kinase activator, represents the first approved disease-modifying therapy for PKD, with efficacy established in the DRIVE-PK, ACTIVATE, and ACTIVATE-T trials. However, evidence in heterogeneous populations with complex comorbidities or uncommon genotypes remains scarce. This study presents the first multicenter real-world evaluation of mitapivat in adult patients with PKD.A retrospective analysis was conducted across 9 Italian centers via compassionate use or post-trial access. Thirty adults (16 males, 14 females; median age 45 years) were included, of whom 10 (33%) were transfusion-dependent (TD) and 20 (67%) had undergone prior splenectomy. Genotypic distribution comprised biallelic missense (BM) (65%), missense/non-missense (M/NM) (12%), and biallelic non-missense (BNM) (23%) variants. Mitapivat was titrated up to 50 mg twice daily. Response was defined as a sustained hemoglobin (Hb) increase ≥1.5 g/dL from baseline or ≥33% reduction in transfusion burden.After a median follow-up of 19 months, the overall response rate was 67% (20/30). In non-TD (NTD) responders, median Hb improved significantly from 9.45 to 11.1 g/dL ($p<0.0001$), with a median sustained increase of 2.2 g/dL. Among TD patients, 70% achieved meaningful reductions in transfusions, with 60% attaining complete transfusion independence. Hemolytic markers improved substantially: reticulocytes declined from 229 to 133×10^9/L ($p<0.001$), LDH from 233 to 201 U/L ($p=0.013$), and indirect bilirubin from 2.6 to 0.82 mg/dL ($p<0.0001$). Most responses occurred within 3 months of initiation.Genotype was the principal determinant of response: response rates were 82% for BM, 33% for M/NM, and 17% for BNM genotypes ($p=0.005$). Baseline PK enzymatic activity and prior splenectomy did not influence response ($p=0.44$ and $p=0.7$, respectively). The safety profile was consistent with clinical trial data: manageable lipid elevations in 20% of patients. Two unintended pregnancies necessitated treatment discontinuation.These findings confirm that mitapivat is highly effective and acceptably safe in a real-world PKD population, offering a functional cure in a substantial proportion of TD patients and meaningful anemia improvement in NTD individuals, with genotype as the key predictor of therapeutic response.

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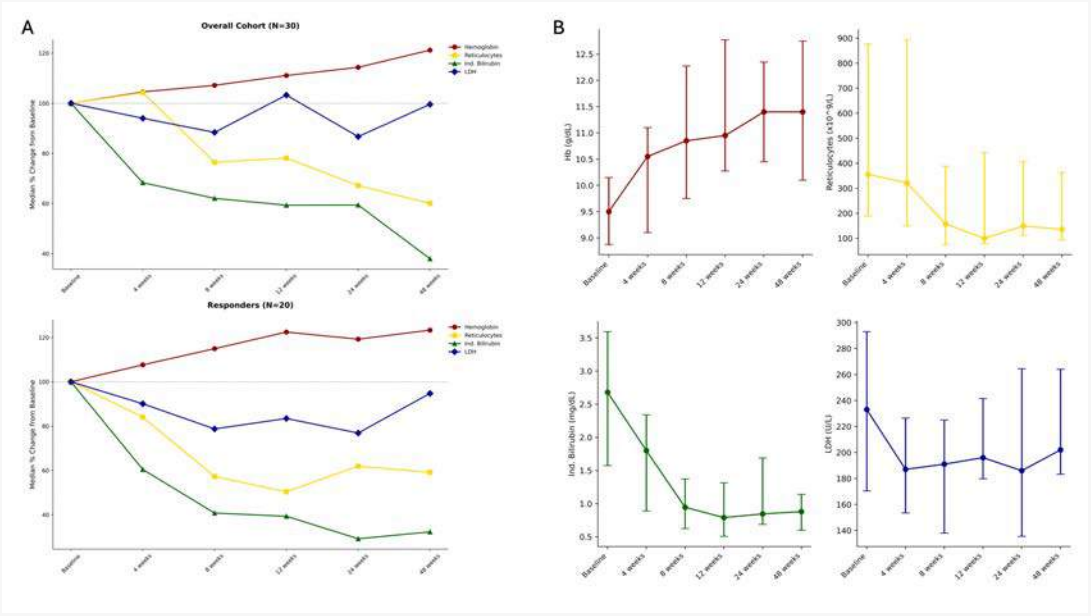
Red blood cell pathologies



Red blood cell pathologies

DARATUMUMAB FOR REFRACTORY IMMUNE-MEDIATED ANEMIAS: REAL-WORLD EVIDENCE FROM A COMPASSIONATE USE PROGRAM

A. Cellini[1], S. Giammarco[2], M. A. Limongiello[2], S. Sica[2], B. Fattizzo[3], G. L. Pedone[3], A. Aroldi[4], M. Fedele[4]. L. Pavan[1], F. Angotzi[1], L. Trentin[1], A. Visentin[1]

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Background. Refractory autoimmune anemias have limited treatment options and substantial steroid-related toxicity. Daratumumab (Dara), an anti-CD38 monoclonal antibody, may reduce autoantibody production by targeting long-lived plasma cells and CD38+ T cells.

Aim. To assess efficacy and safety of Dara in relapsed/refractory autoimmune anemias.

Methods. We retrospectively evaluated patients treated with Dara within a compassionate-use program (Nov 2022--May 2025) for primary or secondary warm/cold autoimmune hemolytic anemia (AIHA) or pure red cell aplasia (PRCA). The primary endpoint was 24-week overall response rate (ORR), defined as hemoglobin (Hb) increase ≥20 g/L in AIHA and reticulocyte recovery with reduced transfusion need in PRCA. Complete response (CR) was defined as Hb ≥12 g/dL without hemolysis.

Results. Sixteen patients were included: 8 AIHA [3 cold, 4 warm, 1 Evans syndrome; 3 secondary] and 8 PRCA. In AIHA, median age at Dara start was 59 years (49-70), median prior therapies 4 (2-7), and all had previously received rituximab. Median baseline Hb was 77.5 g/L (40-125). ORR at 24 weeks was 62.5%, including 3 CRs and 3 partial responses (PRs); 2 patients were non-responders. Although ORR appeared to be similar between primary and secondary AHIA patients, among the latter one subject was a non-responder and another required maintenance Dara to hold the obtained CR. The second non-responder was the subject with Evans syndrome.In PRCA, all but 1 case occurred after allogeneic stem cell transplantation. Median age was 61.5 years (45-69), no patient had responded to the previous therapy, and median baseline Hb was 72 g/L (66-88). ORR at 24 weeks was 87.5%, with all responders achieving CR, and the sole non responder experiencing fatal septic shock before response evaluation.After a median follow-up of 16 months (3-37), 14/16 completed planned Dara cycles. In AIHA, 2 patients required further treatment after a median of 19 months; 1-year time to next treatment was 75% (50.3-100). No PRCA patient required additional therapy. Across 196 infusions, no infusion reactions occurred. Three infections were recorded: 1 grade 5 septic shock, 1 grade 2 pneumonia, and 1 grade 3 pneumonia.

Conclusions. Dara showed activity in heavily pretreated autoimmune anemias, with particularly high and durable responses in refractory PRCA, and acceptable tolerability in this compassionate-use cohort. Prospective studies should define optimal candidates and scheduling.

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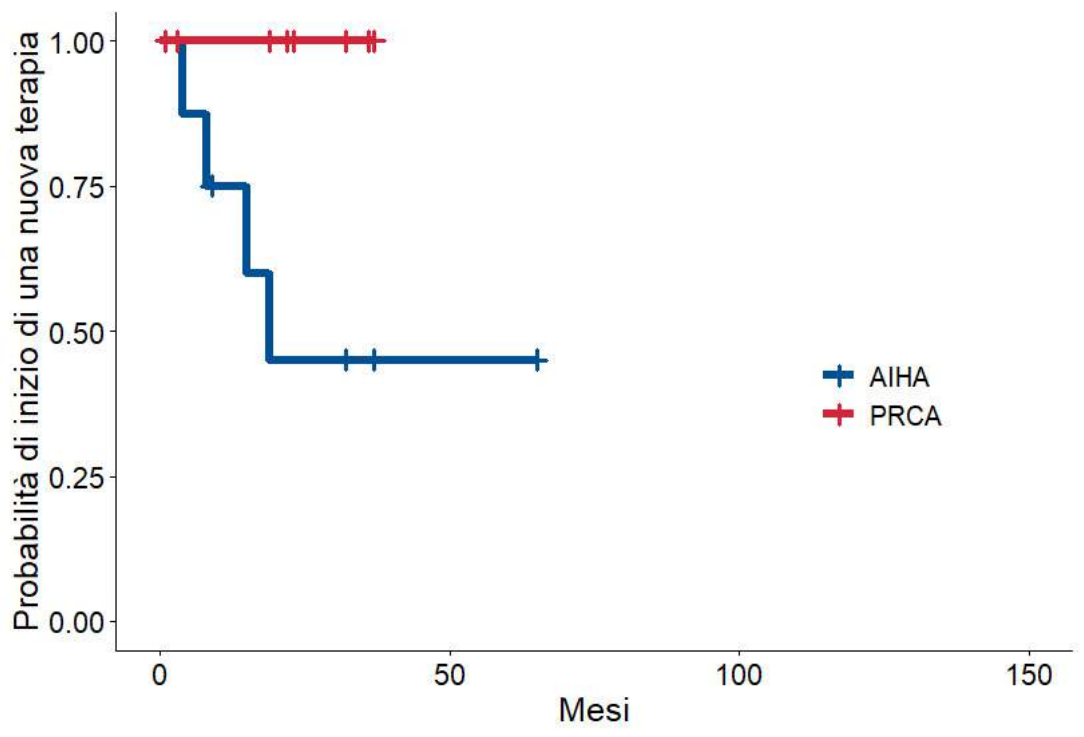
Probabilità di inizio di una nuova terapia
1.00
0.75
0.50
0.25
0.00
0
50
100
150
Mesi
AIHA
PRCA

Red blood cell pathologies

IMMUNOSUPPRESSIVE TREATMENT IN ELDERLY PATIENTS (>60 YEARS) WITH ACQUIRED APLASTIC ANEMIA: A RETROSPECTIVE SINGLE-CENTER ANALYSIS

B. De Marco[1], E. Cerqui[1], E. Borlenghi[1], C. Cattaneo[1], M. Oberti[1], S. Bagnasco[1], E. Accorsi[1], L. Masina[1], G. Magliano[2], A. Tucci[1]

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Patients aged >60 years with acquired aplastic anemia (AAA) present therapeutic challenges due to comorbidities and reduced tolerance to intensive treatments. Standard therapy consists of immunosuppressive treatment (IST) with anti-thymocyte globulin plus cyclosporine (ATG+CSA), with or without eltrombopag (ELT), or hematopoietic stem cell transplantation (HSCT) in selected cases.We retrospectively analyzed 40 consecutive patients aged >60 years diagnosed with AAA according to Camitta criteria and treated at our center between January 1989 and January 2025. The study aimed to evaluate the feasibility and safety of ATG ± CSA in elderly patients with AAA. Horse ATG was administered in 37 patients, whereas rabbit ATG was used in 3 patients.Starting in 2018, ELT (up to 150 mg/day) was introduced after 3 months in non-responders. Treatment responses were assessed according to EBMT criteria: complete response (CR; hemoglobin >10 g/dL, absolute neutrophil count [ANC] >1.5 × 10^9/L, platelets >100 × 10^9/L); partial response (PR; transfusion independence); and no response (NR; persistent transfusion dependence).The median age was 71 years (range, 60–84). Two patients (5%) had non-severe transfusion-dependent AA, 22 (55%) had severe AA, and 16 (40%) had very severe AA. A small PNH clone was detected in 9 patients (22%). The ATG dose was reduced by 50% in 11 of 40 patients (27%).At 3 months, the overall response rate of the whole cohort (ORR; CR + PR) was 37% (15/40).In the pre-eltrombopag era (before 2018), 23 patients received ATG alone or ATG combined with CSA. Among evaluable patients (n=19; 4 not evaluable for early death), the ORR at +12 weeks was 48%, including 8 CRs and 3 PRs.In the post-eltrombopag era, 17 patients received ATG plus CSA. Response was not evaluable in 5 patients for early death. In the evaluable cohort, the ORR at +12 weeks was 33%, with no CRs and 4 PRs, while 8 patients (67%) were non-responders.Among the 8 non-responders, 6 subsequently received ELT. After an additional 4 months, the ORR increased to 75% (9/12), with all initial responders maintaining their response. Five of 6 ELT-treated patients achieved a response (2 CRs and 3 PRs overall).Thirty-three of the 40 patients (83%) developed treatment-related complications including infectious events (53%), cardiac events (20%), cerebrovascular events (16%) and fever of unknown origin (11%).In 11 of 40 patients, a fatal event occured, including aspergillus pneumonia (n=2), acute myocardial infarction (n=1), sepsis (n=6), cerebral hemorrhage (n=1), and hepatorenal syndrome (n=1).Overall, after a median follow-up of 2 years (range, 2–12), 62% (25/40) of patients died.Median overall survival was 5.9 years, and the estimated 30-year overall survival was 25% (Figure 1).Despite achieving hematologic responses, ATG-based IST was associated with substantial early mortality (27%) and significant morbidity in elderly patients. The addition of eltrombopag improved response rates with acceptable toxicity. Prospective studies are warranted to investigate CSA plus eltrombopag, without ATG, as a potentially safer first-line therapeutic strategy in elderly patients with AAA.

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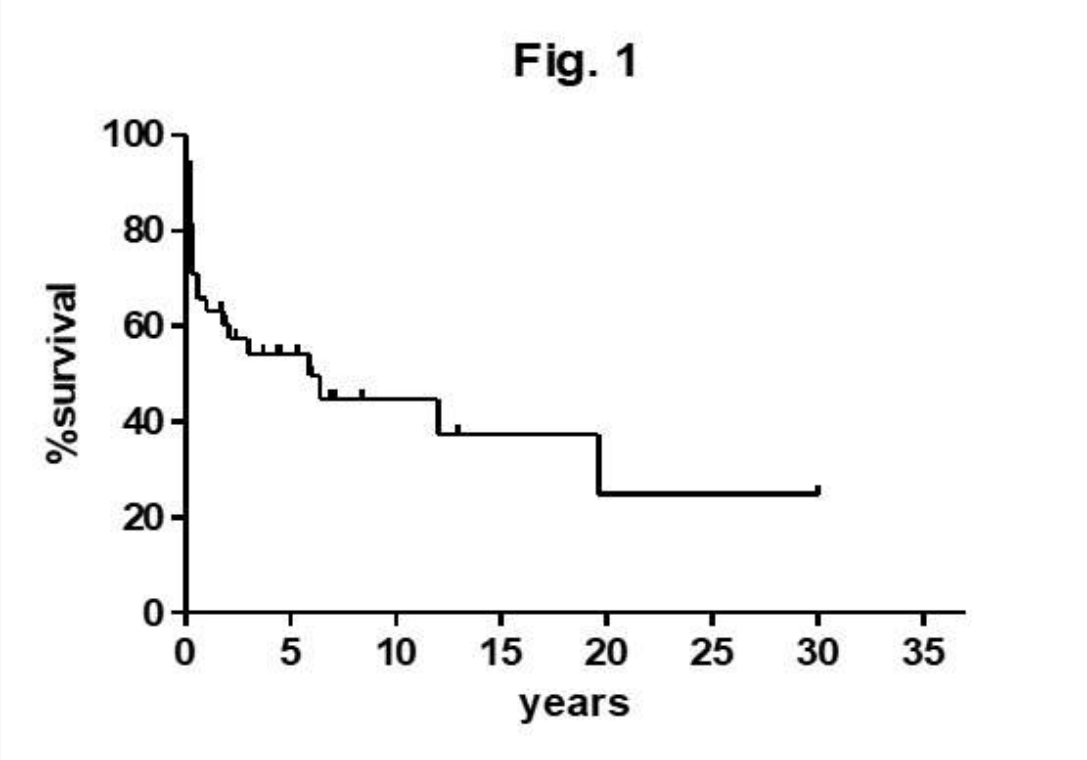
Fig. 1
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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

SAFETY AND EFFICACY OF DOSE-MODIFIED APPROACHES OF FIXED-DURATION IBRUTINIB+VENETOCLAX IN PATIENTS WITH PREVIOUSLY UNTREATED CLL: PRIMARY ANALYSIS OF THE PROSPECTIVE PHASE 2 TAILOR STUDY

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Background. Fixed-duration (FD) ibrutinib+venetoclax (I+V) has transformed 1L treatment for chronic lymphocytic leukemia (CLL), with benefit demonstrated in >1200 patients in phase 2/3 trials (median follow-up up to 5.7 years) and >500 real-world patients. All-oral administration, improved QoL, and patient preference are key factors for I+V initiation (Giza 2025). In May 2024, ibrutinib prescribing information (PI) was updated to recommend AE-guided dose adjustments (DA). TAILOR is the first prospective study to evaluate outcomes and tolerability improvement with both reactive (per PI) and proactive DA.

Aims. We present results from the FD I+V cohorts, assessing efficacy and safety of reactive and proactive DA approaches.

Methods. Patients were randomized 1:1 to reactive (1A) and proactive (1B) DA cohorts and received 12 cycles of FD I+V after a 3-cycle ibrutinib lead-in (420 mg QD) and venetoclax ramp-up/dosing per label. In 1B, ibrutinib was proactively reduced to 280mg QD after lead-in. Primary endpoint was best overall response rate (ORR); secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. TAILOR was not powered for between-cohort comparisons.

Results. 171 pts were randomized to 1A (86) and 1B (85). Median age was 63y. In 1A/1B, 36%/41.2% had unmutated IGHV status, 16.3%/9.4% had TP53/del(17p) aberration, 4.7%/8.2% had CIRS >6, 43.0%/51.8% were high risk. Median follow-up was 14.6mo. ORR was 94.2% (95% CI, 87–98) in 1A and 89.4% (95% CI, 81–95) in 1B. 1 patient per cohort had progressive disease; 12-mo PFS/OS were 98.8%/98.8% (1A) and 97.6%/98.8% (1B). Treatment emergent AEs any grade/grade ≥3 were 95.3%/48.2% in 1A and 94.1%/50.6% in 1B. Grade ≥3 atrial fibrillation was 2.4% in 1A and 7.1% in 1B, hypertension 2.4% and 4.7%, and infections 2.4% and 8.2%, respectively. AEs led to ibrutinib lead-in discontinuation in 2 pts (2.4%) in 1A and in 5 (5.9%) pts in 1B, and in the same rates after cycle 3. Ibrutinib DA during lead-in and after cycle 3 occurred respectively in 4 (4.7%) and 13 (15.3%) pts in 1A, and in 4 (4.7%) and 6 (7.1%) pts in 1B. 2 deaths occurred, due to intracranial hemorrhage (1A) and pneumonia (1B). MRD data will be presented.

Conclusions. Reactive and proactive I+V DA strategies yielded significative improvement in ORR, with similar safety profile in both cohorts. These results strengthen the dosing flexibility of I+V in 1L CLL.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

UPDATED EFFICACY AND SAFETY DATA FROM AN ONGOING PHASE 1A/B TRIAL OF THE BTK DEGRADER BEXOBRUTIDEG (NX-5948) IN PATIENTS WITH CLL ACROSS LINES OF THERAPY

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Bexobrutideg (NX-5948) is a highly selective, orally administered small molecule degrader of wild-type and mutant BTK. We report new and updated efficacy and safety data with bexobrutideg from a Phase (Ph) 1a/b trial.NX-5948-301 (NCT05131022) is a Ph1, first-in-human trial of bexobrutideg in advanced B-cell malignancies. In CLL/SLL, bexobrutideg is being evaluated in relapsed/refractory pts in the Ph1a dose-escalation part and then in Ph1b dose-expansion cohorts that include heavily pre-treated, earlier-line and treatment-naïve patients (pts). Safety is presented for all pts. Efficacy is presented for all Ph1a dose-escalation pts and for selected Ph1b dose-expansion cohorts treated at the recommended Ph2 dose (RP2D) of 600 mg: Cohort 1 (C1; primarily BTKi and BCL2i exposed), C5 (BTKi-exposed and BCL2i-naïve), and C15 (BTKi-naïve, incl. treatment-naïve).As of 1 Jan 2026, 142 CLL/SLL pts have been enrolled. Ph1a and Ph1b C1 had a median 4 and 5 prior lines of treatment (LoT) respectively; Ph1b C5 and Ph1b C15 had a median 2 and 1 prior LoT, respectively.Bexobrutideg was well tolerated across all doses. The safety profile was maintained over the duration of treatment and across different prior LoT. Most adverse events (AEs) were grade 1/2. The most common treatment-emergent AEs included purpura/contusion, neutropenia, and petechiae.High objective response rates (ORRs) were observed across all cohorts: Ph1a 83.0% (22.4 months follow-up [f/u]); Ph1b C1 83.3% at 600 mg (13.1 months f/u); Ph1b C5 86.7% (5.3 months f/u); Ph1b C15 84.2% (4.9 months f/u). The high ORRs in Ph1b C5 and Ph1b C15 are notable, given the short duration of treatment and f/u. Lymph node size decreases were observed regardless of prior treatments or mutational burden at baseline (see Figure). Median progression-free survival (mPFS) was 22.1 months in Ph1a (mPFS f/u 19.8 months).In this Ph1a/b trial, bexobrutideg demonstrated a favorable safety profile in pts with CLL/SLL with longer f/u across doses and prior treatments. Durable responses were maintained in the Ph1a dose-escalation cohort, which has the longest f/u to date. High response rates were observed across populations with different prior therapies, incl. pts previously treated with BTKi and BTKi-naïve pts, supporting further clinical development. Bexobrutideg is being evaluated in the Ph2 DAYBreak-201 study (NCT07221500) and a Ph3 DAYBreak-306 study (NCT07516093) investigating bexobrutideg vs pirtobrutinib is planned.

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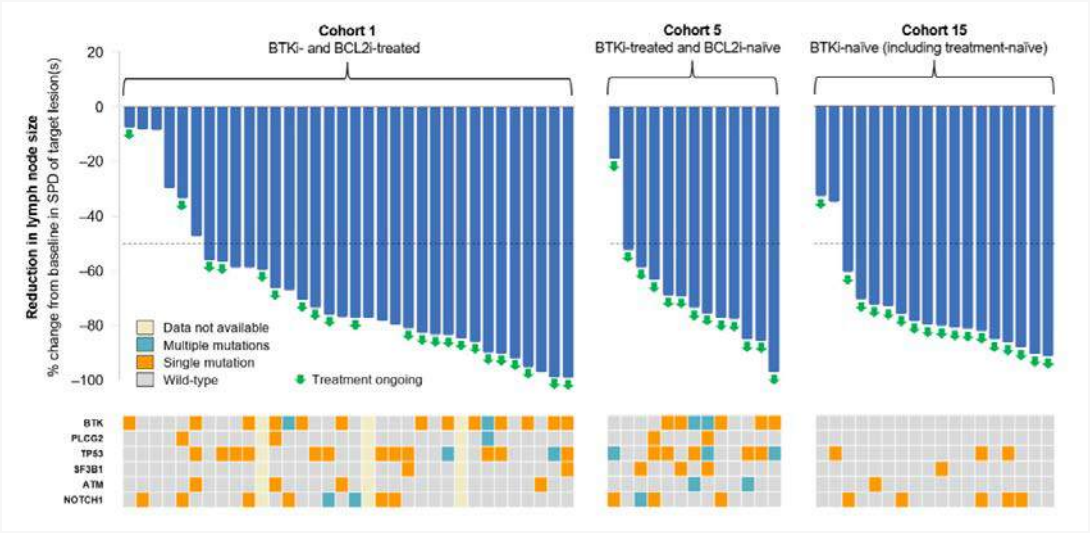
Chronic lymphocytic leukemia and other lymphoproliferative syndromes



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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

NON-INVASIVE PROGNOSTICATION AND MINIMAL RESIDUAL DISEASE MONITORING OF MYD88^{L265P} IN IGM-GAMMOPATHIES: INSIGHT FROM THE "BIO-WM" PROSPECTIVE TRIAL OF THE FONDAZIONE ITALIANA LINFOMI

E. Amaducci[1], D. Drandi[1], S. Zibellini[2], L. Marcheselli[3], C. Varraso[2], E. Genuardi[1], I. Dogliotti[4], E. Cappello[2], F. Cavallo[1|4], C. Sasso[1], A. Ferrari[5], B. Bianchi[6], M. Deodato[7], L. Laurenti[8], P. Tosi[9], E. Cencini[10], G. Loseto[11], D. Marino[12], M. Marchetti[13|14], F. Russo[15], A. Sica[16], J. Olivieri[17], G. Favrin[2], C. Jiménez Sánchez[18], N. Puig[18], L. Arcaini[2], B. Bruno[1|4], R. García-Sanz[19], S. Ferrero[1|4], M. Varettoni[2]

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Background. MYD88^{L265P} is the hallmark mutation in IgM-gammopathies traditionally assessed through bone marrow (BM) aspirate, an invasive procedure.

Aims. The multicenter “BIO-WM” trial (NCT03521596) of the Fondazione Italiana Linfomi (FIL) evaluated droplet digital PCR (ddPCR) for MYD88^{L265P} screening and minimal residual disease (MRD) monitoring in minimally invasive specimens (peripheral blood, PB, and plasma-derived cell-free DNA, cfDNA) versus the gold standard BM aspirate.

Methods. In a retro-prospective series of 300 WM and IgM-MGUS patients 274 paired BM, PB, and plasma samples were analyzed for MYD88^{L265P} by ddPCR at diagnosis and post-treatment. For survival analysis, MRD data were considered as measured in cfDNA or, when unavailable, in BM.

Results. MYD88^{L265P} rates and median mutational burden in cfDNA closely mirrors BM specimens in WM (91% vs 96% and 1.4E-02 vs 3E-02) while genomic DNA from PB cells showed lower sensitivity and mutational burden (85% and 1.2E-03). In IgM-MGUS similar results were described with significantly lower rates (BM: 75% and 1.5E-03, PB: 58% and 8E-04, cfDNA: 67% and 2.6E-03). CART models integrating baseline cfDNA MDY88^{L265P} levels with serum IgM values may discriminate WM from IgM-MGUS and predicted treatment initiation without BM examination: cfDNA MYD88^{L265P} >5.9 conferred 94% probability of WM, while values <5.9 with IgM <2100 indicated 70% probability of IgM-MGUS. Among patients with IgM <2100, treatment was required in 15% if cfDNA MYD88^{L265P} <6.9 versus 90% if >6.9. MRD was prospectively evaluated in 60 WM patients after chemo-immunotherapy. MRD negativity rates increased across tissues: 33% in BM, 55% in cfDNA, and 91% in PB (P<0.001). Patients achieving CR/VGPR were more likely MRD-negative (69%, 11/16) versus PR/MR (16%, 16/38). Bendamustine-rituximab yielded higher MRD negativity (43%, 12/28) compared to DRC (9%, 2/23). MRD negativity predicted improved PFS (4-year: 93% vs 62%, p=0.018), with an initial trend for OS (4-year: 94% vs 83%, p=0.264). MRD evaluation outperformed conventional clinical response criteria as PFS prognosticator: HR 3.44 (1.03-11.5, p=0.045) for MRD+ vs 2.59 (0.77-8.71, p=0.123) for <VGPR (Figure 1).

Conclusions. These results provide prospective evidence for MYD88^{L265P} assessment by ddPCR as a non-invasive tool for diagnosis, outcome prediction and MRD monitoring in IgM gammopathies, supporting its integration into clinical practice and future trial design.

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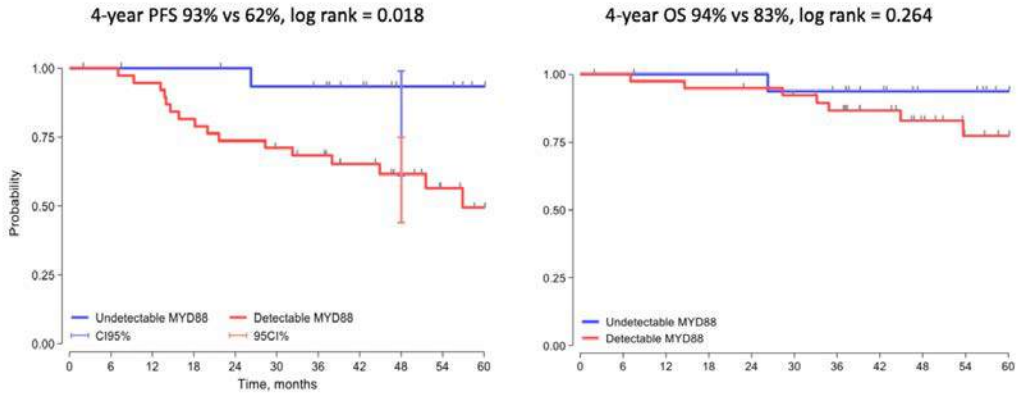

Figure 1. Landmark progression-free and overall survival analysis stratified by minimal residual disease at the end of treatment

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

EFFECTS OF IBRUTINIB AND VENETOCLAX ON CAR T CELL GENERATION IN CHRONIC LYMPHOCYTIC LEUKEMIA: INTERIM RESULTS FROM THE GIMEMA CLL2020 STUDY

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The therapeutic efficacy of CAR T cells in chronic lymphocytic leukemia (CLL) remains suboptimal, largely due to intrinsic dysfunctions of patient-derived T cells. The immune determinants affecting CAR T-cell functionality in CLL, as well as the impact of targeted therapies on T-cell fitness, remain incompletely defined. We analyzed 15 CLL patients enrolled in the GIMEMA CLL2020 trial, with samples collected at pre-treatment and after 6 and 12 months of therapy with ibrutinib (Ibr, n=7) or venetoclax (Ven, n=8). Anti-CD19-4-1BB CAR T cells were generated by lentiviral transduction and evaluated for manufacturing efficiency, phenotype and in vitro function by flow cytometry. CAR T cells were successfully generated in 87% of patients at both pre-treatment and 6 months, and in all samples at 12 months. Transduction efficiency remained consistent across timepoints. In the Ven group, CAR expression was 47% at pre-treatment, 41% at 6 months and 57% at 12 months. In the Ibr group, respective values were 47%, 42% and 64%. Therapy had no impact on final CAR T-cell yield. CAR T products were enriched in CD4+ T cells compared with the starting material, irrespective of therapy. After 12 months of treatment, both CD4+ and CD8+ T cells in the CAR T product exhibited a significant shift toward less differentiated subsets. Moreover, a significant increase in the rate of Th1 cells was found in CAR T cells produced after 12 months of Ibr treatment. Immune checkpoint analysis revealed that Ven induced progressive changes, including reduced PD-1 expression in CD4+ T cells and decreased CTLA-4 in both CD4+ and CD8+ T cells at 6 and 12 months, while TIM-3 remained stable and TIGIT increased selectively in CD8+ T cells. Functionally, CAR T cells retained their proliferative capacity, degranulation and cytotoxic activity after exposure to CD19+ target cells across all timepoints, with no differences between treatment groups. Ven therapy was associated with a trend toward increased CD4+ T-cell degranulation at 12 months, whereas cytokine production remained comparable overtime. In conclusion, exposure to targeted agents, particularly prolonged venetoclax therapy, promotes a more favorable differentiation profile and partial modulation of exhaustion markers. However, no corresponding improvement in in vitro functional activity is observed. Future efforts should focus on optimizing CAR T-cell manufacturing processes to better harness the favorable modulation of T-cell fitness.

Myelodysplastic syndromes

EPIGENETICS OF VEXAS AND MDS REVEALS AGE-DEPENDENT SIGNALS AND INVARIANT LONGITUDINAL METHYLATION PATTERNS AFTER HYPOMETHYLATING AGENTS THERAPY

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VEXAS is an adult-onset autoinflammatory syndrome driven by somatic *UBA1* mutations, frequently associated with myelodysplastic syndromes (MDS). Given the clinical success of hypomethylating agents (HMA) in VEXAS and its interface with MDS, we studied VEXAS/MDS epigenetics to identify disease-specific signatures and HMA interactions.We analyzed data from 10 patients with VEXAS, 38 MDS (MDS-LR,n=15; MDS-HR,n=23), and 7 healthy donors (HD). Promoter methylation was assessed by pyrosequencing for *OTP*, *PRRX2*, *ANXA4*, and *BCL2L10*, including mean methylation and individual CpG-level measurements.In VEXAS, *ANXA4* methylation correlated positively with age (mean: Spearman ρ=0.84, q=0.03, BH-FDR,q=0.03). The age–*ANXA4* relationship differed significantly between VEXAS and MDS: in the latter, *ANXA4* mean decreased with age (slope≈−0.86% per year), whereas increased in the former (slope≈+2.18% per year), with a significant age×VEXAS interaction ($p=2.75\times10^{-6}$).In age/sex/HD-adjusted models, *ANXA4* methylation was lower in MDS-HR compared with VEXAS across all CpGs (e.g.,mean −27.8%,p=0.01; within-ANXA4 BH-FDR,q≤0.02). This contrast was driven by genotype: within MDS-HR, *RUNX1* mutation was associated with *ANXA4* hypomethylation (mean 16.7% in *RUNX1*-mut vs 53.7% in *RUNX1*-wt;p<0.01; FDR q<0.01). *RUNX1* mutation status remained independently associated with lower *ANXA4* methylation (−32.5%, p<0.01) when adjusting for disease-context.*PRRX2* mean methylation and CpGs-level values were higher in MDS-HR than LR (59.9% vs 42.8%; p=0.02; within-*PRRX2* BH-FDR q=0.04), whereas VEXAS showed intermediate values, not significantly differing from MDS groups. No signal was identified with regards to *OTP* and *BCL2L10*.Longitudinal methylation analysis of VEXAS (n=5) and MDS-HR (n=6) undergoing HMA showed an 18% mean reduction (p=0.07) after HMA in all VEXAS cases, paralleled by UBA1 mutational clearance and clinical remission. Conversely, no differences were noticed in *OTP*, *ANXA4*, and *BCL2L10* in VEXAS. Longitudinal profile in HR-MDS did not reveal meaningful changes for any tested genes.Our results reveal a VEXAS-specific age dependency for *ANXA4* methylation, directionally opposite to that seen in MDS, suggesting that inflammatory context and/or clonal architecture may shape epigenetic regulation differently from canonical MDS. *PRRX2* methylation remains a robust marker of MDS risk stratification, also correlating in VEXAS with HMA therapy exposure, corroborating VEXAS-specific epigenetic dynamics.

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Myelodysplastic syndromes

CARDIOVASCULAR COMORBIDITY BURDEN IN VEXAS SYNDROME: GENOTYPE-STRATIFIED, IMAGING AND LONGITUDINAL FINDINGS FROM THE ITALIAN COHORT

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VEXAS syndrome is an adult-onset autoinflammatory syndrome caused by somatic UBA1 mutations. Cardiovascular (CV) comorbidities remain sparsely described. We characterized CV burden, genotype associations, imaging and longitudinal outcomes in an Italian VEXAS study.Cardiac involvement was defined as 1 among heart failure (HF), advanced diastolic dysfunction (DD), valvular heart disease (VHD), pericardial signs, atrial fibrillation (AF), reduced Global Longitudinal Strain (GLS) on echocardiogram. Genotype analyses focused on UBA1 M41 variants; treatment lines served as a marker of cumulative treatment exposure.100/109 total patients had integrable data, including 89 M41 patients. CV risk factors were similar across M41 variants: hypertension in 56%, diabetes in 23%, dyslipidemia in 33%, smoking history in 33%.At baseline CV involvement was present in 60% of evaluable M41 patients with comparable rates in M41L, M41T, M41V genotypes (63%, 53%, and 60%). At last follow-up CV involvement was present in 58%. Notably follow-up involvement was higher in M41T (p=0.03; OR 3.34, 95% CI 1.14–9.77) while M41V was enriched for tricuspid VHD (p<0.01).Paired analyses showed no significant increase in HF, DD, VHD, pericardial signs, AF or total cardiac features over time (Wilcoxon p≈0.66) at a median follow-up duration of 0.93 years (IQR 0.31–2.04). Baseline cardiac involvement was the strongest predictor of follow-up CVD (OR 4.95, 95% CI 1.44–17.00; p=0.01), with M41T remaining significant after adjustment (OR 4.35; p=0.03). Among patients without baseline CV disease, new involvement occurred in 27% and related with a higher number of treatment lines (median 4 vs 2; p=0.05).In a monocentric cohort of nine patients, echocardiography and cardiac MRI were performed. VHD was documented in all cases and enlarged atrial volumes in 55.6%. Impaired GLS despite preserved EF was observed in 66.7%. Cardiac MRI, performed in 7/9 patients, confirmed VHD in 71.4% patients. Reduced GLS was associated with clinical worsening and MRI abnormalities. In one patient, T1 mapping during disease flare showed abnormal myocardium tissue characterization (Fig.1).In our VEXAS cohort, CV comorbidities were common: M41V showed a distinct valvular pattern, whereas M41T was associated with higher follow-up cardiac involvement. Treatment burden correlated with baseline and follow-up involvement, supporting longitudinal monitoring with GLS/MRI to better define cardiologic trajectories in VEXAS.

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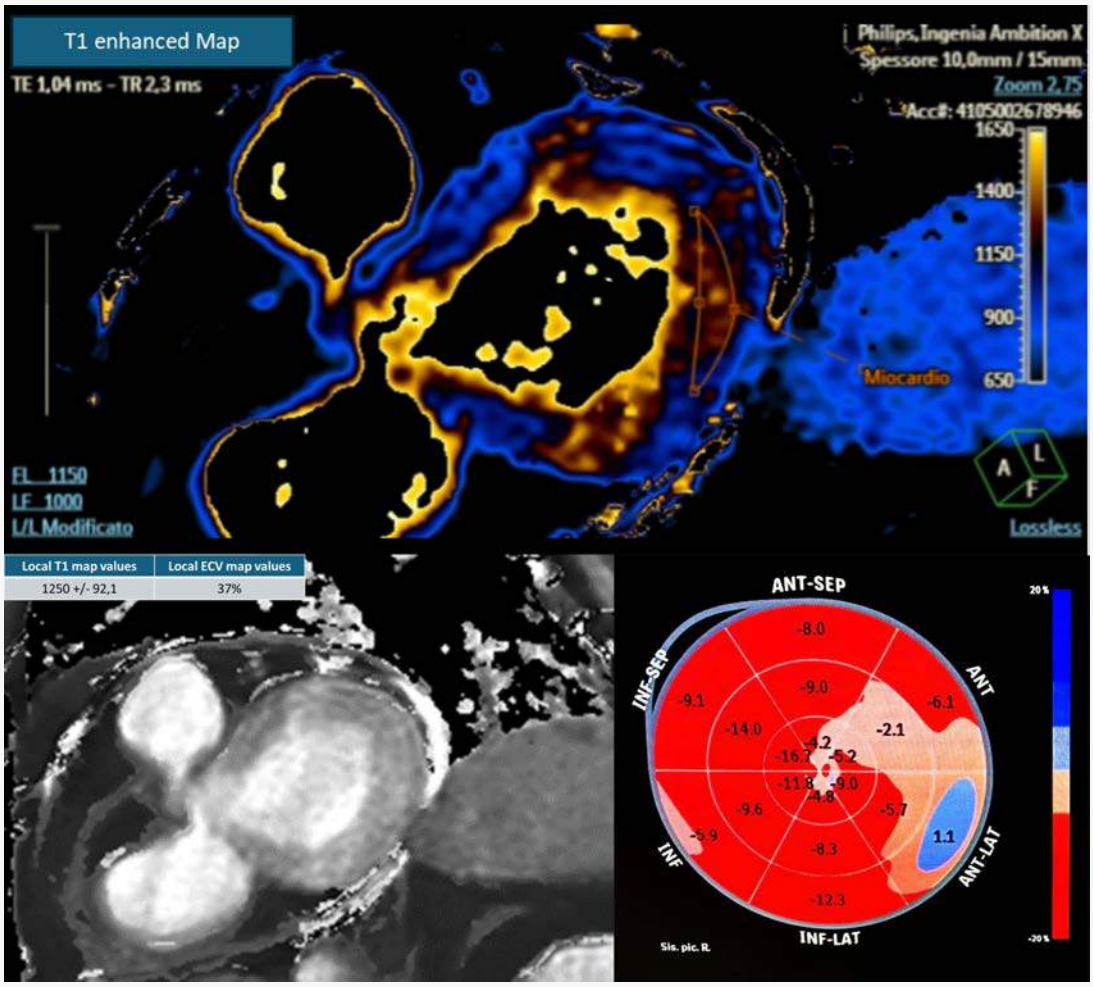

Myelodysplastic syndromes

UPDATED OVERALL SURVIVAL AND LONG-TERM TRANSFUSION INDEPENDENCE FROM THE PHASE 3 COMMANDS TRIAL IN ERYTHROPOIESIS-STIMULATING AGENT-NAIVE PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES

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Background. In the ph 3 COMMANDS trial (NCT03682536), luspatercept (LUSPA) significantly improved RBC-TI ≥12 wks with concurrent mean hemoglobin (Hb) increase ≥1.5 g/dL (Wks 1–24; primary endpoint) vs epoetin alfa (EA) in pts with ESA-naive transfusion-dependent (TD) LR-MDS. Longer follow-up (FU; >2.5 y) showed a favorable OS trend and durable TI responses with LUSPA vs EA. We report updated results with 6 more mos of FU (>3 y).

Methods. Pts (≥18 y; ESA-naive; TD; LR-MDS) were stratified by baseline (BL) transfusion burden (TB), ring sideroblasts (RS), and serum erythropoietin (sEPO), and randomized 1:1 to LUSPA (1.0–1.75 mg/kg; SC Q3W) or EA (450–1050 IU/kg; SC QW) for ≥24 wks. OS (from randomization), RBC-TI and Hb improvement (all Wk 1–end of treatment [tx]), predictive BL biomarkers of OS, and safety were evaluated.

Results. At cutoff (Oct 6, 2025), median (min–max) FU was 35.9 (1–73; LUSPA) and 30.8 (0–77; EA) mos. Median OS was not reached (NR) for LUSPA and 46.0 mos for EA (HR, 0.78; 95% CI, 0.56–1.09), with similar trends in subgroups (Table). RBC-TI ≥12 wks (LUSPA vs EA) occurred in 76.4% vs 55.8% of pts, and in 60.4% vs 39.2% with concurrent mean Hb ≥10 g/dL; median cumulative duration (95% CI) of RBC-TI ≥12 wks was 184.4 (118.4–NE) and 95.1 (74.9–180.1) wks (HR, 0.54; 95% CI, 0.36–0.80). RBC-TI ≥2.5 y (LUSPA vs EA) occurred in 25.3% vs 10.5% of pts. Mean Hb increase ≥1.5 g/dL (LUSPA vs EA) occurred in 80.2% vs 58.6% of pts; median duration (95% CI) of Hb increase ≥1.5 g/dL was 72.9 (53.9–89.9) and 47.9 (35.9–60.0) wks (HR, 0.61; 95% CI, 0.44–0.85). Improved OS was associated with BL biomarkers of favorable immune (LUSPA) and CV function (LUSPA and EA), less aggressive disease (EA), and preserved megakaryopoiesis (EA); these characteristics may enhance response to tx.Overall, 17.6% (LUSPA) and 7.8% (EA) of pts remained on tx; 84.6% and 83.2% had ≥1 dose escalation. No new safety concerns emerged. Deaths (any cause) occurred (LUSPA, 36.3%; EA, 43.0%), fewer LUSPA pts progressed to HR-MDS (3.3%; 7.3%), and AML progression was comparable (4.9%; 5.5%).

Conclusions. Long-term FU demonstrated improved OS trends and sustained responses with LUSPA vs EA, overall and in subgroups. No new safety concerns emerged, reinforcing superior clinical benefit as first-line tx in LR-MDS.
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Table.

Median OS, mos	LUSPA	EA	HR (95% CI)
Overall	(n=182) NR	(n=181) 46.0	0.78 (0.56–1.09)
Stratification subgroup			
TB <4 RBC U/8 wks	(n=118) 57.5	(n=111) 47.2	0.87 (0.57–1.33)
TB ≥4 RBC U/8 wks	(n=64) NR	(n=70) 39.9	0.62 (0.37–1.05)
RS+	(n=133) NR	(n=130) 47.2	0.70 (0.47–1.04)
RS–	(n=49) 54.8	(n=50) 46.2	0.96 (0.53–1.72)
sEPO ≤200 U/L	(n=145) NR	(n=144) 51.4	0.81 (0.55–1.20)
sEPO >200 U/L	(n=37) 43.0	(n=37) 35.4	0.67 (0.35–1.28)

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Myelodysplastic syndromes

MOMELOTINIB IN VEXAS SYNDROME: A PRELIMINARY REPORT EVALUATION OF SAFETY AND EFFECTIVENESS

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Background. VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is an acquired autoinflammatory disease caused by somatic UBA1 mutations. Janus kinase inhibitors, particularly ruxolitinib (RUXO), have shown efficacy in VEXAS, but RUXO-associated anemia often leads to dose reduction or discontinuation. Momelotinib (MMB), a JAK1/JAK2 and activin A receptor type 1 inhibitor, improves anemia in myelofibrosis and may represent a therapeutic option in VEXAS.

Aims. To evaluate the safety and effectiveness of MMB in a single-center cohort of patients with VEXAS syndrome.

Methods. Patients with genetically confirmed VEXAS syndrome treated with MMB were identified. Clinical features, variant allele frequency (VAF) of UBA1 mutations by droplet digital PCR, hemoglobin (Hb), C-reactive protein (CRP), and prednisone dose were collected at baseline and during the first 3 months of treatment. Results: Six male patients with VEXAS (median age 67 years) were included; all had concomitant lower-risk myelodysplastic syndrome. Four patients had previously received RUXO, discontinued for worsening anemia (n=3) or skin rash (n=1). At baseline, all patients were on prednisone (median 15 mg/day) and four were on erythropoiesis-stimulating agents (ESA). All started MMB 200 mg daily. One patient discontinued MMB for subjective intolerance by day 30, and one required dose reduction to 100 mg/day for drug interactions. Three patients developed respiratory tract infections, requiring admission in two cases. One patient experienced a disease flare in the first month, requiring prednisone escalation. No thrombotic events occurred. Median Hb increased by 1 g/dl [IQR 0.5-2] after 1 month and by 2 g/dl [IQR 0-3] at 3 months. In one patient ESA was discontinued at month 3. Median CRP decreased from 25 mg/L [IQR 4.6-48.6] at baseline to 16 mg/L [IQR 8-27.6] at 3 months. Median prednisone dose decreased from 20 mg/day [IQR 15-25] at baseline to 15 mg/day [IQR 10-17.5] at 3 months since MMB initiation. Furthermore, UBA1 VAF decreased from a median of 67% [IQR 62.7-67.9] at baseline to a median of 29.8% [IQR 23.8-40.5] at 3 months.

Conclusions. This preliminary experience suggests that MMB has an acceptable safety profile and may provide clinical benefit in VEXAS syndrome, with improvement in anemia, inflammatory markers, steroid-sparing effect, and reduction in UBA1 clonal burden. These findings support further investigation of MMB in VEXAS in larger prospective studies.

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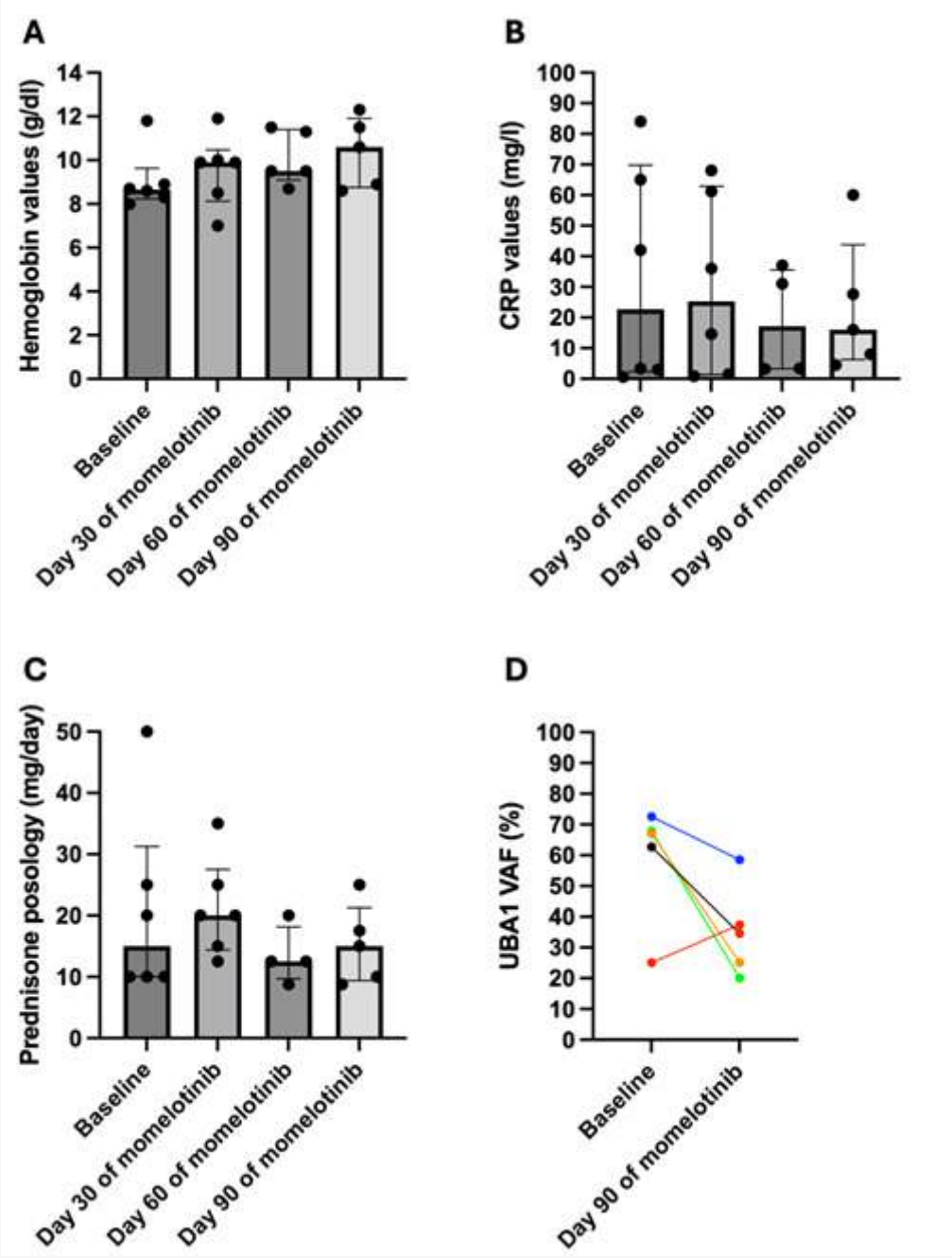

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Myelodysplastic syndromes

PROTEOMIC LANDSCAPE OF VEXAS SYNDROME

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VEXAS is a complex autoinflammatory syndrome defined by UBA1 somatic mutations lying at the interface between MDS and other Systemic Inflammatory Autoimmune Diseases (SIADs).We explored the proteomic landscape of VEXAS to identify its distinct disease signatures vs MDS clinical spectrum, evaluating also the impact of Disease-Modifying Therapies(DMTs) and Disease-Modifying Antirheumatic Drugs(DMARDs).We performed a proteomic analysis through the Olink® Proximity Extension Assay technology, simultaneously investigating 1034 proteins in 86 plasma samples.Our 73 patients cohort(median age 69 years, range 37-89; M/F: 64/9) included:VEXAS onset(n=18),VEXAS post-DMT(n=7),VEXAS post-DMARDs(n=10),UBA1-negative cases with SIAD with no hematological malignancies(UBA1-; n=17),LR-MDS(n=10),LR-MDS+SIAD(n=11),HR-MDS(n=10), and HR-MDS post-DMT(n=3). Principal Component Analysis(PCA) and differential expression(DE) analysis were employed for data interpretation.All p-value were Fals Discovery Rate-adjusted.Baseline PCA showed strong clustering of VEXAS group compared to the others. Conversely, post-therapy PCA revealed patient-specific clustering rather than time-point dependent distribution.DE analysis identified a unique proteomic signature for VEXAS compared to all other groups.Specifically, VEXAS showed 83 DE proteins vs HR-MDS, 39 vs LR-MDS, 27 vs UBA1- patients, and 7 vs LR-MDS+SIAD.Most proteins were upregulated in VEXAS, with RPH3A being the most significantly overexpressed($p<0.0001$).Other consistently upregulated proteins included DAPK2, TFEB, HCLS1, EGLN1, IPCEF1, and NCF1($p<0.05$).Notably, comparisons between non-VEXAS groups (e.g., HR-MDS vs. LR-MDS or UBA1-) yielded only 1,2 or no DE proteins.Furthermore, longitudinal analysis of paired available VEXAS samples (onset vs post-DMT) identified 6 DE proteins:IL12A, IL12B, and IDO1 increased post-treatment, while ERG, TYMP, and ZBTB16 decreased($p<0.05$).No DE proteins were found by comparing VEXAS onset vs post-DMARDs or HR-MDS vs HR-MDS post-DMT.Our data demonstrates that VEXAS syndrome possesses a distinct proteomic signature from MDS and SIADs.The significant overexpression of RPH3A (Rabphilin-3A), a key regulator of calcium-dependent exocytosis, identifies a novel potential biomarker for VEXAS, possibly reflecting biological alterations underlying its pathogenesis. Overall, high-throughput proteomics provides a robust framework for better understanding the biological complexity and the impact of therapy of VEXAS.

Myeloproliferative Neoplasms

SELINEXOR PLUS RUXOLITINIB IN JAK INHIBITOR–NAÏVE MYELOFIBROSIS: PHASE 3 SENTRY TRIAL

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Background. JAK inhibitors (JAKi), such as ruxolitinib (R), are standard frontline therapy for myelofibrosis (MF), a debilitating myeloproliferative neoplasm (MPN); however, only ~1/3 of R-treated patients (pts) achieve spleen volume reduction ≥35% (SVR35). Despite symptom improvements, durable modification of underlying disease biology, including reductions in variant allele frequency (VAF), is limited. Importantly, overall survival (OS) gains remain modest, highlighting a critical unmet need. Selinexor (S), an XPO1-mediated nuclear export inhibitor, has biologic activity in MF and synergy with R in MPN models. SENTRY evaluated S+R in pts with JAKi–naïve MF.

Methods. Pts with JAKi-naïve MF were randomized 2:1 to S 60 mg weekly + R (per label) or placebo + R, stratified by DIPSS risk, spleen volume, and baseline platelet count. Eligibility included spleen volume ≥450 cm^3, active symptoms, DIPSS Int-1 or higher and platelets ≥100×10^9/L. Co-primary endpoints were SVR35 and absolute mean change in TSS (AbsTSS; excluding fatigue) at Week (Wk) 24. Secondary endpoints included safety and OS.

Results. 353 pts randomized (S+R n=235; R n=118). Baseline characteristics were balanced. At Wk 24 SVR35 was achieved in 49.8% of pts in S+R vs 28.0% in R (OR 2.58; P < .0001). Benefits occurred early and were sustained, with SVR35 rates of 49.4% vs 20.3% at Wk 12 and 46.9% vs 23.0% at Wk 36. SVR35 was achieved at any time in 67.7% vs 44.9%. Mean percent change in spleen volume at Wk 24 was −40.0% vs −26.7%. Mean AbsTSS change at Wk 24 was −9.9 vs −10.9 adjusted mean difference 0.97 (P = .825). As of Feb 20, 2026, 95.3% pts in S+R and 89.8% in R were alive. With median follow-up of 11.6 and 12.6 months, OS favored S+R (HR 0.43; nominal P = .022) with early Kaplan–Meier curve separation around Month 9. VAF reduction ≥20% at Wk 24 occurred in 32.0% vs 23.9% and correlated with SVR35 response. TEAEs occurred in 99.1% in S+R and 97.4% in R (grade ≥3 in 70.1% vs 50.0%); TEAEs leading to treatment discontinuation were low (14.5% and 8.6%). TEAEs leading to death occurred in 0.9% vs 2.6%. Confirmed leukemic transformation was 1.7% in each arm.

Conclusions. S+R significantly improved spleen response vs R alone with earlier, deeper, and sustained response rates, comparable symptom improvement from baseline, and a manageable safety profile. Improved spleen response, promising OS signal, and VAF reductions observed in SENTRY position S+R as a novel combination for frontline MF treatment.

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Myeloproliferative Neoplasms

IMPROVED OVERALL SURVIVAL IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS TREATED WITH AVAPRITINIB VERSUS REAL-WORLD THERAPY BASED ON MUTATION-ADJUSTED RISK SCORE STRATIFICATION

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Introduction. Avapritinib is a potent, selective KIT D816V inhibitor indicated for adults with advanced systemic mastocytosis (AdvSM). MARS is a prognostic tool that stratifies patients with AdvSM based on age, anemia, thrombocytopenia, and SRSF2/ASXL1/RUNX1 mutations, where patients with MARS-defined intermediate-and high-risk have poor prognoses. We compared OS between MARS-defined patients receiving avapritinib 200 mg/day starting dose in the PATHFINDER trial (NCT03580655) versus best available therapy (BAT) in real-world (RW) clinical practice.

Methods. PATHFINDER and RW retrospective study (NCT04695431) data were used to compare OS between patients treated with first-line (1L) avapritinib vs 1L midostaurin, and second-line or later (2L+) avapritinib vs 2L+ BAT. Analyses were restricted to lines of therapy (LOT) within combined MARS-intermediate or high-risk (score >1) cohorts. Inverse probability of treatment weighting (IPTW) adjusted for baseline differences in key prognostic covariates; covariate balance confirmed by standardized mean differences <0.1. IPTW-weighted Cox proportional hazards models compared OS between cohorts.

Results. 1L analysis. Median OS was not reached (NR) (95% CI: not estimable [NE], NE) with avapritinib (n=24, mean follow-up 33.1 months) and 26.8 months (95% CI: 14.4, 49.8) with midostaurin (n=43; 22.5 months). OS was significantly longer with avapritinib vs midostaurin (hazard ratio [HR] [95% CI]: 0.08 [0.02, 0.29]; p<0.001).1L SM-AHN subgroup. Median (95% CI) OS was NR (NE, NE) with avapritinib (n=19), and 22.1 months (13.0, 61.5) with midostaurin (n=34). OS was significantly improved with avapritinib vs midostaurin (HR [95% CI]: 0.09 [0.02, 0.36]; p<0.001).2L+ analysis. Median (95% CI) OS was 50.2 months (50.2, NE) with avapritinib (n=55, 28.4 months), and 14.8 months (13.2, 32.6) with BAT (n=55, 71 LOT; 17.6 months). OS was significantly longer with avapritinib vs BAT (HR [95% CI]: 0.28 [0.13, 0.61]; p=0.001).2L+ SM-AHN subgroup. Median (95% CI) OS was 50.2 months (23.0, NE) with avapritinib (n=29), and 13.2 months (7.7, 27.5) in the BAT cohort (n=38, 50 LOT). OS was significantly improved with avapritinib vs BAT (HR [95% CI]: 0.31 [0.13, 0.74]; p=0.008).

Conclusions. In patients with intermediate- or high-risk MARS, avapritinib treatment significantly improved OS versus 1L midostaurin and 2L BAT, including in the SM-AHN subgroup, further characterizing the survival benefit of avapritinib.

Myeloproliferative Neoplasms

SPLICING MUTATIONS PREDICT ANEMIA PROGRESSION AND INFERIOR SURVIVAL IN RUXOLITINIB-TREATED MYELOFIBROSIS PATIENTS

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Background. Mutations in the splicing machinery (*U2AF1*, *SRSF2*, *SF3B1*, *ZRSR2*) play a cross-cutting role across myeloid neoplasms. While *U2AF1* and *SRSF2* have established prognostic value in primary (PMF) and secondary (SMF) myelofibrosis, the impact of the broader spectrum of splicing mutations (SpM) on anemia dynamics and survival remains unclear.

Aims. To assess the impact of SpM on worsening anemia, RUX-emergent anemia and outcome in RUX-treated MF patients (pts).

Methods. This sub-analysis of the real-world RUX MF study (NCT06516406) included 344 MF pts with NGS data. Baseline anemia was defined as Hb<10 g/dL; worsening anemia as Hb decline ≥1.5 g/dL; RUX emergent anemia as Hb<10 g/dL and/or transfusion requirement at 6 months; thrombocytopenia as platelets (plt) <100x10^9/L. High molecular risk mutations (HMRm) were defined according to MIPSS70v2 (PMF) or MYSEC-mPM (SMF). Overall (OS), blast phase free (BPFS), and progression free survival (PFS) were calculated from RUX start, by KM analysis accounting for time from diagnosis to RUX initiation.

Results. Eighty pts (22.6%) harbored SpM: *SRSF2* (9.9%), *U2AF1* (7.6%), *ZRSR2* (3.5%), and *SF3B1* (4.1%). Median age was similar between SpM and SpM wild type (SpMwt) pts; SpM were more frequent in males and PMF (both p .02). No differences were observed in driver mutations, leukocyte count, marrow fibrosis, TSS, spleen size, transfusion requirement, DIPSS/MYSEC risk, or RUX starting dose.-Conversely, SpM pts had lower baseline Hb (10.5 vs 11.5 g/dL, p=.002) and Plt (275 vs 370×10^9/L, p=.006) and a higher prevalence of ASXL1 (51.3% vs 32.6%, p=.002) and IDH1 mutations (7.5% vs 1.5%, p=.005) among HMRm.Baseline anemia was more frequent in SpM (48.8% vs 30.3%, p=.002), while thrombocytopenia rates were similar. At 6 months, anemia prevalence (60.3% vs 39%, p=.002) and RUX emergent/worsening anemia incidence (38.2% vs 20.6%; OR 2.38, p=.003) were higher in SpM pts, but not thrombocytopenia (p .30).Median OS (5.6 vs 8.8 years; HR 1.86, p=.002), PFS (4.7 vs 8.4 years; HR 1.91, p=.001), and 5 year BPFS (75.5% vs 89.7%, p=.045) were inferior in SpM pts; associations remained significant after adjustment for co occurring HMRm.

Conclusions. MF pts harboring SpM exhibit an anemic phenotype and a 2 fold higher risk for RUX-emergent and worsening anemia, identifying a vulnerable molecularly defined subgroup with inferior outcomes and higher progression risk. These findings support exploring alternative, anemia focused strategies for this pt subset.

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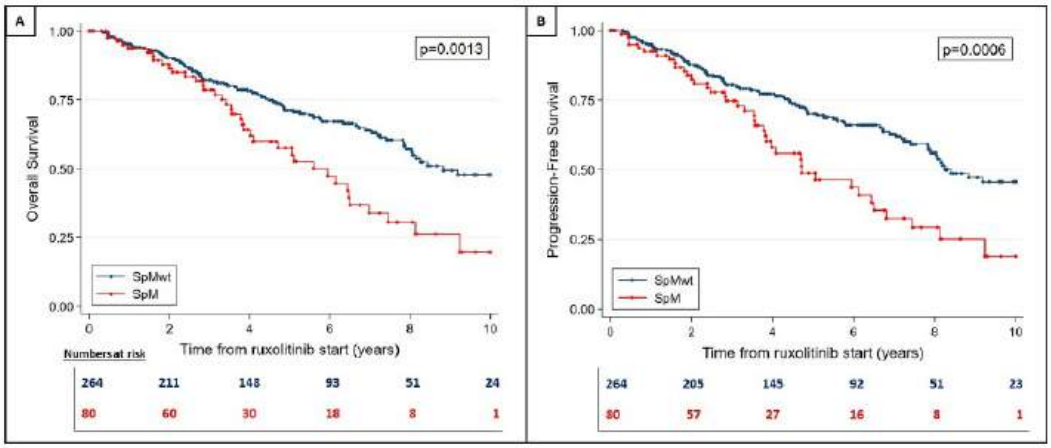
Figure: Kaplan-Meier Curves of Overall Survival (A) and Progression-Free Survival (B) by presence of splicing mutations (SpM)



Myeloproliferative Neoplasms

EFFECT OF RUSFERTIDE ON CYTOREDUCTIVE THERAPY USE IN PATIENTS WITH PHLEBOTOMY DEPENDENT POLYCYTHEMIA VERA: POST HOC ANALYSIS FROM THE RANDOMIZED CONTROLLED PHASE 3 VERIFY STUDY

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Background. Rusfertide is a first-in-class hepcidin peptide mimetic. In phase 3 VERIFY (NCT05210790), rusfertide with standard of care (SOC) met the prespecified primary endpoint (clinical response: absence of phlebotomy [PHL] eligibility) and all four key secondary endpoints vs. placebo (PBO) with SOC (Kuykendall AT, et al Blood. 2025;146(S1):81). Safety was consistent with prior studies.

Aims. Describe rusfertide effect on cytoreductive therapy (CRT) use in VERIFY.

Methods. VERIFY randomized pts (1:1) with PV to rusfertide or PBO with SOC therapy (PHL with or without CRT). After the 32-week double blind period, pts could receive rusfertide open-label for 3+ years. Post-hoc analysis reviewed 285 rusfertide-exposed pts to identify pts who (1) discontinued CRT without restarting; (2) reduced weekly CRT dose from that used at randomization lasting ≥12 wks without returning to baseline; or (3) started a new CRT or increased weekly CRT dose.

Results. As of 10 December 2025, median duration of exposure for 285 rusfertide-treated pts was 88.1 (2–158) wks; >80% (n=242) remain ongoing on rusfertide with or without CRT. More than half (156/285; 54.7%) were receiving CRT at baseline. For pts receiving PHL with CRT, 12.2% discontinued CRT, 41.7% reduced and/or discontinued CRT (29.5% reduced without discontinuing CRT), and 12.2% started a new CRT or increased weekly CRT dose from baseline (Table). In pts who discontinued CRT without restarting, median time from first dose rusfertide to CRT discontinuation was 28.1 (5.4–125.9) wks. In pts who reduced CRT dose, time from first rusfertide dose to first CRT dose reduction was 20.1 (2.0–96.1) wks. Median hematocrit (Hct) remained <45% in patients who reduced or discontinued CRT dose up to 48 wks prior and 48 wks after CRT change. During rusfertide exposure for the year following CRT dose reduction or discontinuation, median PHL rate was 0 PHL/yr.

Conclusions. This analysis showed 41.7% of pts with PHL-dependent PV treated with CRT at baseline discontinued or reduced CRT dose following rusfertide exposure with Hct levels remaining under 45%; suggesting rusfertide may reduce PHL and/or CRT burden in pts with PV who have poorly controlled Hct.*2026 European Hematology Association (EHA). Reused with permission. This abstract was previously accepted and presented at the 2026 EHA Annual Meeting. All rights reserved.*

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	PHL+CRT n=156					PHL Only n=129	PHL+CRT Or PHL Only* n=285
	HU n=109	Interferon n=38	Ruxolitinib n=7	Other n=2	Any CRT n=156		
Discontinued CRT, n (%)	15 (13.8)	4 (10.5)	0	0	19 (12.2)	N/A	19 (6.7)
Reduced and/or discontinued CRT, n (%)	47 (43.1)	16 (42.1)	1 (14.3)	1 (50.0)	65 (41.7)	N/A	65 (22.8)
Increased dose/ New CRT, n (%)	14 (12.8)	4 (10.5)	1 (14.3)	0	19 (12.2)	20 (15.5)	39 (13.7)
No CRT change, n (%)	48 (44.0)	18 (47.4)	5 (71.4)	1 (50.0)	72 (46.2)	109 (84.5)	181 (63.5)

HU, hydroxyurea; N/A, not applicable.
*All pts treated with rusfertide (n=285). In VERIFY (N=293 pts), 2 pts were randomized but not dosed; 6 pts (PBO group) discontinued VERIFY before receiving rusfertide.

Myeloproliferative Neoplasms

LIMITATIONS OF NEXT-GENERATION SEQUENCING IN DETECTING LOW-ALLELE BURDEN *JAK2* V617F MUTATION: IMPLICATIONS FOR DIAGNOSIS AND MOLECULAR MONITORING IN 3,888 PATIENTS

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The *JAK2* V617F mutation is a key driver in chronic myeloproliferative neoplasms (MPNs), characterized by clonal myeloid proliferation in bone marrow (BM) and peripheral blood (PB). Quantitative PCR (qPCR) remains the recommended method for mutation detection and allele burden quantification according to current international guidelines. NGS-based targeted panels allow simultaneous profiling of multiple myeloid genes, but their sensitivity for low variant allele fraction (VAF) *JAK2* variants remains debated. Although high concordance between NGS and qPCR has been demonstrated at VAF >5% (detection limit of our NGS assay), limitations persist at lower VAF levels.The aim of this study was to evaluate the frequency of *JAK2* V617F mutations identified by qPCR but not detected by NGS, analyzing allele burden and the diagnostic and monitoring implications, particularly for minimal residual disease assessment in the era of potential disease modifying agents.Between 2023 and 2025, 3,888 patients with suspected MPNs were analyzed. DNA was extracted from BM or PB samples and analyzed using both NGS and qPCR. NGS analysis was performed using the Myeloid Solution panel or the Ion Torrent Genexus system. Concurrently, the samples were analyzed by qPCR using the Ipsogen *JAK2* MutaQuant 24 V1, with a detection limit of 0.061%.A total of 1,163 (29.9%) tested positive for *JAK2* V617F by qPCR (Fig. 1A). Among samples analyzed by both methods, 48 (4.13%) were positive by qPCR with VAF <2%; of these, 29 (60.4%) were not detected by NGS. Additionally, 7 of the 19 cases positive by both methods (36.8%) showed discrepant VAF values, leading to inaccurate allelic burden estimation (Fig. 1B-C). Despite these discrepancies in low-burden cases, Cohen's kappa showed almost perfect overall agreement between qPCR and NGS (κ = 0.98).qPCR remains the gold standard for *JAK2* V617F detection and monitoring. While NGS enables simultaneous multi-gene analysis, its sensitivity limitations may yield false-negative results at low allele burden. A combined qPCR-NGS approach is therefore essential for accurate diagnosis. Particularly in view of potential treatment discontinuation or in the evaluation of response to therapies such as ruxolitinib and interferon, VAF represents an increasingly important parameter for disease monitoring and clinical decision-making, especially at very low levels where it enables a more precise quantification of minimal residual disease and molecular response.

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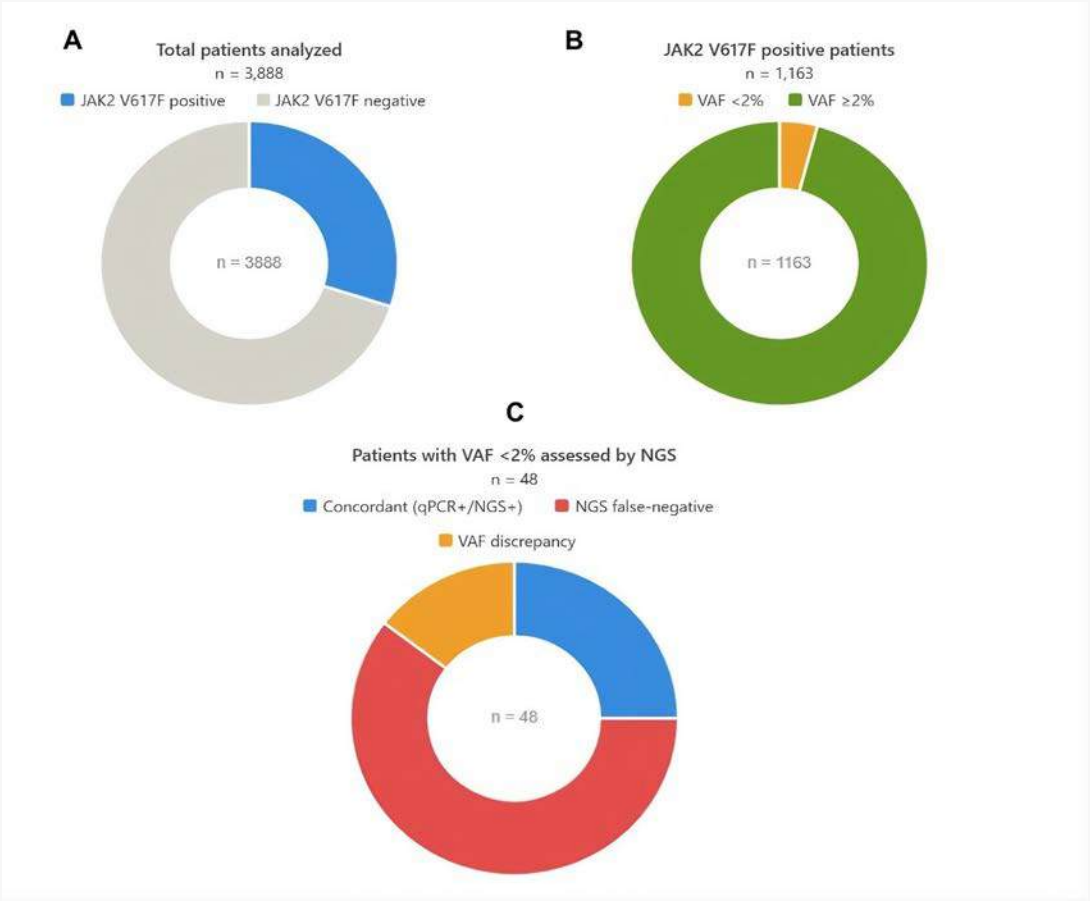
A
Total patients analyzed
n = 3,888
JAK2 V617F positive
JAK2 V617F negative
n = 3888
B
JAK2 V617F positive patients
n = 1,163
VAF <2%
VAF ≥2%
n = 1163
C
Patients with VAF <2% assessed by NGS
n = 48
Concordant (qPCR+/NGS+)
NGS false-negative
VAF discrepancy
n = 48

Fitness, palliation, quality of life and pharmacoeconomics

PATIENT-REPORTED OUTCOME ENDPOINTS IN RANDOMIZED CONTROLLED TRIALS OF PATIENTS WITH HEMATOLOGIC MALIGNANCIES: A STATE-OF-THE-ART OVERVIEW OF STUDIES PUBLISHED BETWEEN 2015 AND 2025

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Patient-reported outcomes (PROs) are now frequently used in randomized controlled trials (RCTs) of hematologic malignancies and play a critical role in informing regulatory decisions. For example, they have contributed to drug approvals in myeloproliferative neoplasms (MPN). We aimed to investigate the use of PRO endpoints in hematologic RCTs over the last decade.Data were gathered through the IMPROVE project, which identified RCTs with PRO endpoints published between 2015 and 2025. Two independent reviewers extracted information from each RCT on patients' and study characteristics, clinical and PRO endpoints. PRO differences were defined based on statistically significant differences between study arms across PRO scales.A total of 143 RCTs conducted in multiple myeloma (MM) (n=55), lymphomas/chronic lymphocytic leukemia (CLL) (n=42), leukemias/myelodysplastic neoplasms (MDS) (n=27), and MPN (n=19) were analyzed. Most trials were open-label (71%), international (79%), and industry-supported (87%), with a higher proportion of open-label studies in MM (80%) and lymphomas/CLL (76%) and more frequent blinding in leukemias/MDS (44%). Sample size varied by disease, with larger studies in MM (median 478 patients) and smaller in MPN (median 195 patients). Immunotherapy was the most frequent experimental treatment in lymphomas/CLL (79%), while targeted therapies were more frequent in MPN (74%). Progression-free survival was the most common primary endpoint (54%), particularly in MM (84%) and lymphomas/CLL (74%), while overall survival was more frequently used in leukemias/MDS (37%). PROs were most often used as secondary/exploratory endpoints (96%). In MPN trials, they were more frequently used as primary endpoints (16%) compared to other diseases. The choice of PRO measures varied across disease groups. EORTC questionnaires were most frequently used overall (64%), particularly in MM (80%), whereas most MPN studies (90%) used the specific MPN-SAF instrument. Overall, PRO results favored the experimental arm in 46% of RCTs, the control arm in 8%, and showed no difference in 22%, while in 24% of studies statistical significance was not reported. A secondary paper on PRO results was available in 55% of RCTs, with a median delay of 1.7 years from primary publication.This study provides a state-of-the-art overview of the use of PROs in RCTs of hematologic malignancies and provides insights for planning the design and implementation of PRO endpoints in future trials.

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SUSTAINED RELAPSE-FREE SURVIVAL IN MULTIPLE MYELOMA ITALIAN PATIENTS WHO DISCONTINUED THERAPY IN CLINICAL PRACTICE: A PRELIMINARY REPORT FROM THE ODISSEY STUDY

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Introduction. Continuous treatment until disease progression or unacceptable toxicity remains the main approach in multiple myeloma (MM). However, time-limited regimens has recently renewed interest in whether discontinuation may be feasible and safe in selected cases.

Methods. The on-going ODISSEY study (Observational stuDY of multiple myeloma patientS who diScontinuEd therapY in clinical practice) was designed to describe clinical features and outcomes of responding MM patients who discontinued treatment for reasons other than disease progression or death and were alive without progression for at least 12 months post-discontinuation.

Results. One hundred and seventy patients (55.9% male) diagnosed between 2002 and 2024 have been so far enrolled. The median age at discontinuation was 69 years. At diagnosis, 71 patients (47.3 %) were in ISS stage I, 38 (22.3%) in stage II, 16 (9.4%), in stage III; ISS was not available in 16 patients. Treatment was discontinued during first, second and third or subsequent lines in 92 (54.1%), 57 (33.6%) and 21 (12.3%) patients, respectively. The most frequent first line therapy discontinued included lenalidomide or thalidomide maintenance after ASCT (63%), while combinations of lenalidomide and dexamethasone with daratumumab (DRd) or carfilzomib (KRd) where those more frequently interrupted during second line therapy (57.9%). The median duration of treatment before discontinuation was 18 months (range 1-85). At suspension, 155 patients (91.2%) were in VGPR or better. Main reasons for discontinuation were medical decision (26.5%), newly acquired comorbidities (21.8%), non-hematologic toxicity (15.3%), patient's choice (12.9%), hematologic toxicity (12.3%), and other causes (11.2%). At a median follow-up of 28 months (range, 12-162) from treatment discontinuation, median relapse-free survival was 94 months (95% CI 66–NR) (Figure 1). Among 35 patients who relapsed (20.6%), 31 received a new treatment and VGPR or better was re-obtained in 80.8% of cases. To date, 157 (92.4%) patients are still alive, and only one death due to progression disease has occurred.

Conclusions. The ODISSEY study, one of the first experiences exploring treatment discontinuation in MM outside of clinical trials, suggests that treatment interruption may be feasible and that durable off-therapy remissions may be maintained in a significant subset of not heavily treated patients, with less advanced disease at diagnosis and good quality responses.

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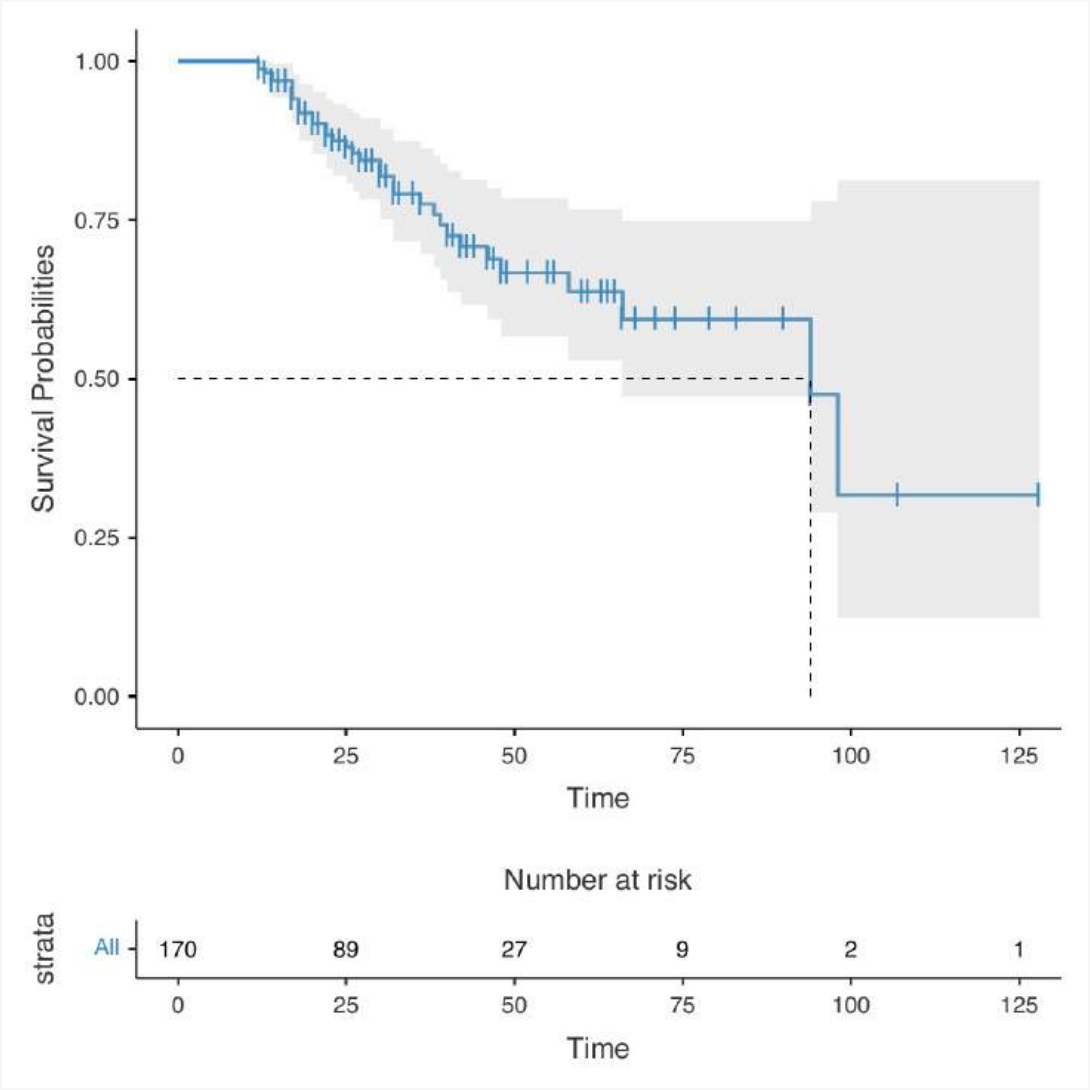
Fitness, palliation, quality of life and pharmacoeconomics



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Fitness, palliation, quality of life and pharmacoeconomics

HEALTHCARE COSTS OF DLBCL IN ITALY: A REAL-WORLD COMPARISON BETWEEN AXI-CEL AND ELIGIBLE PATIENTS TREATED WITH NON-CAR T ALTERNATIVES, AND THE IMPACT OF VEIN-TO-VEIN TIME

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Axi-cel is a potentially curative one shot option for relapsed/refractory diffuse large B cell lymphoma (DLBCL), yet a proportion of eligible patients (pts) are still treated with alternative non CAR T approaches. In CAR T pathway, shorter vein to vein (VTV; from apheresis to infusion) has been associated with improved outcomes and lower resource consumption[1].We evaluated healthcare resource utilization–related costs (HCRU; excluding acquisition costs of CAR T) in Italy by comparing pts treated with axi cel with pts potentially eligible for CAR T but managed with alternative non CAR T therapies; we also analyzed costs along the CAR T pathway, with a focus on the VTV and infusion to discharge (ITD) phases.Using administrative databases from Local Health Units, we identified 51 DLBCL pts treated with axi cel in second or third line (2L/3L) and 147 potentially CAR T eligible pts treated with alternative regimes, mainly CT based with or without autologous stem cell transplantation. The inclusion period ranged from January 2019 (3L) or November 2023 (2L) to September 2025. The index date was axi cel infusion or initiation of alternative therapy. HCRU related costs (including hospitalizations, outpatient services, and all non CAR T drug prescriptions) were compared using generalized linear models adjusted for age, sex and Charlson Comorbidity Index, over the 3 months before and ≥6, ≥9 and ≥12 months after index. Adjusted HCRU costs were higher for axi cel pts in the 3 months prior to index, reflecting pre infusion management. Post index, adjusted costs ratios were significantly higher among pts treated with alternative therapies (2.19x at ≥6 months, 2.06x at ≥9 and 2x at ≥12 months vs axi cel; p<0.01), mainly driven by repeated hospitalizations and treatment related resource use; CT and transplant related admissions accounted for most inpatient costs.Within the CAR T pathway, mean variable costs per pts were €9,757 during the VTV phase (excluding acquisition costs of CAR T and DRG reimbursement) and €494 during ITD, largely attributable to supportive care (e.g., anakinra, tocilizumab) and transfusions.These real--world data show that axi-cel is associated with lower downstream HCRU compared with alternative non-CAR T strategies. Importantly, strategies aimed at optimizing the VTV interval, such as faster manufacturing processes, optimized treatment capacity and slot availability, confer an economic benefit by reducing HCRU along the CAR T treatment pathway.

Fitness, palliation, quality of life and pharmacoeconomics

QUALITY OF LIFE AND CARE ORGANIZATION OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA WITHIN THE LOMBARDY HEMATOLOGY NETWORK: UPDATED RESULTS OF THE CML-OPERAP STUDY

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Background. CML accounts for 10-15% of adult leukemias. Tyrosine kinase inhibitors have transformed CML into a chronic condition with near-normal life expectancy, but whether CML patients' (pts) quality of life (QoL) also approaches that of the general population remains unclear. The organizational model of CML care may influence QoL and patient experience.

Aims. The CML-OPERAP study (Outcome and PErformances Reported and Analyzed by Patients) evaluates the impact of care organization on QoL and care satisfaction of CML pts.

Methods. Cross-sectional, multicenter observational study involving 22 REL centers. Eligible pts are ≥18 with CML, followed for ≥6 months.Data includes clinical data and patient-reported outcomes:- Custom CML Hematology Center Questionnaire (CCHCQ): assessing satisfaction with physicians, nurses and logistics- EORTC QLQ-C30/CML24 QoL surveyCenters are classified as:- Categories 1-2: large centers (>100 CML pts) with/without a dedicated CML clinic-Categories 3-4: small centers (<100 CML pts) with/without dedicated time slots for CML ptsAnalyses used regression (linear and logistic) models adjusted for clustering and confounders and t-tests.

Results. As of April 2026, 19 centers provided data on 1026 pts: 383, 317, 170, 156 pts from Category 1-4 respectively.Overall, QoL scores were favorable and comparable or better than Italian general population reference values. Mean Global Health Status (GHS) was 76.0 in males (n=616) vs 67.6 and 69.3 in females (n=410) vs. 62.4 in references (both p<0.01).Differences among organizational categories were small and of limited clinical relevance.Pts in treatment free remission (n=271) reported slightly better QoL than those on treatment (n=755), with higher GHS (76.8 vs 72.1, p<0.01).Category 1 centers reported more "excellent" CCHCQ ratings than Category 2 across several items (all p<0.05) regarding physicians (Overall evaluation, 96.2% vs 92.4%; attention to symptoms, 67.0% vs 58.2%; time dedicated, 69.9% vs 60.4%) and nurses (Overall, 89.5% vs 84.7%; attention to comfort, 64.7% vs 47.3%; care information, 60.9% vs 49.0%; symptoms management, 48.6% vs 40.9%; time dedicated, 66.4% vs 53.3%). Category 3 showed better center accessibility than Category 4 (46.1% vs 28.6%).

Conclusions. Data from ~50% of REL CML pts show that QoL is very good and comparable to the general population. Dedicated CML care is associated with higher satisfaction. Further results will be presented at the meeting.

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Fitness, palliation, quality of life and pharmacoeconomics

A LONGITUDINAL COMPREHENSIVE GERIATRIC ASSESSMENT TO DEFINE FITNESS IN FIRST-LINE CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS AGED ≥65 YEARS: A PROSPECTIVE MULTICENTER ITALIAN STUDY (CLYF TRIAL)

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As frailty in chronic lymphocytic leukemia (CLL) is mostly based on chemo-derived parameters (Creatinine Clearance [CrCl]<70 and/or CIRS>6: traditional fitness), we evaluated an integrated geriatric and quality of life (QoL) approach to define fitness with target agents.In this prospective, multicenter, observational study, consecutive pts ≥65 yrs receiving 1L treatment completed Practical Geriatric Assessment (PGA) and EORTC QLQ-C30 at treatment start (baseline), 6, 12, 18 months. PGA domains: physical, functional, psychological, cognitive function, nutritional status, social support, self-perceived comorbidities. Primary objective: define frailty in CLL by PGA. Secondary: feasibility, impact of baseline characteristics on PGA domains; distribution of PGA/EORTC QLQ-C30 global health status (GHS) across treatments, longitudinal changes.167 pts were included (Mar 2025–Jan 2026): 58% BTKi, 33.5% ibrutinib-venetoclax, 8.4% venetoclax-obinutuzumab. BTKi vs fixed-duration pts were older (p<.001), unfit by traditional fitness (p<.001), had higher ECOG-PS (p=.036), more concomitant meds (p<.001), and TP53 aberrations (p=.005). 98% had≥1 altered PGA domain (median 3). BTKi pts had higher PGA burden (p=.003) and impaired physical function (p=.001). Median GHS was 67 (0–100), no differences among treatments. Comparing traditional fitness vs PGA burden for treatment choice, discordance emerged in fit pts, with higher PGA burden in BTK-i-treated. Of 115 pts (68%) without anamnestic severe comorbidities, 84.3% self-reported relevant coexisting conditions. Age independently predicted higher PGA burden (p=.002). Fig.1 shows relation between baseline characteristics and single PGA domains. Low platelets (p=.006), musculoskeletal CIRS (p=.010), psychological (p<.001), cognitive (p=.025), functional status (p=.013) independently affected GHS.At 6 months (90 pts), PGA burden significantly improved (median 5 vs 4, p=.001), with benefit in nutritional status (p=.003). Treatment choice did not impact 6-month PGA burden. No GHS changes at 6 months, no treatment effect. Median PGA+QLQ-C30 completion time: 20 min (pts), 5 min (physicians).This interim analysis of the first prospective CLL cohort using PGA, shows feasibility and ability to capture changes during targeted therapies. Even among "fit" by traditional criteria, PGA identified frailer pts not considered suitable for fixed-duration. These findings support integrating dynamic PGA and QoL assessment into CLL management.

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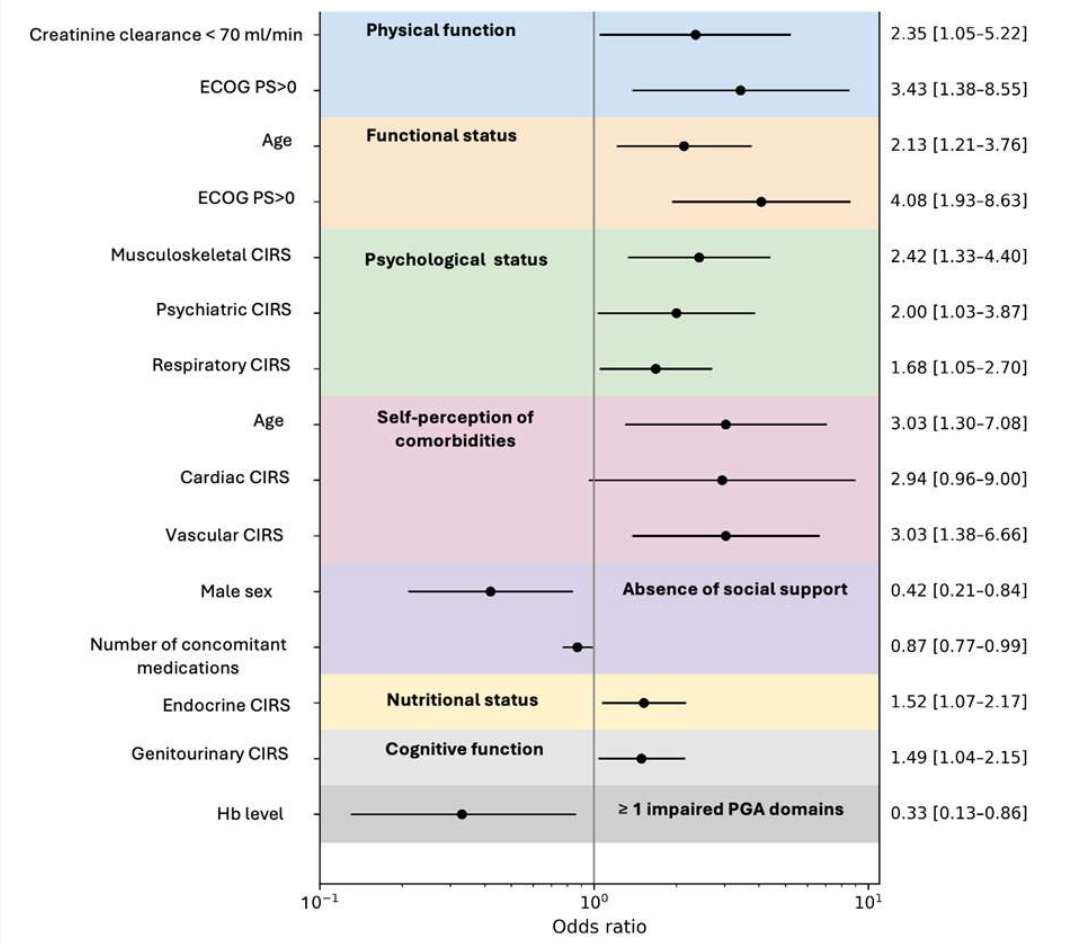
Creatinine clearance < 70 ml/min
ECOG PS>0
Age
ECOG PS>0
Musculoskeletal CIRS
Psychiatric CIRS
Respiratory CIRS
Age
Cardiac CIRS
Vascular CIRS
Male sex
Number of concomitant medications
Endocrine CIRS
Genitourinary CIRS
Hb level
Physical function
Functional status
Psychological status
Self-perception of comorbidities
Absence of social support
Nutritional status
Cognitive function
≥ 1 impaired PGA domains
2.35 [1.05-5.22]
3.43 [1.38-8.55]
2.13 [1.21-3.76]
4.08 [1.93-8.63]
2.42 [1.33-4.40]
2.00 [1.03-3.87]
1.68 [1.05-2.70]
3.03 [1.30-7.08]
2.94 [0.96-9.00]
3.03 [1.38-6.66]
0.42 [0.21-0.84]
0.87 [0.77-0.99]
1.52 [1.07-2.17]
1.49 [1.04-2.15]
0.33 [0.13-0.86]
10^{-1}
10^{0}
10^{1}
Odds ratio

Acute myeloid leukemia

REAL WORLD OUTCOMES IN 390 PATIENTS WITH ACUTE MYELOID LEUKEMIA ARISING FROM CHRONIC MYELOMONOCYTIC LEUKEMIA: A MULTINATIONAL STUDY

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Secondary acute myeloid leukemia evolving from chronic myelomonocytic leukemia (CMML-AML) represents a high-risk entity with limited real-world data on treatment outcomes. We conducted a retrospective, multicenter study including 390 adults diagnosed with CMML-AML across Italy, Spain, UK (1998-2025) treated with intensive (IC: 3+7, CPX-351, fluda-based) or non-intensive regimens (hypomethylating agents [HMAs], HMA-venetoclax [HMA-VEN], low-intensity CHT). Primary objectives were response and overall survival (OS) rates across treatment groups. Median age was 69.5, with male prevalence. Leukocytosis was present in 60%, adverse risk ELN2022 category in 66%. Karyotype was normal in 50%, MDS-related in 17% and complex in 7%. Molecular profiling showed MDS-related mutations in 79% (ASXL148%, SRSF2 46%, TET2 42%, RUNX1 33%). Signalling/tyrosine kinase mutations occurred in 82% (RAS 41% CBL 9%, TK 26%). SF3B1, TP53 mutations were rare (<5%), de novo AML mutations identified in 33%. Overall, 174 (44.6%) received IC and 206 (59%) non-intensive regimens. CR/CRi rate for IC was 42% with induction mortality rate of 9%; CR/Cri rate for non-intensive was 34% with an induction mortality of 12%. HMA-VEN yielded superior CR/CRi rates (58%) vs HMAs (25%) and low-intensity CHT (3%)(p<0.001). Median OS for the entire cohort was 8.5 mos (7.2-9.5), 8.6 for IC (7.7-11.9) and 8.0 for non-intensive (6.4-9.4). Within IC, 3+7 showed 11.2 mos median OS (8.5-17.3), 7.8 with CPX-351 (3.9-12.7) and 9.2 for Fluda-based (5.7-nr: p<0.01), with no difference after adjustment for age (HR1.28, 0.79-2-05, p=0.316). Within non-intensive, median OS for HMA-VEN was 11.6 mos (8.1-17.1), 6.7 for HMAs (5.3-14.4) and 5 for low-intensity CHT (3.1-8; p<0.001). Allo-SCT was performed in 23% of IC and 5.6% of non-intensive patients and was associated with improved OS (25.8 vs 6.8 months, p<0.001). In patients aged 60-75 years, HMA-VEN showed superior OS compared to IC (12.0 vs 7.0 months, p=0.045), with similar transplant rates (6.4% vs 13.5%, p=0.2). In this large real-world cohort, CMML-AML presents with a distinct molecular landscape dominated by high-rate of MDS-related and signalling/TK mutations. CMML-AML confirms poor outcomes and low response rates. HMA-VEN appears the preferred option for unfit patients and shows benefit also in those aged 60–75 years. Allo-SCT remains the only strategy associated with meaningful survival improvement.

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ACUTE MYELOID LEUKEMIA

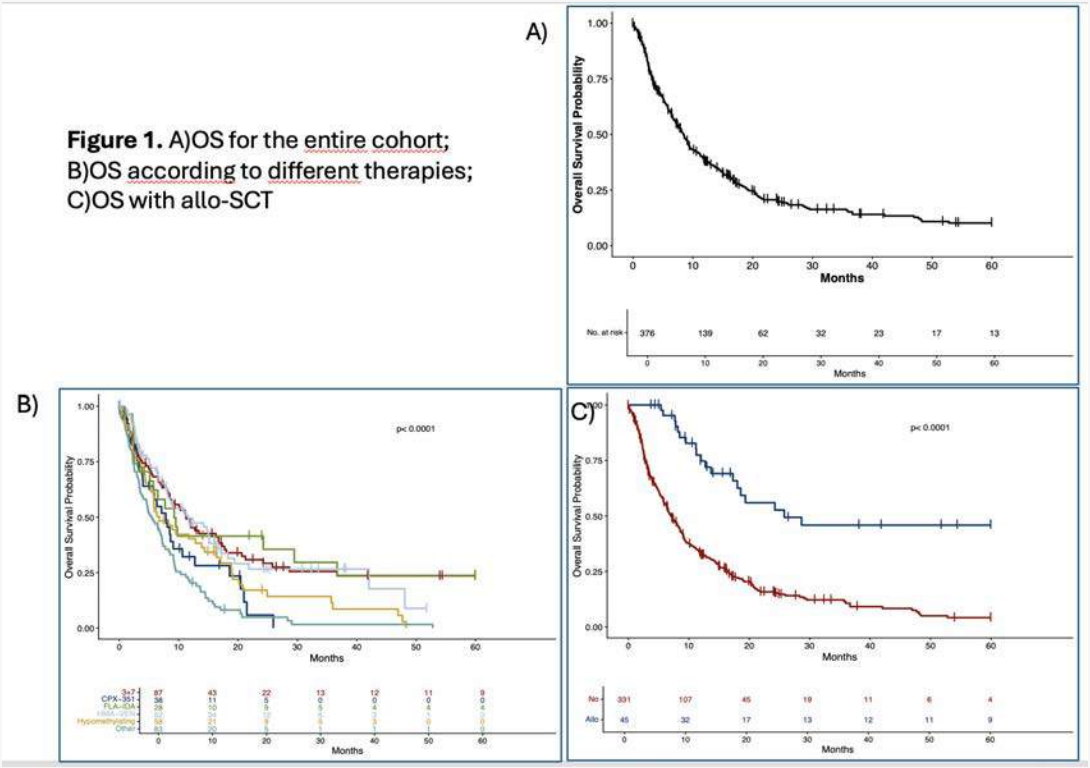

Figure 1. A)OS for the entire cohort; B)OS according to different therapies; C)OS with allo-SCT

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Acute myeloid leukemia

ADRENOMEDULLIN/CRLR AXIS PROTEIN EXPRESSION IN ACUTE MYELOID LEUKEMIA PATIENTS TREATED WITH NON-INTENSIVE REGIMENS: PRELIMINARY RESULTS FROM THE AML2220 STUDY

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CRLR gene expression has been extensively studied in acute myeloid leukemia (AML), mainly in intensively treated patients. Data on protein expression of the Adrenomedullin (ADM)/CRLR axis in patients treated with non-intensive regimens remain limited.AML2220 is a prospective study enrolling newly diagnosed AML patients without major cardiovascular comorbidities. Bone marrow samples were collected at baseline and follow-up. ADM/CRLR axis proteins (ADM, CRLR, RAMP2, RAMP3) and adhesion molecules (CD31, CD38, CD44/CD44v6) were assessed by multiparametric flow cytometry and expressed as the percentage of positive blasts.This analysis focuses on patients treated with hypomethylating agents ± venetoclax (HMA±Ven). Associations with response were evaluated using non-parametric tests. Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan–Meier method; patients were stratified by expression tertiles.Of 72 enrolled patients, 47 had baseline samples analyzed; 19 received non-intensive regimens (5 HMA, 14 HMA+Ven). Median age was 75.8 years (range 57.4–84.7). According to the WHO 2022 classification, 58% had myelodysplasia-related AML, 32% had defining genetic abnormalities, and 10% had AML defined by differentiation. TP53 mutations were observed in 21%.Median baseline expression was 54.3% (IQR 25.8–63.9) for ADM, 41.6% (IQR 13.5–62.1) for CRLR, 16.7% (IQR 9.8–28.5) for RAMP2, and 21.4% (IQR 12.6–39.7) for RAMP3.Across molecular and clinical features, NRAS-mutated cases (n=6) compared with wild-type showed a higher RAMP3/RAMP2 ratio (p=.028), but no other significant differences in ADM system expression.Increased level of ADM and its receptors positively correlated with CD31 and CD44v6 (p<.01), molecules involved in vascular/angiogenic processes and microenvironment-mediated resistance signaling.No differences in ADM/CRLR axis expression were observed between responders and non-responders, while higher CD38 expression was associated with achievement of CR/CRi (p=.009).Lower ADM system expression was associated with shorter EFS (ADM p=.010; CRLR p=.009; RAMP3 p=.009) and OS (ADM p=.012; CRLR p=.006; RAMP3 p=.006) across tertiles. Median OS for ADM was 1.61, 6.92, and 9.61 months (95% CI 0.00–3.38, 0.00–14.28, and 0.00–21.29).These data suggest that ADM/CRLR axis expression is linked to adhesion-related signaling pathways and may be a useful predictor of outcomes in patients treated with HMA±Ven, warranting validation in larger cohorts.

Acute myeloid leukemia

COMPARISON OF CAPILLARY ELECTROPHORESIS AND NGS-PCR BASED APPROACH FOR FLT3-ITD FOR MRD DETECTION IN AML

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Introduction. Molecular measurable residual disease (mMRD) in FLT3–internal tandem duplication (FLT3-ITD)-positive patients (pts) has emerged in recent years as a novel tool for the follow-up of acute myeloid leukemia (AML) pts. This next-generation sequencing (NGS) method has been proposed to achieve deep coverage of the FLT3 gene to identify FLT3-ITD variants with low variant allele frequency (VAF). In this study, we compared capillary electrophoresis (CE) and NGS to validate this approach in clinical practice.

Methods. We analyzed a cohort of 62 AML pts who were FLT3-ITD–positive at diagnosis, who were evaluated at different MRD time points during therapy. A total of 89 samples were assessed using both CE and NGS. CE was performed on the SeqStudio analyzer, while NGS was performed on the MiSeq Illumina. CE results were analyzed by GeneMapper software, NGS results were analyzed using the getITD software.

Results. Of the 89 samples, 59 were negative by both CE and NGS, 22 were positive by both methods, whereas 6 were positive only by NGS, and 2 were positive only by CE. The GetITD software requires at least two distinct supporting reads and cannot detect insertions shorter than 6 base pairs (bp), with a limit of detection of 0.006%. In contrast, the GeneMapper software can detect duplications or insertions as short as 1 bp. The two positive samples only by CE had an ITD of 6 bp, that GetITD could not detect. Upon repeating both CE and NGS analyses, CE results were reproducible. In contrast, among the six NGS-positive samples, only three were confirmed, whereas the remaining three were negative upon repeat sequencing. Of these, one sample showed a different ITD compared to that observed at diagnosis, while the other two showed the same ITD as at diagnosis.

Discussion. Our results suggest that CE is more reliable than NGS and that NGS is more prone to false-positive results. Furthermore, although CE is generally believed to have a sensitivity of 1–5%, by comparing NGS and CE results we demonstrated that CE can detect very low VAFs, down to 0.008%. In addition, CE is a user-friendly technique, characterized by lower cost, shorter turnaround time (TAT) (1–2 days), and the availability of validated software for data analysis. In contrast, NGS is a high-cost technique with longer TAT (5–7 days) and lacks fully validated analysis software. In summary, our findings indicate that, for FLT3-ITD mMRD assessment, CE represents a reliable and cost-effective alternative to NGS.

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Acute myeloid leukemia

HYPERLEUKOCYTOSIS IN ACUTE MYELOID LEUKEMIA: IMPACT ON EARLY MORTALITY AND OVERALL SURVIVAL

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Background. Hyperleukocytary presentation of acute myeloid leukemia (AML) is associated with a high incidence of life-threatening complications. However, its prognostic significance in AML patients remains highly debated and is not formally incorporated into the latest ELN 2022 risk stratification.

Aim. To investigate the impact of hyperleukocytosis, at thresholds of 50.000/µL and 100.000/µL, on early mortality (30- and 60-days) and survival in intensively treated AML patients (pts).

Results. Between 2006 and 2025, 425 pts were retrospectively studied at our centre; ELN risk classification was available for 402 (ELN 2010), 346 (ELN 2017), and 295 (ELN 2022) pts. In our cohort 78 pts (18.4%) presented with WBC ≥100.000/µL, while 178 (41.9%) had WBC ≥50.000/µL. No significant differences were observed in complete remission (CR) rate according to WBC-related thresholds (p=0.49 for WBC ≥50.000/µL, and p=0.87 for for WBC ≥100.000/µL). The cumulative incidence (CI) of early mortality was significantly higher in pts with WBC ≥50.000/µL (p=0.0006 at 30 days; p=0.0025 at 60 days) and ≥100.000/µL (p<0.0001 at both time points) (Fig1). In multivariable analysis, both WBC thresholds remained independently associated with 60-day mortality (HR 2.04, p=0.032; HR 2.67, p=0.003, respectively), together with age (HR 1.04; p=0.002 and p=0.005, respectively). In pts aged >60 yrs, CI of early mortality remained significantly higher for WBC ≥50.000/µL (p=0.045 at 30 and p=0.003 at 60 days), while only a trend was observed for WBC ≥100.000/µL, likely due to limited sample size. Furthermore, the CI of major clinical events (CTCAE grade >3) was significantly higher for both WBC thresholds (p<0.001). These findings were reflected in significantly inferior OS in pts with WBC ≥50.000/µL (p=0.0003), with no differences in DFS (p=0.27). Subgroup analysis across ELN 2010, 2017, and 2022 showed significantly worse survival in the intermediate-risk group at both WBC thresholds (ELN 2010: WBC ≥50.000/µL p=0.0003 and ≥100.000/µL p=0.0046; ELN 2017: p=0.0047 and p=0.044 respectively; ELN 2022: p=0.0006 for both) (Fig2). However, the smaller number of patients classified according to ELN 2017 and 2022 warrants cautious interpretation.

Conclusions. Hyperleukocytosis was associated with early mortality and appeared to be linked to reduced OS in the ELN intermediate-risk group. Further studies are warranted to determine whether less intensive approaches may reduce early mortality in this category.

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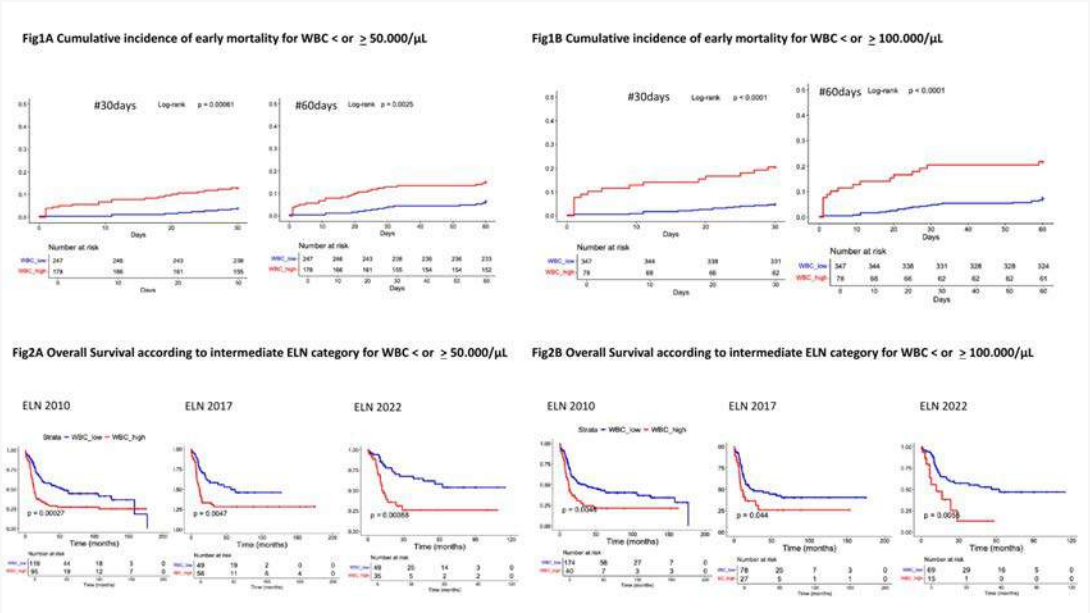
Acute myeloid leukemia



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Acute lymphocytic leukemia

GENOMIC INSTABILITY AS A PREDICTOR OF RELAPSE IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

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Background. T-ALL/LBL is characterized by a complex and highly heterogeneous genomic landscape. The integration of cytogenetic, molecular, and NGS approaches has enabled the identification of recurrent disease-associated alterations, several of which have emerging prognostic relevance. Among these, alterations of *NOTCH1/FBXW7*, *PHF6*, *EP300*, *IDH1/2*, *DNMT3A*, *IKZF1*, and components of the RAS and PI3K/AKT pathways emerged as relevant biomarkers in both pediatric and adult patients (Simonin 2024; 2025). Additionally, also genomic instability and chromothripsis have been associated with a higher risk of relapse (Arniani 2022; Balducci 2024).

Aim. To identify predictive genomic markers at diagnosis in T-ALL/LBL.

Materials and Methods. Systematic application of CytoScan HD and OncoScan CNV Plus arrays (Affymetrix) was incorporated into a multimodal molecular-cytogenetic diagnostic algorithm to investigate copy number variations (CNV)/cnLOH in 447 T-ALL/LBL, which included 359 adults and 88 children; 44% immature and 56% typical forms. Whole Transcriptome Expression array (Human Clariom S, Affymetrix) was performed in 381/447 cases to identify differentially expressed genes (DEGs).

Results. Overall, genomic instability, defined as the presence of ≥15 genomic events, was identified in 77 cases (17%), of which 35 exhibited chromothriptic events (CTH). Genomic instability was more frequent in adults than in children (19% vs 10%) and was significantly associated with blast immaturity (23% vs 11%; p=0.0006). Stratification by genetic subgroup revealed an enrichment of CTH within the *NOTCH1* (22%) and *HOXA* (15%) subgroups. Notably, within the *HOXA* category, cases harboring the oncogenic driver *NUP214* showed the highest proportion of CTH positivity (37%). CTH was significantly associated with alterations in the PRC2 complex (*SUZ12*, *EZH2*, and/or *EED*) (p=0.0008). Consistent with their immature transcriptional profile, upregulated DEGs included *CD34*, *MEF2C*, *MYCN*, *BAALC*, and the recently described high-risk marker *ZBTB16* (Lim, 2025).

Conclusions. Chromosomal instability appeared to be associated with relapsed/refractory (R/R) disease in children (55% vs 37%), but not in adults (52% vs 55%). In adults, however, 68% of CTH cases experienced R/R disease, suggesting a potential association between this genomic phenomenon and poorer outcomes in the adult population. These findings support the routine inclusion of CNV/cnLOH analysis in the diagnostic work-up of T-ALL/LBL.

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

FIRST-LINE TREATMENT OF CLL/SLL WITH THE ALL-ORAL COMBINATION OF SONROTOCLAX AND ZANUBRUTINIB ACHIEVES UNDETECTABLE MINIMAL RESIDUAL DISEASE RATES OF >90%, INCLUDING IN PATIENTS WITH DEL(17P)/TP53

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Background. Oral, fixed-duration BTKi-BCL2i combinations are effective, convenient first-line options for CLL. However, current regimens, including those using 2nd-generation BTKi, can be limited by low uMRD rates. Upgrading the BCL2i component of BTKi-BCL2i with sonro, a next generation BCL2i with ~14x pharmacological potency vs venetoclax, may lead to improved uMRD rates.

Aims. To report safety and efficacy results in patients with treatment-naive CLL/SLL treated with zanu+sonro (320 mg cohort) in a phase 1/1b study (NCT04277637), with a median follow-up of 30.9 months (range, 3.1-41.9 months).

Methods. Study treatment consisted of lead-in zanu 320 mg QD for 8-12 weeks, after which sonro was added with ramp-up to target dose (320 mg QD). Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose. Primary endpoint was safety. Secondary endpoints included overall response rate (ORR). Exploratory endpoints included blood uMRD4 rates per flow cytometry and next generation-sequencing (NGS).

Results. Of 86 patients in the sonro 320 mg cohort, 45 (52%) remained on treatment at data cut-off. Of patients who discontinued sonro, 85% (35/41) did so due to protocol-defined elective discontinuation. The most common (≥30%) treatment-emergent adverse events (TEAEs) were neutropenia (38%), contusion (38%), COVID-19 (33%), and upper respiratory tract infection (30%). Neutropenia was the most common grade ≥3 TEAE (29%). No TLS occurred, and no AEs led to death. In 84 efficacy-evaluable patients, the ORR was 100%, with 46 (55%) achieving complete response. Median time to response was 2.6 months (range, 1.5-9.1 months). No patients in the 320 mg cohort had progression (estimated 30-month PFS: 100%). The best uMRD4 rate assessed by flow cytometry was 99% (83/84) and 100% (10/10) in patients with del(17p)/TP53 mutations. Median time from reaching sonro target dose to uMRD was 3.0 months (range, 2.3-27.4 months), and the best uMRD4 rates by weeks 24, 48 and 96 were 81% (69/85), 91% (63/69) and 98% (55/56), respectively. No patient with uMRD4 reverted to detectable MRD4. In the NGS evaluable set, best uMRD5 (<10-5) was 86% (66/77). Updated results to be presented.

Conclusions. Sonro+zanu was well tolerated and achieved uMRD rates of >90%, including in patients with high-risk cytogenetics, and is being evaluated in two phase 3 clinical trials (NCT06073821, NCT07277231).

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD COMPARATIVE EFFECTIVENESS AND SAFETY PROFILE OF ACALABRUTINIB VERSUS ZANUBRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA: A MULTICENTRE ITALIAN STUDY

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Background. Bruton tyrosine kinase inhibitors (BTKis) have transformed the treatment landscape of chronic lymphocytic leukemia (CLL). Second-generation BTKis, acalabrutinib and zanubrutinib, were developed to improve tolerabili-

ty while maintaining efficacy. However, direct real-world comparative data between these agents remain limited.

Aims. To compare the effectiveness, safety, and treatment discontinuation patterns of acalabrutinib versus zanubrutinib in treatment-naïve and relapsed/refractory (R/R) CLL patients in routine clinical practice.

Methods. We conducted a multicentre observational study including 556 CLL patients treated outside clinical trials across 52 Italian centres. The primary endpoints were time to treatment discontinuation (TTD) and time to next treatment or death (TTNTD). A target trial emulation approach with inverse probability of treatment weighting (IPTW) was applied to adjust for baseline imbalances. Cox proportional hazards models were used to identify predictors of outcomes.

Results. The cohort included 415 patients treated with zanubrutinib and 141 with acalabrutinib. The median age was 76 years zanubrutinib cohort and 69 years acalabrutinib cohort. The two cohorts did not significantly differ in terms of sex, line of therapy, IGHV *mutational status, TP53* disruption and numbers of cardiovascular risk factors. At 12 months, discontinuation rates were significantly lower with zanubrutinib (9.0%) compared to acalabrutinib (28.7%; P<0.001) (Figure 1A). The 12-month TTNTD rate was higher with zanubrutinib (94.1% vs 76.5%; P<0.001) (Figure 1B). In weighted analyses, acalabrutinib was associated with shorter TTD (HR 3.68; 95%CI 2.28–5.94; P<0.001) (Figure 1C) and shorter TTNTD (HR 5.59; 95%CI 3.24–9.64; P<0.001) (Figure 1D). Age and TP53 disruption (after 6 months) were independent predictors of worse outcomes. Discontinuation occurred in 11.1% of zanubrutinib-treated and 28.4% of acalabrutinib-treated patients, mainly due to disease progression and toxicity, with similar rates of grade ≥3 adverse events of clinical significance.

Conclusions. In this large real-world cohort, zanubrutinib was associated with significantly longer treatment duration and improved survival free from next treatment or death compared to acalabrutinib. These findings support zanubrutinib as an effective and well-tolerated option in both frontline and R/R CLL settings, highlighting the importance of real-world evidence in guiding treatment selection.

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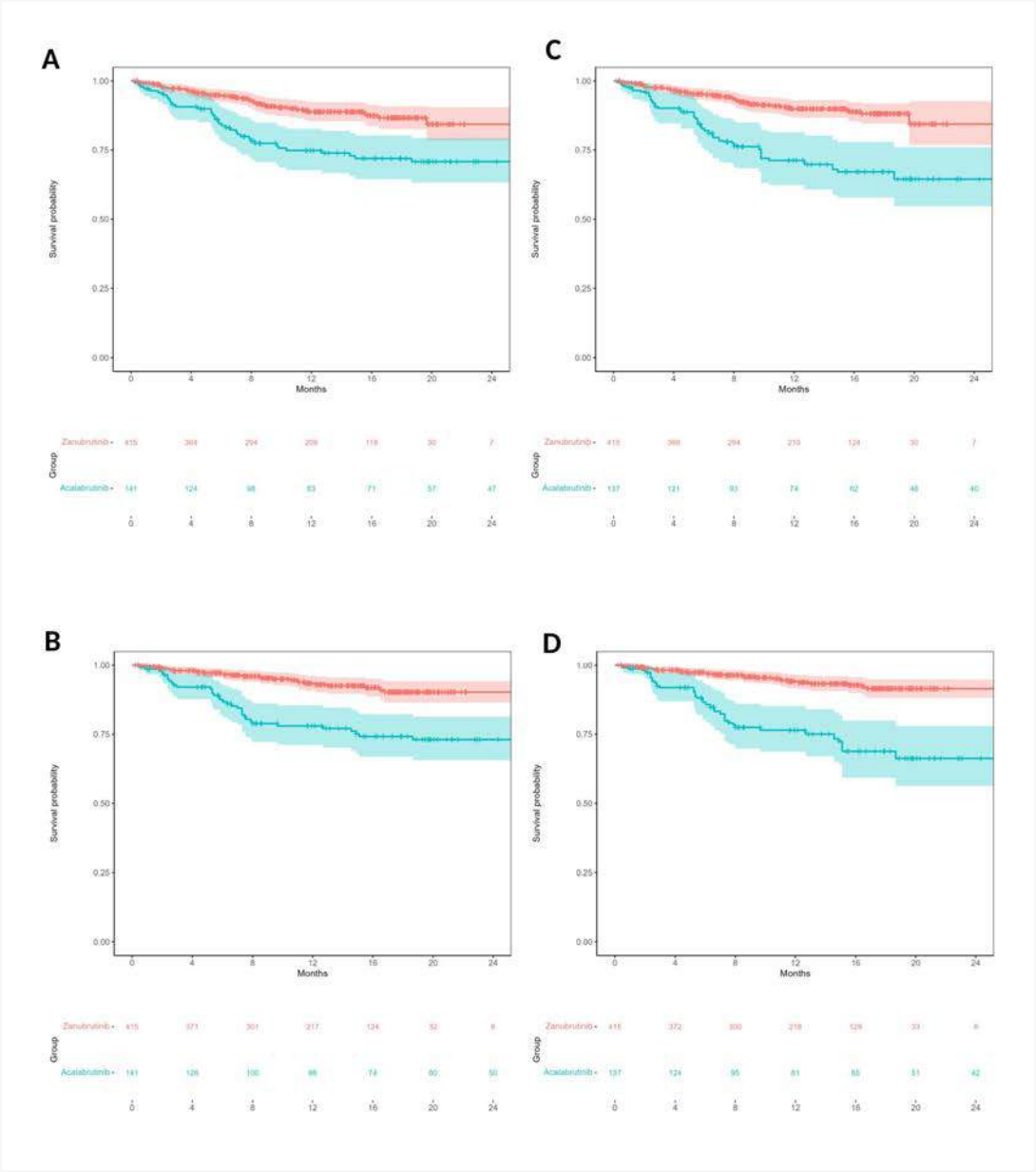
A
B
C
D
Survival probability
Months
Group
Zanubrutinib
Acalabrutinib

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-LIFE EXPERIENCE OF IBRUTINIB PLUS VENETOCLAX AS FRONT-LINE THERAPY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AN ERIC STUDY

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Background. Clinical trials have shown the efficacy of ibrutinib plus venetoclax (I+V) in CLL. This all-oral, fixed-duration regimen is approved for treatment-naïve CLL/SLL based on the phase II CAPTIVATE and phase III GLOW trials. Discontinuation due to adverse events (AEs) was 5% in CAPTIVATE and 10.4% in GLOW, which enrolled more comorbid patients. We hypothesized that appropriately selected patients of all ages can tolerate and benefit from I+V.

Methods. This is an interim analysis of the THRIVE study, a retrospective multicenter study evaluating afety and efficacy of I+V outside clinical trials. Eligible patients had untreated CLL/SLL, were ≥18 years, completed 3 ibrutinib (I) lead-in and initiated venetoclax (V). Treatment consisted of 3 cycles of I (420 mg daily), followed by 12 cycles of V with standard ramp-up (20–>400 mg). The primary endpoint was discontinuation due to toxicity; secondary endpoints included response rate, survival and safety.

Results. Data from 220 patients from 45 institutions of 11 countries were collected, 4 discontinued I before V and 14 had <3 months of follow-up; 202 was our treated population. Median age was 65 years (IQR 56–70); 59.9% were male. ECOG ≥2 was present in 12.3%. Unmutated IGHV was seen in 62.6%; del(17p) in 3.6%, and TP53 mutations in 4.1%After a median follow-up of 10.3 months, 7 (3.4%) patients discontinued treatment, 1 developed Richter transformation and 1 died of lung cancer. Discontinuation rate in a

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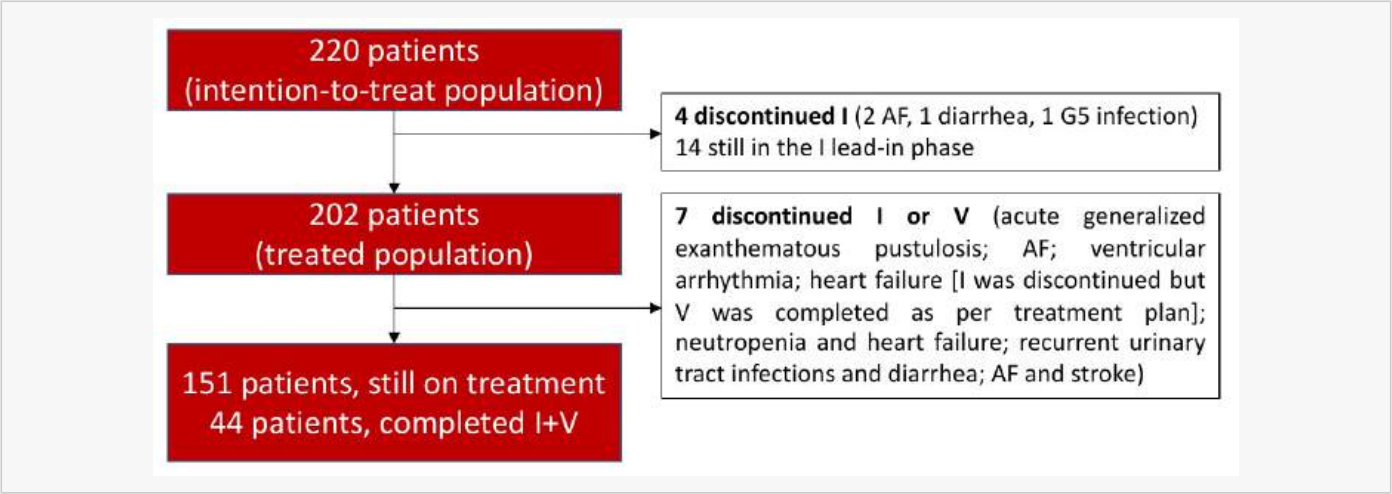
CAPTIVATE-like population (i.e. ≤70 years) was 3.2% and GLOW-like (i.e ≥65 without del(17p)) 4.9%. Among patients who discontinued treatment, 5 (71.4%) had at least one co-morbidity, the most common was hypertension (3/7)Among 190 evaluable patients with at least 6 months of follow-up, overall response rate was 95.6%. Any-grade adverse events (AE) occurred in 61.6%, and the most common grade ≥3 AE were neutropenia (23.8%), infections (7.09%) and anemia (4.5%). Nineteen (9.4%) patients developed cardiovascular events, 11 (5.4%) arrythmias (7 of grade ≥3 and 1 ventricular arrythmias), 6 (3.0%) hypertension (4 of G≥3), 2 (1%) heart failure.Laboratory TLS was seen in 3.6%, without clinical TLS cases. No severe bleeding occurred. No treatment-related deaths occurred.

Conclusions. I+V is effective and well tolerated in real-world practice, with lower discontinuation rates than clinical trials, including older patients. Longer follow-up is needed to assess progression-free survival and time to next treatment



Chronic lymphocytic leukemia and other lymphoproliferative syndromes

PIRTOBRUTINIB IN TREATMENT-NAÏVE PATIENTS WITH CLL/SLL: POOLED RESULTS FROM BRUIN CLL-313 AND BRUIN CLL-314

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Background. Pirtobrutinib, a highly selective, non-covalent Bruton tyrosine kinase inhibitor (BTKi), is approved globally for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent BTKi. BRUIN CLL-313 and BRUIN CLL-314 are open-label, randomized phase 3 studies evaluating pirtobrutinib for therapy of pts with CLL/SLL, including in the treatment-naïve (TN) setting [versus bendamustine plus rituximab (BendaR; CLL-313, NCT05023980) and versus ibrutinib (CLL-314, NCT05254743)].

Methods. Pooled data from TN CLL pts randomized to receive pirtobrutinib from CLL-313 and CLL-314 were used to assess efficacy [overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)] and safety. PFS and OS estimates were calculated by the Kaplan-Meier method. All pts (253) randomized within each study to receive pirtobrutinib were included in efficacy analyses and all pts (252) who received pirtobrutinib treatment were included in safety analyses.

Results. A total of 253 TN pts, median age of 66 yrs, were assigned to receive pirtobrutinib (CLL-313 n=141; CLL-314 n=112); all but one received treatment. Among pts with evaluable samples 134/233 (58%) had unmutated IGHV, 14/253 (6%) had del(17p) and 21/220 (10%) had mutated TP53. Efficacy was consistent between the two studies (Table). Overall, ORR was 93.3%. Median PFS was not reached; the 24-month PFS rate was 93.2% (95%CI, 89.1-95.8). Median OS was also not reached; the 24-month OS rate was 97.5% (95%CI, 94.6-98.9). Median duration of therapy was 29.1 months. Treatment discontinuation due to TEAEs occurred in 4.8% of pts with 1.6% treatment related. Any-grade infection occurred in 59.9% of pts; neutropenia in 18.3% and grade ≥3 bleeding in 2.4%. Any-grade hypertension occurred in 10.7% of pts and atrial fibrillation/flutter was reported in 2.8%.

Conclusions. In 253 TN pts with CLL randomized on two phase 3 studies, pirtobrutinib showed a high ORR and favorable 24-month PFS and OS rates. The safety profile was consistent with prior studies using pirtobrutinib in more heavily treated pts, with low rates of atrial fibrillation/flutter, hypertension and TEAE-related discontinuations. These findings reinforce the potential of pirtobrutinib as a meaningful and clinically relevant treatment option for pts with TN disease.

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Table. Efficacy of Pirtobrutinib in TN patients with CLL/SLL

ORR includes a best response of partial response or better

	Parameter	CLL-313 N = 141	CLL-314 N = 112	Pooled TN pts N=253
ORR	ORR, % (95% CI)	94.3 (89.1, 97.5)	92.0 (85.3, 96.3)	93.3 (89.5, 96.0)
PFS	24-month PFS rates, % (95% CI)	92.7 (86.8, 96.0)	94.3 (87.8, 97.4)	93.2 (89.1-95.8)
	Median FU, months	28.1	22.4	27.7
OS	24-month OS rates, % (95% CI)	97.8 (93.3, 99.3)	97.2 (91.5, 99.1)	97.5 (94.6-98.9)
	Median FU, months	32.7	26.7	29.5

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL WORLD OUTCOMES OF 50 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH PIRTOBRUTINIB AFTER A COVALENT BRUTON TYROSINE KINASE INHIBITOR AND A BCL2 INHIBITOR: A GIMEMA STUDY

G. M. Rigolin[1], A. Visentin[2], M. Nicolosi[3], A. Tomasso[4], R. Murru[5], S. Pepe[6], R. Marasca[7], L. Farina[8], A. Fresa[9], A. Arcari[10], V. Innao[11], E. Albi[12], C. B. Savelli[13], C. Giordano[14], E. Pennese[15], C. Vitale[16], J. Oliveri[17], I. Ferrarini[18], C. Salvetti[19], M. Foglietta[20], L. Arletti[21], M. Cavallari[22], N. Franzoni[23], R. Moia[24], E. Conte[25], A. Liso[26|31], M. Bullo[27], M. I. Del Principe[28], V. Arena[29], F. Paoloni[29], A. Piciocchi[29], L. Scarfò[12|30], P. Ghia[12|30], A. Cuneo[1]

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Because real-world data on the effectiveness of the non-covalent BTKi pirtobrutinib in CLL patients who had received a covalent BTKi and venetoclax are limited, we analyzed the outcome in a nationwide named-patient program. The data were obtained from the GIMEMA CLL2121 study, an observational study aimed at collecting clinicobiologic data of CLL patients diagnosed in Italy.The endpoints of this analysis were overall response rate (ORR), time to discontinuation for progression, death and toxicity (TPDT), obtained by censoring all patients who discontinued the study drug for reasons other than progression, death or toxicity, time to treatment discontinuation (TTD) and overall survival (OS).-Fifty patients with double exposed CLL were treated with pirtobrutinib at 28 Italian centers. Median age was 70y (range 51- 87). Median time from diagnosis to first dose of pirtobrutinib was 9.6y (IQ: 7.5-14.22). Other baseline characteristics are shown in table 1.ORR was 57%. With a median follow-up of 9.7 months (IQR 3.39;24.38) the estimated 12--month probability to be on treatment, using TPTD as endpoint, was 66% (95% CI: 50 - 87). The median TTD was 13.3 months (95% CI: 10.1 - NA), with a 58% probability of being on treatment at 12 months (95% CI: 42 - 79). The reasons of discontinuation in 16 patients were failure in 5, death in 6, toxicity in 1 and other causes in 4. An estimated 80% probability of being alive at 12 months was observed (95% CI: 68 - 94). ORR, TPDT, TTD and OS by subgroup analyses by age and TP53 showed results consistent with the overall trend. Causes of death were CLL progression in 6 patients, Richter transformation in 4, others in 5.Grade 3-4 adverse events were reported in 11 patients: 3 had an infection, 3 had neutropenia; febrile neutropenia, diarrhea, chest pain, pulmonary toxicity, and increased transaminase levels were recorded in 1 patient each. One patient had fungal pneumonia, and 1 patient had an episode of atrial fibrillation (grade not reported).In this real-world analysis objective endpoints were adopted. Our findings show that pirtobrutinib was highly effective in a heavily pre-treated patient population. Though the number of patients is relatively small the effectiveness was not influenced by unfavorable clinicobiologic characteristics.

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Table 1

Characteristic	% of pts
Sex (*M/F*)	60/40
uIGHV/mIGHV	74/26
TP53 mutated (yes/no)	50/50
17p- (yes/no)	30/70
Binet stage A or B/C	62/38
N. of previous therapies (2/3/4+)	14/42/44

Hodgkin's Lymphoma

LONG-TERM RISK OF SECOND MALIGNANCIES FOLLOWING SURVEILLANCE IMAGING IN YOUNG ADULTS AND ADULTS SURVIVORS WITH HODGKIN LYMPHOMA

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Federico II University

Several studies suggest that ionizing radiation from medical imaging is associated with an increased risk of cancer among young adults and adults (YA&A), even at cumulative doses < 50 mSv. The estimated radiation from a single 18FDG PET/CT is approximately 14.5 mSv vs 0.1 mSv for a single chest radiography (C-XR). Studies have shown that excess exposure to ionizing radiation from medical imaging occurred during follow-up in survivors of Hodgkin lymphoma (HL).The previously published multicenter randomized trial on routine surveillance imaging for relapse detection in YA&A with advanced-stage HL enrolled 300 patients (in 2 arms) achieving complete response after first-line treatment in the Hematology, Internal Medicine and Oncology units of the Federico II University (Naples, Italy). All patients completed the 6 anthracycline-based chemotherapy scheme; a similar proportion in the two arms received consolidative radiotherapy. In the standard arm, surveillance was performed with 18FDG PET/CT; in the experimental arm modern ultrasonography combined with C-XR was used. Imaging was scheduled at 4, 8, 12, 16, 20, 24, 30, 36, 48, 60, 84, and 108 months after treatment completion. After a median 5-year follow-up, 80 patients (27%) relapsed. The study met its equivalence objective: sensitivity was 100% for PET/CT and 97.5% for US/C-XR. Extended follow-up provided mature data on second malignancies. The cumulative radiation dose per detected relapse was 449.5 mSv with PET/CT vs 10.2 mSv with US/C-XR. After a median 20-year follow-up (range, 16-24 years), a total of 23 secondary malignancies occurred in the PET/CT group (five solid cancers, and 18 hematological malignances), and a total of 9 secondary malignancies occurred in the US/C-XR group (4 solid cancers, and 5 hematological malignancies), yielding a cumulative second malignancy rate of 14% in the PET/CT group versus 6% in the US/C-XR (P= 0.013; 95% CI, 1.16–5.10; Table). In univariate analysis, age at exposure and receipt of radiotherapy was not significantly associated with the second malignancy risk rate. After a median follow-up of 20 years, overall survival was 90% in the PET/CT group and 96% in the ultrasonography/C-XR group, with 15 and 5 deaths observed, respectively (Figure). These findings suggest that additional radiation from surveillance imaging increases long-term risk of second malignancies, especially hematologic cancers, consistent with radiation-related bone marrow carcinogenesis suggesting that repeated exposure from surveillance scans may preferentially contribute to the development of early radiation-associated hematologic neoplasms.Although newer PET uses lower-dose CT, PET/CT remains important for accurate relapse detection and for diagnostic accuracy by reducing false-positive and false-negative findings associated with PET alone. Overall, our results underscore the importance of carefully balancing benefits and risks when selecting follow-up imaging strategies and support minimizing radiation exposure whenever clinically feasible in survivors of HL.

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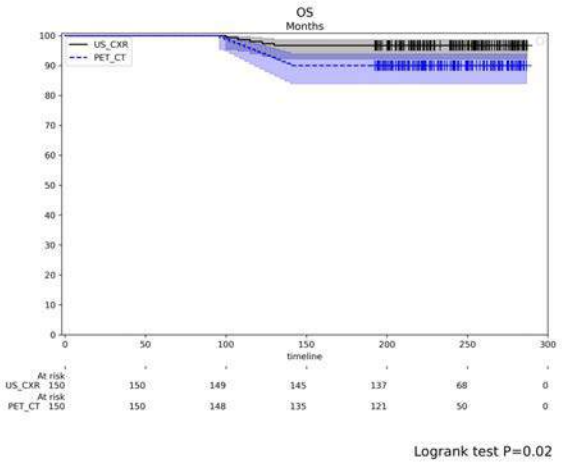
Table. Estimated Radiation Exposure and Characteristics of Second Tumors

Radiation Exposure and Second Tumor Characteristics	US/Chest Radiography Arm (n = 150)	PET/CT Arm (n = 150)	*P* Value
Radiation exposure from imaging (mSv)			
Dose for each scan	0.1	14.5	
Dose needed to detect one relapse	10.2	449.5	0.0002
Second malignancy characteristics			
No. of second malignancies	9 (6%)	23 (15%)	0.013
Sex			
Female	3	8	1
Male	6	15	
Age (y)†	46.5 (20–69)	45 (23–70)	0.85
First-line treatment			
Chemotherapy only	3	8	
Chemotherapy plus radiation therapy	6	15	1
Time to second malignancy (mo)†	37 (12–108)	74 (12–280)	0.10
Second malignancy type			
Solid cancer	4	5	0.45
Thyroid papillary cancer	1	2	
Colon adenocarcinoma	2	2	
Gastric adenocarcinoma	1	1	
Hematologic malignancies	5	18	0.09
Large B-cell NHL	..	6	
Acute myeloid leukemia	3	5	
Acute lymphoblastic leukemia	2	5	
Chronic myeloid leukemia	..	1	
Multiple myeloma	..	1	

Note. —Unless otherwise indicated, data are number of patients.
† Data are reported as medians, with ranges in parentheses.
For statistical analyses, the χ^2 test (or Fisher exact test, as appropriate) was used to compare categorical variables, and the Mann–Whitney U test was used to compare continuous variables between the two groups.
Among the five patients with AML in the PET/CT arm, three had acute leukemia of ambiguous lineage. Among the five patients with ALL in the PET/CT arm, two had mixed-phenotype acute leukemia.
NHL, non-Hodgkin lymphoma.



Hodgkin's Lymphoma

MANAGING TOXICITY IN REAL-WORLD BV-AVD FOR ADVANCED HODGKIN LYMPHOMA: IMPACT ON TREATMENT FEASIBILITY AND OUTCOMES

C. Mazzoni[1|2], B. Casadei[2], L. Argnani[1], V. Stefoni[1|2], C. Pellegrini[2], G. Gugliotta[2], A. Broccoli[1|2], M. Carella[1|2], G. Bagnato[1|2], N. Fabbri[1|2], G. Gabrielli[1|2], M. Mutti[1|2], M. Gentilini[1|2], A. Desiderio[1|2], S. Citro[1|2], F. Visini[1|2], F. D'Aniello[1|2], P. L. Zinzani[1|2]

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Background. Brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) has shown superior efficacy versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in advanced Hodgkin lymphoma (aHL) in the ECHELON-1 trial (Connors et al., N Engl J Med 2018). However, its increased toxicity may limit real-world feasibility.

Methods. We conducted a monocentric retrospective study on 55 treatment-naïve stage IV HL patients treated with BV-AVD, assessing toxicity, feasibility, and effectiveness.

Results. Fifty-two patients were evaluable and stratified into BV-AVDx6 (n=36), completing six cycles, and BV-AVD_hold (n=16), who switched to ABVD or discontinued due to toxicity or progression. BV-AVD_hold patients were older (median 47.5 vs 29.1 years; p=0.0173) and had more cardiovascular and renal comorbidities (p=0.0344 and p=0.0308). Dose reductions in the BV-AVDx6 group were frequent (BV n=11; AVD n=2; both n=3), mainly due to peripheral neuropathy (PNP), constipation, or hematologic/infectious toxicity. Despite this, the overall response rate was 97.1% (35 CR, 1 progressive disease (PD)). In the BV-AVD_hold group, 13 patients switched to ABVD after a median of 1.5 cycles; among 11 receiving reduced-dose ABVD, responses included 6 CR, 2 PR, and 3 PD. Four discontinued BV-AVD without further treatment. Overall, 208 non-hematologic and 79 hematologic adverse events (AEs) occurred, leading to 47 and 32 treatment delays (median 7 days), respectively. The most frequent AEs were PNP (61.8%, 47.1% grade ≥2), constipation (44.2%), and neutropenia (60%, all grade ≥3). BV doses >80 mg were significantly associated with grade ≥2 PNP (OR 14.25; p=0.004). Median progression-free survival (PFS) was 8–10 months in BV-AVD_hold patients, whereas it was not reached in the BV-AVDx6 group (p=0.0001); on multivariable Cox analysis adjusted for age, completion of 6 cycles was associated with a significantly reduced risk of progression (HR 0.065, 95% CI 0.007–0.580; p=0.014).

Conclusions. BV-AVD confirms high real-world effectiveness in aHL, despite frequent dose modifications. However, treatment feasibility is reduced in older and comorbid patients, with toxicity—particularly PNP—representing a major concern. Notably, patients who discontinue treatment early due to toxicity have worse outcomes. These findings underscore the importance of careful *a priori* patient selection and proactive toxicity management to preserve treatment benefit.

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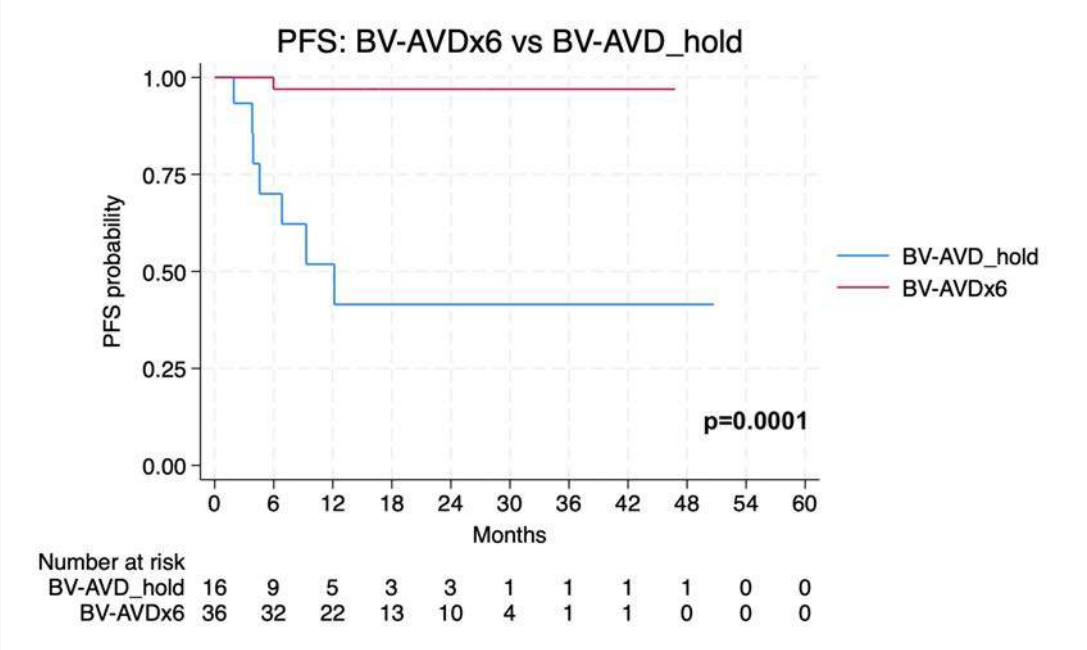
PFS: BV-AVDx6 vs BV-AVD_hold
PFS probability
1.00
0.75
0.50
0.25
0.00
p=0.0001
0 6 12 18 24 30 36 42 48 54 60
Months
BV-AVD_hold
BV-AVDx6
Number at risk
BV-AVD_hold 16 9 5 3 3 1 1 1 1 0 0
BV-AVDx6 36 32 22 13 10 4 1 1 0 0 0

Hodgkin's Lymphoma

E-HIPI PROGNOSTIC SCORE AS A TOOL FOR IDENTIFYING LOW-RISK PATIENTS AT DIAGNOSIS: A MULTICENTRIC ITALIAN COHORT

M. De Ferrari[1], A. Cellini[1], G. Manfredi Assanto[2], A. Romano[3], G. Santuccio[3], C. Vitale[4], M. Montalbano[4], F. Angotzi[1], A. Serafin[1], N. Danesin[1], A. Bevilacqua[1], M. D'Antiga[1], G. Leone[1], M. Coscia[5], F. Di Raimondo[3], I. Del Giudice[2], F. Piazza[1], L. Trentin[1], A. Visentin[1]

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Classic Hodgkin Lymphoma (cHL) has currently an extremely favourable prognosis, owing to modern therapeutic PET-guided strategies. Consequently, the need to update traditional prognostic factors has led to the development of the Early-Stage Hodgkin Lymphoma International Prognostic Index (E-HIPI), which relies on baseline characteristics at the time of diagnosis.We evaluated the ability of the E-HIPI to predict 2-year Progression-free survival (PFS) stratifying the cohort into risk classes.Patients with early stage cHL treated between 2007 and 2025 at 4 different Italian centres were included. All were treated with PET-guided approaches based on ABVD or BEACOPP. E-HIPI was calculated using published coefficients for sex, maximum tumor diameter (MTD), albumin and hemoglobin (hb). Eligible patients were selected according to the E-HIPI's plausibility exclusions, in keeping with the variable ranges described in the original publication [AM Rodday, NEJM Evid, 2025].A total of 264 patients were included, of whom 130 (49%) were female; the median age at diagnosis was 31 years. Overall, 244 (92%) subjects had stage II disease, bulky disease was present in 84 (32%) patients, and 64 (24%) presented with B-symptoms. Treatment was based on ABVD or HD17-like regimens, 38% received radiotherapy. Mean baseline characteristics of interest were: albumin 4 g/dL (2.6–5.3), MTD 5.6 cm (1.5–15) and hb 13 g/dL (8.5–16.5). E-HIPI was first validated in our cohort, with a C-index of 0.654 (95% CI 0.55–0.75). After a median follow-up of 62 months (2–178), 8 (3%) patients died and 38 (14%) experienced disease progression or relapse. Overall, the 2-year PFS was 87.4% (95% CI 83.5–91.6). We stratified patients into risk categories defined as low risk (<25th percentile), high risk (>75th percentile), and intermediate risk in between. Focusing on the low-risk group, PFS differences were statistically significant compared with both high- and intermediate-risk groups, with HR=0.25 (CI 95% 0.08–0.76; p=0.015) and HR=0.34 (CI 95% 0.12-0.98; p=0.047) respectively. The 2-year OS was 100% in every risk group.E-HIPI demonstrated strong performance in predicting 2-year PFS in early-stage cHL. Specifically, it may identify low-risk patients at diagnosis which can be cured with a short course of chemotherapy, supporting less intensive treatment strategies in this subgroup. Novel combinations should be explored in high-risk cHL.

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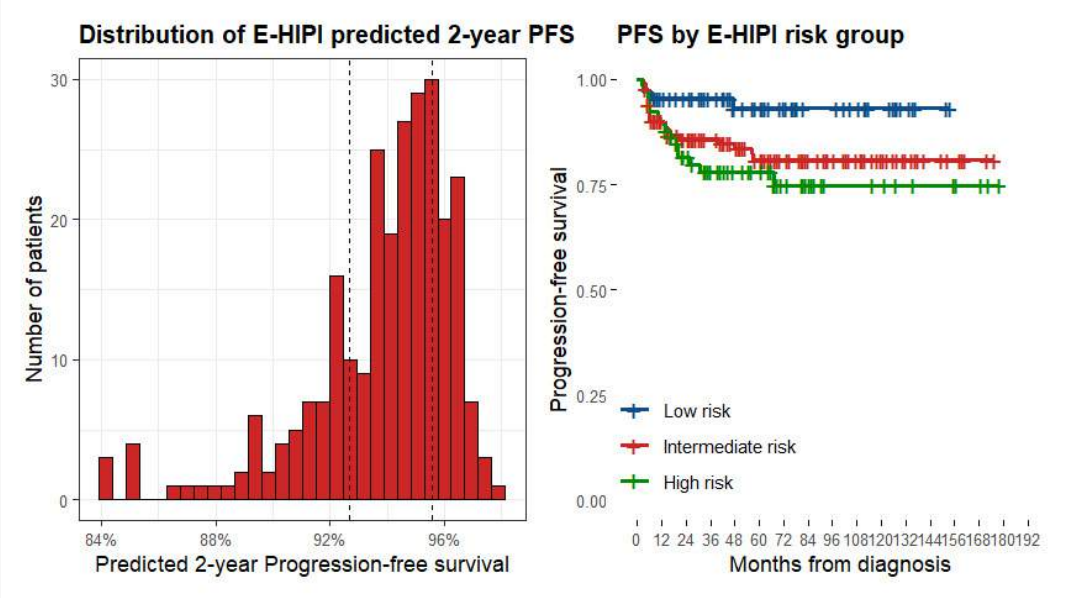
Distribution of E-HIPI predicted 2-year PFS
Number of patients
Predicted 2-year Progression-free survival
84%
88%
92%
96%
PFS by E-HIPI risk group
Progression-free survival
Months from diagnosis
Low risk
Intermediate risk
High risk

Hodgkin's Lymphoma

PROGNOSTIC VALUE OF INTERIM PET IN YOUNG ADULTS AND ADULTS FRONTLINE TREATED WITH BRENTUXIMAB VEDOTIN+AVD FOR CLASSIC HODGKIN LYMPHOMA

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Background. BV+AVD is increasingly used for frontline treatment of advanced-stage cHL, but real-world data in young adults and adults (Ya&A) remain limited. We conducted a multicenter retrospective study to evaluate efficacy and safety of frontline BV+AVD in patients aged 18–59 years with newly diagnosed stage III-IV cHL treated in specialized centers.

Methods. We retrospectively analyzed 150 consecutive real-life patients scheduled to receive 6 cycles of BV+AVD across four institutions in Southern Italy. The primary endpoint was PFS. Secondary endpoints included end-of-treatment (EoT) complete metabolic response, treatment delivery, and toxicity. Interim FDG-PET (iPET) was assessed using the Deauville score (DS), defining negativity as DS 1–3 and positivity as DS 4–5; it was assessed post hoc and not used to guide treatment.

Results. Fifty patients (30%) had at least one ECHELON-1 ineligibility criterion, including comorbidities and/or adverse performance status. Overall, 147/150 patients (98%) completed six cycles of BV+AVD, with a median relative dose intensity of 100%; 16/150 (11%) received dose reduction and/or discontinuation. At EoT FDG-PET, 140/150 patients (93.3%; 95% CI, 88.1%–96.8%) achieved complete metabolic response. Of the remaining patients, four (2.7%) received consolidative radiotherapy for residual nodal masses with DS 4, three received autologous hematopoietic stem cell transplantation for DS 5 at EoT-PET, and three died for toxicity before EoT-PET. Grade ≥2 peripheral neuropathy, cardiotoxicity, and febrile neutropenia occurred in 13%, 7%, and 3% of patients, respectively. With a median follow-up of 24 months, 2-year PFS was 91% (95% CI, 86.4%–95.8%). After 2 cycles, iPET was negative in 137/150 patients (91%); DS distribution was DS 1–2 in 87/150 (58%), DS 3 in 50/150 (33%), DS 4 in 10/150 (6.7%), and DS 5 in 3/150 (2%).iPET showed strong predictive value: all patients with negative iPET achieved complete metabolic response vs 46.2% with positive iPET ($p<0.001$) (Figure). Within interim PET-positive patients, 60% of DS 4 converted to complete response, whereas DS 5 identified a subgroup with higher risk of treatment failure.

Conclusions. In this large real-world Ya&A cohort with advanced-stage cHL, frontline BV+AVD achieved high dose intensity, durable complete metabolic remission, and favorable 2-year PFS without routine consolidative radiotherapy. iPET was negative in most patients and strongly associated with EoT complete response.

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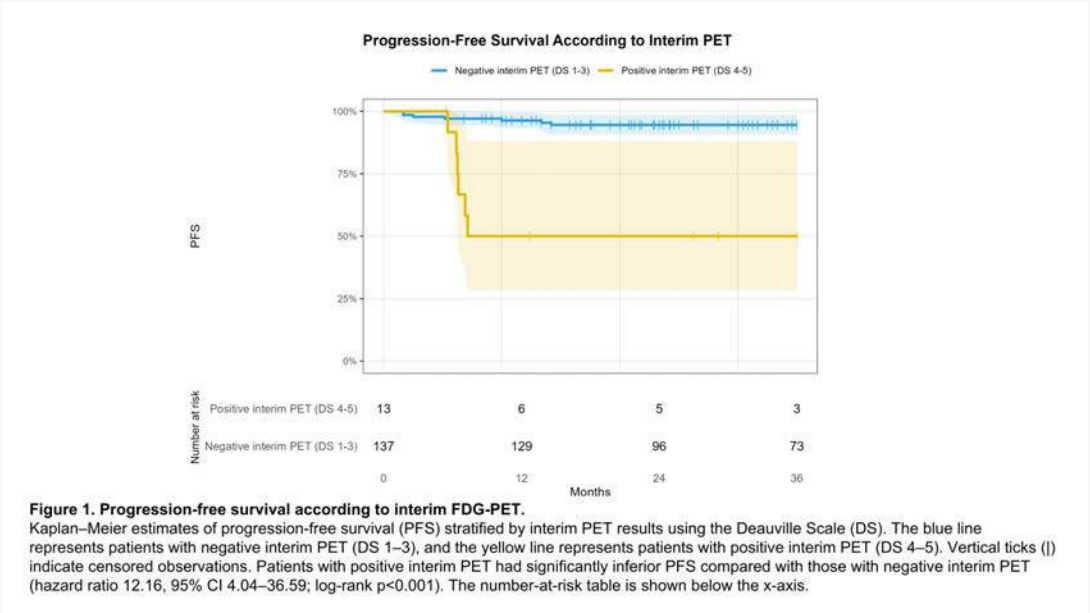

Figure 1. Progression-free survival according to interim FDG-PET.
Kaplan–Meier estimates of progression-free survival (PFS) stratified by interim PET results using the Deauville Scale (DS). The blue line represents patients with negative interim PET (DS 1–3), and the yellow line represents patients with positive interim PET (DS 4–5). Vertical ticks (|) indicate censored observations. Patients with positive interim PET had significantly inferior PFS compared with those with negative interim PET (hazard ratio 12.16, 95% CI 4.04–36.59; log-rank p<0.001). The number-at-risk table is shown below the x-axis.

Chronic myeloid leukemia

PERMANENT DISCONTINUATION OF TYROSINE KINASE INHIBITOR DURING THE FIRST 36 MONTHS OF FRONTLINE TREATMENT IN CHRONIC MYELOID LEUKEMIA: A CAMPUS CML SCORE PROPOSAL

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Background. The first 3 years of frontline therapy with Tyrosine Kynase Inhibitors (TKI) are crucial for optimal response in patients (pts) with Chronic Myeloid Leukemia (CML): in this early phase, different toxicities or suboptimal response/resistance may occur, leading to permanent TKI discontinuation and need for a 2nd-line switch.

Aims. To evaluate in a large real-life cohort of CML pts all events leading to permanent frontline TKI discontinuation in the first 3 years and to propose a new "ad hoc" score.

Methods. 1713 CML pts diagnosed from 1/2012 and 12/2019 at 35 Centres were retrospectively analysed. To derive a clinical score, a stratified data partition was performed, splitting pts into a training cohort (TC) (1/3, n=573) and an independent validation cohort (VC) (2/3, n=1140). Variables significant by univariate analysis were considered for multivariable modeling. A data-driven grid search approach was applied to determine optimal cut-off values for these variables.

Results. Total number of pts who had discontinued frontline TKI at the 36th month of observation was 536/1713 (31.3%), being higher with IM (366/976, 37.5%) than with 2G-TKIs (170/737, 23.0%) (p<0.001). Among the 536 pts who discontinued frontline TKI, the main causes were hematologic toxicity (34, 6.4%), extra-hematologic toxicity (171, 31.9%), primary resistance (228, 42.5%), secondary resistance (27, 5.0%), blast phase evolution (23, 4.3%), unrelated deaths (42, 7.8%) and other causes (11, 2.1%). At multivariate analysis, age (OR 1.01, 95% CI 1.00–1.02; p = 0.002), hemoglobin (OR 0.87, 95% CI 0.82–0.92; p < 0.001) and spleen size (OR 1.07, 95% CI 1.03–1.11; p < 0.001) retained an independent predictive role for TKI discontinuation. The optimal combined cut-offs identified by the grid-search procedure were age ≥ 63.5 years, hemoglobin ≤ 10.2 g/dL, and the presence of any degree of splenomegaly. The score based on these 3 cut-offs (low-risk 0-1 variables, high risk 2-3 variables) enabled a strong risk stratification of pts, effectively predicting the likelihood of TKI discontinuation. This discriminative ability was observed in both the TC and VC, and was maintained across subgroup analyses stratified by frontline imatinib versus 2G-TKI treatment (Figure).

Conclusions. This score, based on simple clinic parameters, enables effective stratification of the risk of TKI early discontinuation, facilitating practical bedside implementation and supporting a more personalized therapeutic strategy.

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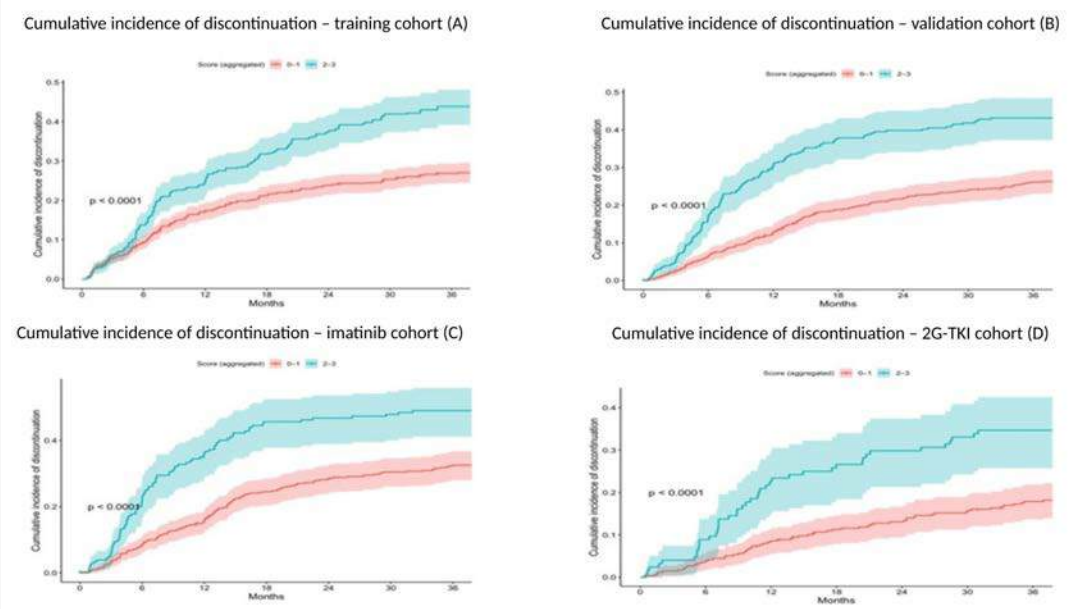
Chronic myeloid leukemia



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Chronic myeloid leukemia

CARDIOVASCULAR EVENTS IN CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH NILOTINIB: LONG-TERM RESULTS OF THE PROSPECTIVE MULTICENTER KIARO STUDY

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The KIARO study is a prospective multicenter trial that enrolled 186 newly diagnosed CML patients (pts) treated with first line TKIs (89 imatinib, 59 nilotinib, and 38 dasatinib). It demonstrated that nilotinib treatment is associated with a significant increase in pro-inflammatory and pro-oxidative biomarkers (hs CRP, oxLDL, and IL 6/IL 10 and TNF α/IL 10 ratios), defining a biological milieu potentially underlying the higher incidence of cardiovascular events (CVEs) compared with imatinib and dasatinib. In the present analysis, we evaluated the long-term incidence of CVEs after an extended 5 year follow-up in pts enrolled in the KIARO study, with particular focus on those treated with nilotinib, and investigated the contribution of traditional cardiovascular risk factors, comorbidities, and genetic predisposition.Cardiovascular risk factors, baseline SCORE risk, occurrence and type of CVEs, ongoing TKI at the time of the event, and selected cardiovascular-related genetic polymorphisms were assessed. Overall, 36 CVEs (19%) were documented: 10 events had been previously reported, while 26 (14%) occurred during the extended follow up. CVE incidence was higher with nilotinib (12/59; 20.3%) compared with imatinib (8/89; 9%) and dasatinib (5/38; 13.2%). Additional CVEs occurred during later lines with bosutinib (8 CVEs) and ponatinib (3 CVEs). Among nilotinib pts, CVEs occurred mainly in first line (8/12, 66,6%) and in younger pts (median age 55 vs 68 years for other TKIs). Half of these pts were classified as low Sokal risk. Ischemic cardiac or cerebrovascular events accounted for 75% of CVEs in the nilotinib group versus 42% with other TKIs, suggesting a predominant atherothrombotic pattern. Pts experiencing CVEs on nilotinib showed a lower burden of traditional CV risk factors (≥2 risk factors: 50% vs 71% other TKIs). No significant differences in CV related genetic polymorphisms were observed between nilotinib associated CVEs and those related to other TKIs.Long-term follow-up of the KIARO cohort confirms a higher incidence of CVEs in CML pts treated with nilotinib, even in the absence of high baseline CV risk. The predominance of ischemic events in younger, low risk pts provides indirect evidence of a nilotinib induced pro-inflammatory and pro-oxidative milieu that appears to persist over time during treatment, contributing to an increased atherothrombotic risk.

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Chronic myeloid leukemia

CHRONIC PHASE CML WITH SOLE P190 (E1A2) BCR::ABL1: PRELIMINARY DATA FROM THE ITALIAN NETWORK/CML CAMPUS

S. P. Pascale[1], R. Nuccorini[1], R. Latagliata[2], M. Tribelli[3], L. De Carolis[4], M. Annunziata[5], D. Rapezzi[6], F. Muriano[7], A. Maggi[8], D. Cattaneo[9], M. D'Adda[10], A. Sicuranza[11], M. Bonifacio[12], U. Markovic[13], D. Facchinelli[14], E. Abruzzese[15], S. Russo[16], G. Binotto[17], G. Spinosa[18], A. Amendola[1], I. Chitarrelli[1], N. Filardi[1], A. Matturro[1], D. Vertone[1], M. Pizzuti[1], M. Cimminiello[1]

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Background. Chronic myeloid leukemia (CML) is typically driven by the BCR::ABL1 p210 transcript, while the p190 (e1a2) isoform is classically associated with acute lymphoblastic leukemia and only rarely reported as the sole molecular driver in chronic phase CML. Published data are limited to isolated case reports and small series and suggest a potentially more aggressive clinical behavior compared with classical p210-CML, although this remains controversial. Evidence from the literature indicates variable responses to tyrosine kinase inhibitors (TKIs), with no established consensus on optimal management or prognosis for this rare entity.

Methods. To evaluate long-term outcomes in a series of patients (pts) with CP-CML harboring isolated p190 BCR::ABL1 in CMLCampus Italian Network, 25 pts from 16 Italian Centers were retrospectively evaluated. All pts were treated in a real-world setting with TKI selected according to physician choice, Hematologic and molecular responses were assessed with standardized quantitative PCR for BCR::ABL1.

Results. Main features at diagnosis are reported in the Table. Eleven pts (median age 71 years) were treated with imatinib (IMA) and 14 (median age 65 years) with second--generation TKIs (2G-TKI). Stratification of pts with p190 according to EUTOS long-term survival (ELTS) score was 40% low, 32% intermediate and 20% high, with a different risk distribution compared with the overall CAMPUS CML cohort of 1,433 pts (59.5% low, 28.2% intermediate, 12.3% high). All pts achieved CHR and 19 (76%) a MMR after a median of 2 lines of TKI therapy, compared with 50% reported in the Mayo Clinic cohort (n=10). Among the 6 pts not in MMR, 1 is receiving imatinib, 2 asciminib and 3 ponatinib. Mutational analysis by NGS was performed in only one of these 6 pts, revealing mutations in the ASXL1 and DNMT3A genes. At a median follow-up of 5.5 years from diagnosis (range 1–20), two (8%) deaths were reported, both from causes unrelated to CML. In addition, no disease transformation into AP-CML or BP-CML or AHSCT was observed.

Conclusions. Chronic phase CML with isolated p190 is a rare and biologically heterogeneous entity: in our cohort, results seem comparable to classical p210 CML, but higher rate of high ELTS score suggests a potential adverse prognostic role. Larger studies are needed to better define prognostic factors and optimize treatment approaches in this uncommon CML subtype.

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Table. Clinical Characteristics of patients

Variables	All patients (n = 25)
Age in years at diagnosis; median (range)	66 (31–88)
Females, n (%)	12 (48)
Leukocytes × 10^9/L; median (range)	51 (9–278)
Blood monocyte %; median (range)	10 (2–67)
Blood eosinophil %; median (range)	2 (0-9)
Blood basophil %; median (range)	2 (0-13)
Blood blast %; median (range)	0 (0-4)
Hemoglobin g/dL; median (range)	13 (7–18.0)
Platelets × 10^9/L; median (range)	302 (78–923)
Palpable splenomegaly, n (%)	6 (30)
ELTS	
Low risk	10 (40)
Intermediate risk	8 (32)
High risk	5 (20)
Not available	2 (8)
Tyrosine Kinase Inhibitor response at any time:	
Complete hematologic response (CHR), n (%)	20 (100)
Major molecular response (MMR), n (%)	19 (76)
Follow-up period from diagnosis in years; median (range)	5.5 (1–20)
Deaths, n (%)	2 (10)
Both deaths were unrelated to CML	

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Chronic myeloid leukemia

IMPACT OF AGE, COMORBIDITIES AND SYSTEMIC INFLAMMATION ON MOLECULAR RESPONSE IN ELDERLY PATIENTS WITH CHRONIC MYELOID LEUKEMIA

A. Votto, M. Maggiorelli, A. Brunetti, F. Guerrini, C. Bono, S. Galimberti

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Background. In elderly patients with chronic myeloid leukemia (CML), treatment outcomes may be influenced not only by disease-related factors but also by age, comorbidities, and systemic inflammation. While the Charlson Comorbidity Index (CCI) is widely used to estimate clinical frailty, its impact on molecular response remains unclear. Inflammatory markers such as the systemic inflammation response index (SIRI) may better reflect biological interactions.AimsTo evaluate the impact of age, comorbidities (CCI), and inflammatory status (SIRI) on molecular response in a cohort of CML patients aged ≥70 years.

Methods. We retrospectively analyzed 53 CML patients aged ≥70 years at diagnosis. Major Molecular Responses (MMR3) and Deep Molecular Response (DMR) were assessed across treatment lines. Patients were stratified by age (<80 vs ≥80 years), CCI, and SIRI at diagnosis and at 6 months. Logistic regression and ROC curve analyses were performed to identify predictors of DMR.

Results. MMR3 and DMR were achieved in 66.0% and 50.9% of patients, respectively. Patients aged ≥80 years showed significantly lower response rates compared to those <80 (DMR: 14.3% vs 64.1%, p=0.0018). CCI was not associated with MMR3 or DMR. In contrast, SIRI at 6 months was significantly lower in patients achieving DMR (p=0.029). ROC analysis demonstrated a good predictive performance of SIRI at 6 months for DMR (AUC 0.76), with an optimal cut-off of 1.1 (sensitivity 80%, specificity 77.8%). In multivariate analysis, neither CCI nor SIRI reached statistical significance, likely due to limited sample size, while age retained a strong impact.

Conclusions. In elderly CML patients, chronological age rather than comorbidity burden appears to influence molecular response. SIRI at 6 months may represent a dynamic and clinically relevant biomarker associated with treatment efficacy, potentially reflecting the biological interaction between systemic inflammation and disease. These findings suggest that inflammatory markers may complement traditional clinical scores in risk stratification of older CML patients.

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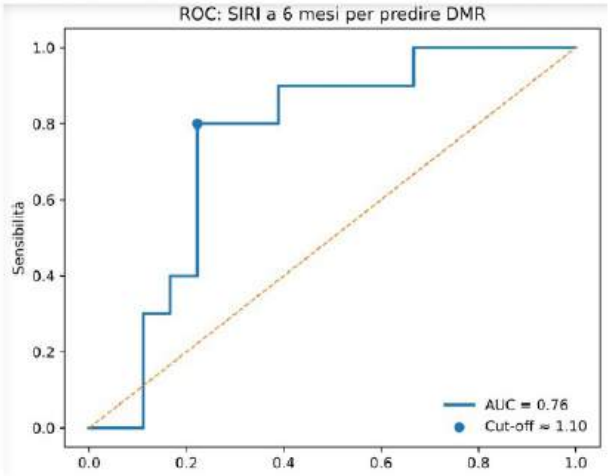
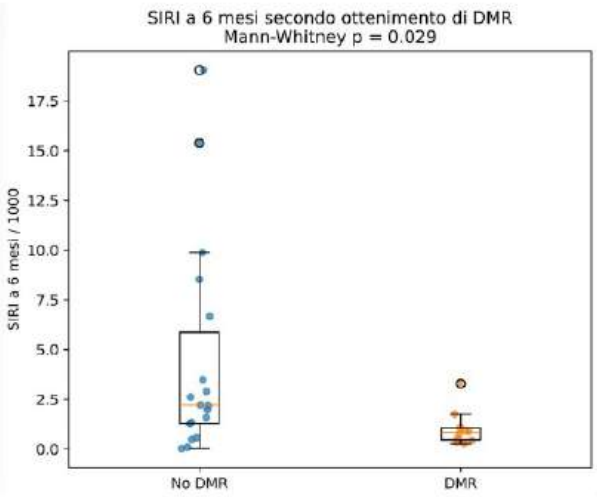
Chronic myeloid leukemia





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Chronic myeloid leukemia

INTEGRATIVE IN VITRO AND TRANSCRIPTOMIC ANALYSIS REVEALS LITHIUM AS A POTENTIAL ADJUVANT IN CML TARGETING PI3K SIGNALLING AND MICROENVIRONMENT REMODELLING

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm driven by the constitutive activity of the BCR::ABL1 tyrosine kinase. While tyrosine kinase inhibitors (TKI) represent the standard of care, additional strategies targeting leukemic cell survival and the bone marrow microenvironment are under investigation. Lithium carbonate (Li), a well-established mood stabilizer, has been reported to modulate hematopoiesis, promote myeloid differentiation, and interfere with signalling pathways relevant to leukemogenesis.Our preliminary results on CML cell lines (K562, LAMA-84, KCL-22) confirmed that lithium, especially with TKIs, reduces cell viability and metabolic activity, decreases BCR::ABL1 expression, and induces myeloid differentiation markers.To further explore lithium-associated molecular effects in a clinical context, we performed total RNA-seq of mononuclear cells isolated from peripheral blood samples of eight subjects: two CML patients treated with TKI+Li because of bipolar disorder (combo group), three bipolar patients treated with Li in monotherapy, two healthy controls, and two CML patients treated with a TKI (age and sex matched to the combo group). Notably, the availability of bipolar patients receiving Li as monotherapy and, even more, CML patients with bipolar disorder represents a rare and scarcely explored clinical setting, providing a unique opportunity to dissect Li-specific and combinatorial effects in vivo.Differential gene expression analysis identified PI3 and CHI3L1 as significantly modulated genes, both showing downregulation with single treatments (TKIs or Li alone) and a further reduction in the combined TKI+Li condition, suggesting an additive or synergistic effect. PI3 is involved in the PI3K signalling pathway, a key downstream axis of BCR::ABL1 that drives leukemic cell proliferation and survival. Its progressive downregulation may reflect enhanced inhibition of this oncogenic pathway. In parallel, CHI3L1, associated with extracellular matrix and microenvironment remodelling, including inflammatory and stromal interactions, was similarly reduced, indicating a potential impact of Li on microenvironmental dynamics.Overall, these findings support a pleiotropic role of Li in CML, affecting both intracellular oncogenic signalling and the leukemic microenvironment, and highlight its potential as an adjuvant therapeutic strategy in combination with TKIs. Further studies are warranted to validate these preliminar observations.

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Non-Hodgkin's Lymphoma

PET-INTEGRATED NOMOGRAMS FOR SURVIVAL PREDICTION IN PATIENTS WITH LARGE B-CELL LYMPHOMA TREATED WITH CAR T-CELL THERAPY

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CAR T-cell therapy is effective in relapsed/refractory large B-cell lymphoma (R/R LBCL), although outcomes remain heterogeneous. Therefore, reliable pre-infusion prognostic stratification is crucial. 18F-FDG PET/CT provides quantitative metabolic parameters reflecting tumour burden and biology, and their integration with clinical and laboratory variables may improve prognostic modelling. We aimed to develop PET-integrated nomograms for predicting PFS and OS in patients with R/R LBCL treated with CART. This post-hoc analysis of a retro-prospective single-center study included 141 (111 DLBCL NOS, 30 HGBCL) patients treated in routine clinical practice. Baseline variables included demographics, histology, prior therapies, bridging therapy (BT), laboratory parameters (LDH, CRP, Hb, WBC and lymphocyte [lym] count), and PET metrics (SUVmax/mean, MTV, TLG, extranodal/bone involvement). Primary endpoints were PFS and OS. Variable selection used adaptive LASSO with bootstrap stability (500 resamples). Multivariable Cox models were developed and evaluated using C-index, time-dependent AUC, and calibration plots. At apheresis, 43% of patients had bulky disease, 73% were at stage III/IV, and 93% were refractory to their most recent line of treatment. 84% received BT. The CART products infused were axi-cel, tisa-cel and liso-cel in 109, 30 and 2 patients, respectively. Median PFS and OS were 13.3 and 40.2 months, with a median f-up of 12.2 months. On univariate analysis, PET parameters (SUVmax/mean, MTV, TLG, bone involvement) and laboratory variables (LDH, CRP, Hb) were associated with outcomes ($p<0.05$). In the multivariable OS model: Hb (HR 0.72,$p<0.001$) and lym (HR 0.41,$p=0.004$) were protective, while bone involvement (HR 2.36,$p=0.006$), WBC (HR 1.17, $p<0.001$) and BT (HR 1.90,$p=0.189$) were adverse. Refractoriness to the last therapy showed the highest risk increase (HR 6.3), though borderline significant($p=0.07$). The OS model showed a C-index of 0.798. In the PFS model, Hb remained protective (HR 0.78,$p<0.001$), while BT (HR 2.53,$p=0.02$) and refractoriness were adverse(HR 1.48,$p=0.108$). AUCs at 12 months was 0.86 for OS and 0.71 for PFS. In conclusion, we developed PET-integrated nomograms predicting outcomes after CART in R/R LBCL highlighting the interplay between host factor (Hb, lym count), tumour burden and clinical resistance patterns (BT, refractoriness). These tools may support individualized decision-making and warrant prospective multicentre validation.

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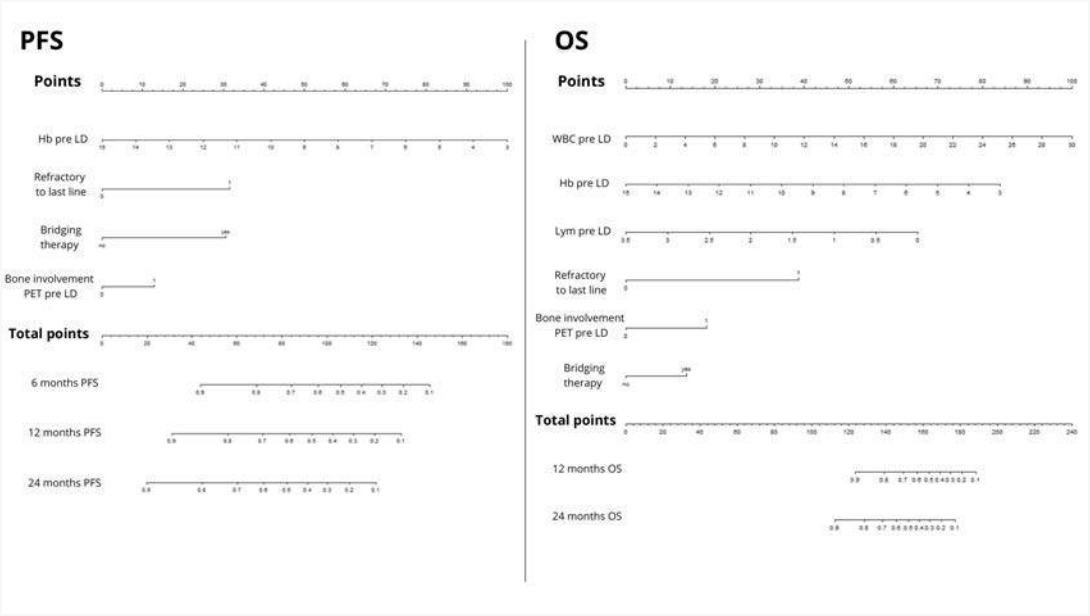
PFS
Points
Hb pre LD
Refractory to last line
Bridging therapy
Bone involvement PET pre LD
Total points
6 months PFS
12 months PFS
24 months PFS
OS
Points
WBC pre LD
Hb pre LD
Lym pre LD
Refractory to last line
Bone involvement PET pre LD
Bridging therapy
Total points
12 months OS
24 months OS

Non-Hodgkin's Lymphoma

PIRTOBRUTINIB IN RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: RESULTS FROM THE PHASE 1/2 BRUIN STUDY (FINAL UPDATE)

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Pirtobrutinib (pirto) a highly selective, non-covalent BTKi and was safe and effective in the phase 1/2 BRUIN study in patients (pts) with R/R MCL. Here, we report final pirto efficacy and safety in R/R MCL assessed over 5 years in the phase 1/2 BRUIN study.Pts who received ≥1 prior therapy (including BTKi) were eligible. Endpoints: overall response rate (ORR), duration of response (DOR) and progression-free survival (PFS) (all IRC-assessed/Lugano 2014 criteria). Data cutoff was 27Jan2025 (median follow-up [f/u] of 17.5 months (mo) [0.5-69.6]).A total of 153/166 pts received pirto 200 mg/day. 92% received prior cBTKi, of which 84.% discontinued (DC'd) due to progressive disease [PD], and 10% due to toxicity. cBTKi-pre-treated pts had a median age of 70 yrs (range, 46-88). Median number of prior therapies: 3 (range:1-9); 11 (7.2%) were cBTKi pre-treated (txd) and 6 (42.9%) cBTKi naïve pts remained on tx. ORR of cBTKi pre-txd pts was 49.3% (95%CI:41.1-57.6), with 15.8% complete responses (CR) (n=24) and 33.6% partial responses (PR) (n=51). Median DOR (n=75) of 21.6 mo (95%CI:9.2-27.2) at a median f/u of 24 mos. ORR was 43.0% and 93.3%, among PD and toxicity groups, respectively. Median PFS and OS for cBTKi pre-txd pts was 5.6 mo (95%CI:5.3-9.2) and 23.9 mo (95%CI:17.3-51.5), respectively. ORR of cBTKi naïve pts was 85.7% (95%CI:57.2-98.2), with 50.0% CR (n=7) and 35.7% PR (n=5); median DOR 42.7 mo (95%CI:25.8-NE) at a median f/u of 43 mos. Median PFS and OS of cBTKi naïve pts: 44.6 mo (95%CI:16.7-NE) and not reached (95%-CI:33.5-NE), respectively. Most frequent TEAEs (n=166): fatigue (31.9%), diarrhea (22.9%), anemia (18.1%), and dyspnea (18.1%). Most common Grade ≥3 TEAE: neutropenia (13.3%), Grade ≥3 infections (21.1%). There were 13 (7.8%) fatal TEAE, with 4 (2.4%) infections; 8 (4.8%) dose reductions, 6 (3.6%) pirto DCs.Pirto continues to demonstrate efficacy in pts with heavily pre-txd R/R MCL regardless of cBTKi use. Safety profile of pirto remained favorable with a low-rate of dose reductions/DCs due to drug-related toxicity. No new safety signals were identified after up to 5 yrs of f/u.

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Non-Hodgkin's Lymphoma

PRO-MIND: EARLY PROGRESSION-FREE SURVIVAL AND RESPONSE TO TAFASITAMAB-LENALIDOMIDE IN PATIENTS WITH AUTOLOGOUS STEM CELL TRANSPLANTATION-INELIGIBLE RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Progression risk in R/R DLBCL is often highest early after treatment initiation. The first 3-month assessment is a critical decision point (Nedved. The Oncologist 2023). The trajectory of pts not achieving CR at this timepoint is poorly characterized (Duell. Haematologica 2021). We evaluated temporal distribution of PFS events and the probability of achieving a CR vs PD among pts not in CR at first assessment in PRO-MIND.PRO-MIND is a prospective, multicenter, observational study evaluating Tafa-Len in ASCT-ineligible adults with R/R DLBCL (NCT06299553). In this interim analysis (N=90; cutoff 25 July 2025), PFS was defined from treatment start to PD/death, with censoring at last contact. Early failure was defined as PFS events within 3 mos. Time-varying progression risk was assessed using a prespecified piecewise exponential model (intervals: 0-3, 3-6, >6 months), reporting event rates (events per patient-mo) with 95% CrI. Using 3-month assessment (T0) as a landmark, post-T0 probabilities of achieving CR vs PD in pts not in CR (PR/SD) were estimated using Bayesian competing-risks model (posterior means, 95% CrI).The cohort was high risk: median age 77 yrs; IPI ≥3 65%; Ann Arbor stage III-IV 84%; primary refractory 58%; most pts had received 1 prior line of systemic treatment (70%). ORR was 53%; the CR rate was 32%. Median follow-up was 4.5 mo (34 PFS events). Early failure occurred in 27% of pts. 71%, 21%, and 9% of PFS events were within 0-3, 3-6, and >6 mos, respectively. Event rates declined over time: 0.11 events per patient-mo (95% CrI, 0.07-0.17) at 0-3 mos, 0.06 (95% CrI, 0.02-0.13) at 3-6 mos, and 0.02 (95% CrI, 0.00-0.06) >6 mos. Among pts not in CR at T0 (PR, n=16; SD, n=3), trajectories diverged. For PR, probability of achieving CR was 0.35 (95% CrI, 0.13-0.67) at 6 mos and 0.42 (95% CrI, 0.17-0.75) at 12 mos, while probability of PD was 0.32 (95% CrI, 0.11-0.65) at 6 mos and 0.40 (95% CrI, 0.15-0.74) at 12 mos. SD estimates were exploratory given the sample size (n=3). Median PFS was 14.4 mos (95% CI, 6-NE).In this analysis, most PFS events in pts with R/R DLBCL treated with Tafa-Len were within the first 3 mos, with fewer events thereafter, indicating declining PD risk. In pts with PR at 3 mos, estimated probabilities of CR conversion and PD over 6-12 mos were similar, suggesting PR may deepen beyond first assessment. Preliminary findings support treatment beyond 3 mos in pts with PR, although longer follow-up and larger sample sizes are needed.

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Non-Hodgkin's Lymphoma

SUB-ANALYSIS OF THE ITALIAN CART-SIE STUDY: OUTCOME AFTER BREXU-CEL THERAPY FAILURE IN MANTLE CELL LYMPHOMAS

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Background. Brexucabtagene autoleucel (brexu-cel) demonstrated high activity in relapsed or refractory mantle cell lymphoma (R/R MCL) after chemoimmunotherapy and Bruton tyrosine kinase inhibitor (BTKi). However, disease recurrence after CAR T-cell remains frequent.

Methods. Aim of the present analysis was to investigate the pattern of treatments and the outcome following progression post CAR T-cell therapy in R/R MCL patients enrolled in the CART-SIE study, an ongoing multicenter observational study collecting data on all consecutive lymphoma patients treated with commercial CAR T-cells in 22 Italian centers.

Results. From 2019 to 2025, 172 R/R MCL patients were infused and evaluable for the analysis. Median age was 64 years (IQR: 56,70), 91% (157) had Ann Arbor stage III or IV; median number of prior therapies was 3 (IQR: 2,3), with 53% (92) refractory to last treatment; 56% (97) failed a prior autologous stem cell transplantation (SCT), 100% were exposed to BTKi. Histological subtypes were 74% (127) classic MCL, 17% (29) blastoid and 9% (16) pleomorphic variant. Bridging therapy was performed in 75% (130) patients. At day 30 after infusion, overall response rate was 78% (135), with 67% (116) complete response; 7 patients died due to treatment related toxicities or progressive disease. At a median follow-up of 18.5 months (IQR: 6.97, 24.67), median progression free survival (PFS) was 30.4 months (CI 95% 16.02-NA), with 1-year PFS of 63% (95% CI: 55.5%-71.4%), and median overall survival (OS) was not reached (CI 95% 30.39-NA), with 1-year OS of 79% (95% CI: 72.4%-85.9%). After Brexu-cel infusion, failures were 51, and the median time to progression was 5.9 months (IQR: 2.99, 11.35); 41/51 received one or multiple salvage therapy: chemotherapy in 31% (13), bispecific antibodies in 19.5% (8), BTKi in 48% (20), and others therapies in 13% (5). The median post relapse OS was 7.3 months, with 1-year pr-OS 40.3% (95% CI: 27.3%-59.5%). In univariable Cox models, the use of bispecific antibodies was associated with improved pr-OS, while a inferior pr-OS was found in case of use of chemotherapy as salvage post-CAR T, inefficacy of the bridging therapy and a high CAR-HEMATOTOX at baseline.

Conclusions. The outcome of R/R MCL patients failing Brexu-cel is very poor. Our data suggest that bispecific antibodies may represent an effective salvage backbone. The role of bispecific antibodies and consolidation with allo-SCT requires further investigation.

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Non-Hodgkin's Lymphoma

DYNAMICS AND CLINICAL IMPACT OF CLONAL HEMATOPOIESIS IN DIFFUSE LARGE B-CELL LYMPHOMA THROUGH MULTI-COMPARTMENT GENOMIC PROFILING

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Background & Aims. Clonal hematopoiesis (CH) in diffuse large B-cell lymphoma (DLBCL) remains incompletely defined across compartments and over time. We aimed to: i) characterize CH from myeloid and plasma cfDNA compartments; ii) evaluate its clinical impact and association with molecular subtypes; iii) assess clonal dynamics at baseline and end of treatment (EOT); iv) determine the prevalence and significance of tumor-infiltrating (TI)-CH.

Methods. We analyzed 453 samples from 157 newly diagnosed DLBCL patients treated with R-CHOP–like regimens using CAPP-Seq–based NGS targeting 28 CH-related genes. Samples included PB granulocytes (n=151), serial plasma cfDNA (baseline n=107, cycle 3 n=47, EOT n=92), and lymph node biopsies (n=56). DLBclass clustering was available in 102 cases.

Results. Median age was 67 years. CH was detected in granulocytes in 37.7% of patients, with DNMT3A (20.5%) and TET2 (14.6%) most frequently mutated (Fig1A). DNMT3A mutations were enriched in the C3 molecular subtype (p=0.005) (Fig1B). Both DNMT3A and TET2 mutations associated with increased secondary malignancy risk (5-year CIF 16.3% vs 7.1%, p=0.03; 19.4% vs 7.3%, p<0.001). cfDNA sequencing showed 97.5% sensitivity for granulocyte CH mutations, with strong inter-compartment VAF correlation (r=0.89, p<0.001). PB CH+ patients showed marginally reduced PFS (55.8% vs 64.1%) and OS (69.8% vs 72.4%), without statistical significance (Fig1C). CH prevalence rose from 34.7% at baseline to 50.5% at EOT (p<0.001), with median VAF increasing from 1.44% to 2.44% (p<0.001). PPM1D mutations, rare at baseline (1.1%), became prominent after CIT (16.3% at EOT) and showed highest clonal fitness (Fig1D). All mutations were detectable by cycle 3, with greater clonal expansion from baseline to C3 than from C3 to EOT, suggesting an early CIT-driven bottleneck effect (p=0.03). In tissue biopsies, TI-CH occurred in 42.9% of patients, predominantly DNMT3A (21.4%) and TET2 (16.1%). TI-DNMT3A+ patients had significantly inferior PFS (33.3% vs 70.9%, p=0.009) and OS (41.7% vs 83.7%, p<0.001), remaining significant after IPI adjustment (Fig1E).

Conclusions. Multi-compartment CH profiling in DLBCL reveals frequent detection, enrichment in specific molecular subtypes, and association with secondary malignancy risk. R-CHOP promotes CH clonal expansion, including early PPM1D emergence. While PB-CH did not significantly impact survival, TI-DNMT3A mutations are an independent adverse prognostic factor for PFS and OS.

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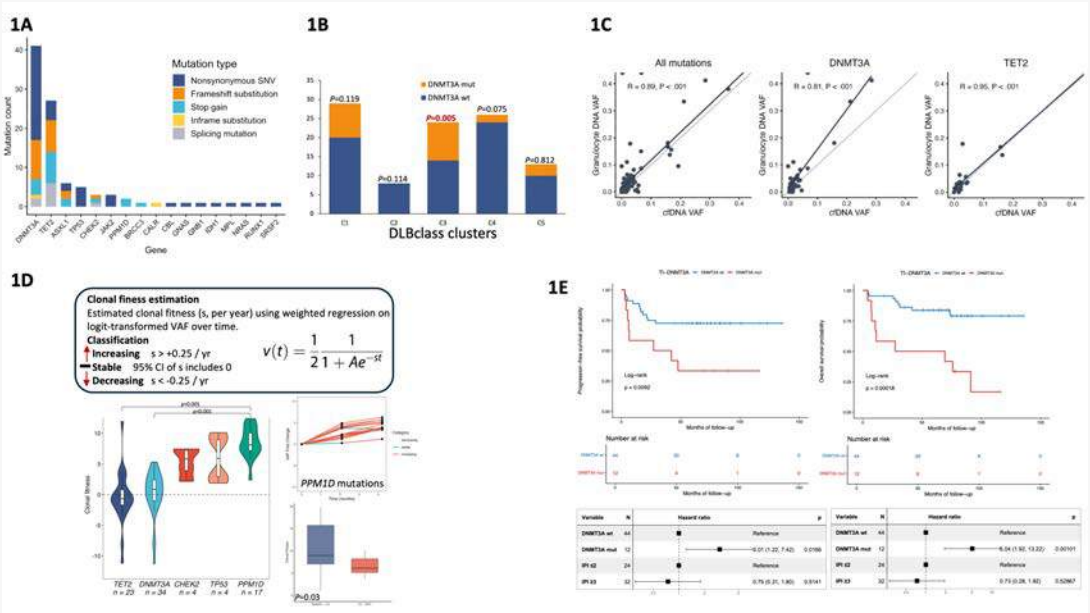
NON-HODGKIN'S LYMPHOMA



Myeloma and other monoclonal gammopathies

INITIAL EFFICACY AND SAFETY DATA FROM THE PHASE 1/2 LINKER-AL2 STUDY OF LINVOSELTAMAB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY SYSTEMIC LIGHT CHAIN AMYLOIDOSIS

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Background. Systemic AL amyloidosis causes organ dysfunction via deposition of amyloid free light chains (FLCs) and is generally treated with combination therapies. Rapid hematologic and organ responses are associated with longer overall survival. Here, we report initial efficacy and safety data from the Phase 1/2 LINKER-AL2 study (NCT06292780) of Linvo (human BCMA×CD3 bispecific antibody) monotherapy in R/R systemic AL amyloidosis.

Methods. Eligible adult patients (pts) with R/R systemic AL amyloidosis received intravenous step-up doses of Linvo 5 mg and 25 mg followed by 28-day cycles of subcutaneous full 80 mg or 240 mg doses once weekly (Cycles 1–2) and once every 4 weeks (Cycles 3–12). The Phase 1 primary endpoint was incidence of dose-limiting toxicities (DLTs). Secondary endpoints included safety, rates of investigator-assessed hematologic responses (complete response [hCR] assessed by FLC ratio and absence of AL), and organ responses.

Results. As of Dec 1, 2025, 20 pts (median age: 64 years; European modified Mayo stage: II, 40%; IIIa, 35.0%) received Linvo 80 mg (n=7) or 240 mg (n=13), with a median follow-up of 5.13 months (range 1.6–9.2). Pts received a median of 1 prior line of therapy (range: 1–4; 60.0% had prior daratumumab-based therapy).Linvo elicited high rates of rapid and deep hematologic responses (**Table**), with mean involved FLC levels normalizing (iFLC <20 mg/L) by Day 15. hCR rates were 71.4% (80 mg) and 84.6% (240 mg).As of Dec 16, 2025, of the pts with baseline cardiac and renal involvement, 4 of 8 and 8 of 10, respectively, achieved investigator-assessed, sponsor-validated organ response, most within 3 months.All pts had ≥1 treatment-emergent adverse event (TEAE; Grade [Gr] ≥3, 55.0%; no DLTs). One pt with pre-existing coronary artery disease had Gr 5 ventricular fibrillation after coronary artery stent placement, which was assessed as unrelated to Linvo.The most common TEAEs were infections (80.0%; Gr 3/4, 25.0%; no Gr 5), CRS (50.0%; Gr 1, 35.0%; Gr 2, 15.0%; 90% during step-up dosing), infusion-related reactions (30.0%; all Gr 1/2), neutropenia (30.0%; Gr 3/4, 25.0%), and transaminase elevations (30.0%; Gr 3/4, 10.0%). One Gr 1 ICANS occurred.

Conclusions. With no approved treatments for R/R disease, Linvo monotherapy showed clinically meaningful activity, with high rates of hCR and organ responses, mean iFLC level normalization by Day 15, and generally manageable safety, supporting continued development of Linvo in AL amyloidosis.

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Table. Investigator-assessed hematologic responses (ISA criteria)

Response, n (%)*	Linvo 80 mg (n=7)	Linvo 240 mg (n=13)
hOR	7 (100)	13 (100)
hCR	5 (71.4)	11 (84.6)
Median time to hCR, weeks (range)	4.3 (2.1–18.3)	6.3 (1.0–12.1)
hVGPR	2 (28.6)	1 (7.7)
Low dFLC response†	0	1 (7.7)
iFLC <10 mg/L	7 (100)	13 (100)
Median time to iFLC <10 mg/L, weeks (range)	2.1 (2.0–10.3)	2.7 (1.1–7.1)
Median follow-up, months (range)	5.4 (1.6–9.2)	4.6 (3.3–7.0)

*Unless specified otherwise; †If baseline dFLC ≥20 mg/L and <50 mg/L, response other than hCR reached with dFLC <10 mg/L.
dFLC, difference between iFLC and uninvolved FLC; FLC, free light chain; hCR, hematologic complete response; hOR, hematologic overall response; hVGPR, hematologic very good partial response; iFLC, involved FLC; ISA, International Society of Amyloidosis; Linvo, Linvoseltamab.

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Myeloma and other monoclonal gammopathies

SALVAGE TREATMENT PATTERNS OF PATIENTS PRIMARY REFRACTORY OR WITH SUB-OPTIMAL RESPONSE TO D-VTD: A REAL-LIFE STUDY FROM EUROPEAN MYELOMA NETWORK ITALY

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In recent years, Daratumumab-Bortezomib-Thalidomide-Dexamethasone (D-VTD) has represented the standard of care for newly diagnosed transplant eligible (TE) Multiple Myeloma patients. However, a significant proportion of patients either progressed or achieve a sub-optimal response, resulting in dismal outcome, and the optimal treatment of these patients remains unclear.The aim of this study is to retrospectively and prospectively evaluate the efficacy of the standard second-line treatments in real-life settings for fit patients who progressed or achieved a sub-optimal response (≤partial response) to D-VTD induction.Between 1th January 2022 to 28th February 2026, 143 patients (median age: 60 years) from 28 Italian centers were included in this study. After a median of 4 cycles of D-VTD, all patients switched to a second line treatment. The reasons were progressive disease in 88/138 (64%) cases (57% symptomatic, 43%, biochemical), sub-optimal response in 33/138 (24%), and refractory disease in 17/138 (12%). In the remaining 5 cases, this info was not available. Concerning second line treatment, most patient received KRD as salvage (108/136, 79%), followed by intensive chemo-based (VD/KRD-PACE) regimens in 11 cases (7.9%) and Isa-KD in 5 cases (3.6%). The overall response rate to second line treatment was 75.1%, with ≥ VGPR rate of 49.1% and 15.1% of CR/sCR.With a median follow up of 18.4 months, the median PFS was 15 months, and the median OS has not yet been reached (12-months OS: 74%). A shorter PFS was observed in patients with baseline HR cytogenetic (6.8 months vs not reached, p=0.007), high LDH levels at relapse (5.9 months vs 24 months, p=0.022) and b2 microglobulin >3.5mg/dL at relapse (6.8 months vs 43 months, p=0.0032). Treatment with KRD showed a longer PFS compared to the other combinations (20 months, vs 6.8 months, p=0.11). Finally, 56/142 (39.4%) patients received at least an autologous stem cell transplantation (ASCT) and displayed a significantly improved PFS compared to those who did not (not reached vs 4.5 months, p<0.0001).To our knowledge, this is the first study evaluating the outcomes in patient's refractory or with sub-optimal response following D-VTD. The data herein presented confirmed the dismal prognosis of these functional high-risk cases, especially in case of aggressive relapse. Nevertheless, a significant proportion of patients can be rescued by the second line treatment, especially with KRD re-induction and ASCT.

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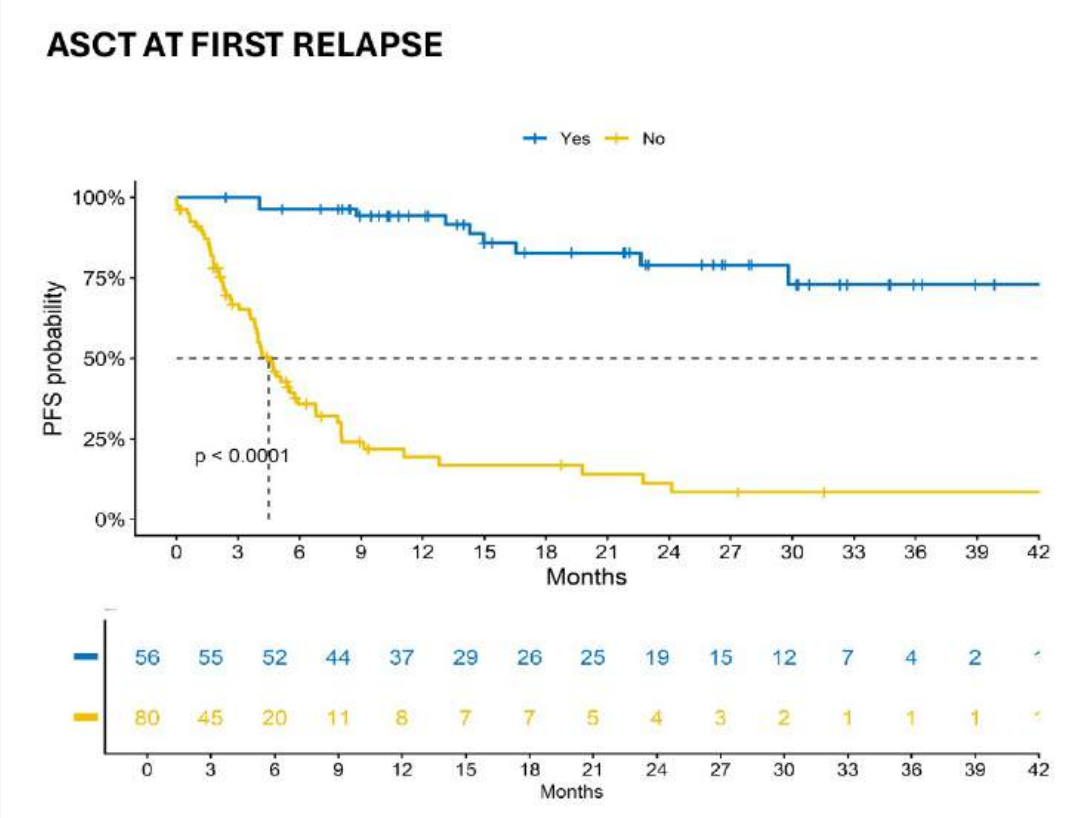

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Myeloma and other monoclonal gammopathies

SAFETY AND FEASIBILITY OF OUTPATIENT BISPECIFIC ANTIBODIES STEP-UP DOSES ADMINISTRATION FOR THE TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA: A REAL-WORLD MULTICENTER STUDY

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The increasing use of bispecific antibodies (bsAbs) for relapsed/refractory multiple myeloma (RRMM), has led to a growing interest in outpatient (outpt) step-up dosing (SUD), but guidelines are lacking.We designed a real-world (RW) multicentric study to evaluate feasibility, safety, and protocols in use for outpt bsAb SUD in RRMM. Overall, 86 patients (pts) received outpt bsAb SUD (30 teclistamab, 16 elranatamab, 40 talquetamab) in 18 Italian centers, with a median follow up of 7 (range 1-35) months (m). All centers had an Intensive Care Unit and neurology on site, 17 (94%) an Emergency Department, and 16 (89%) a Day Hospital operating for ≥8 hours/day and a 24/7 hematologist on call. Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome prevention strategies (CRS/ICANS-PS) consisted in per label premedication for all pts; in addition, 26 (30%) received prophylactic tocilizumab (PT), 33 (38%) dexamethasone post medication and 6 (7%) both. Median age was 71 years (range 34-85) and median number of prior lines 4 (range 2-8) (Table 1). No differences were observed in baseline characteristics between pts receiving additional CRS/ICANS-PS or not, except for a higher incidence of CRAB criteria in the former (p<0.001). CRS occurred in 32 (37%) pts, all grade (G) 1 save 1 G2; median time of onset was 7 days (d) (range 1-30) and median duration 2 d (range 1-10); 22 (26%) pts were treated with tocilizumab and/or steroids. 1 G2 ICANS case was recorded, with onset at d 30 and resolution after 1 d of steroids. During SUD, 26 (31%) pts experienced complications, defined as: additional visits (20 pts [23%], median 1, range 1-3), dose delays (17 pts [20%]), and/or need of hospitalization (7 pts [8%]; median 9 d, range 2-33). PT was significantly associated with less frequent CRS (p=0.011) and higher probability of SUD completion with no complications (p=0.020). Throughout treatment, infections occurred in 49 (57%) pts (15% ≥G3) with no difference between different CRS/ICANS-PS. The overall response rate was 76%, with a complete response rate of 34%. Median progression-free survival (PFS) was 12 m, and the 12 m overall survival rate 82%. The absence of complications during SUD was associated with longer PFS (HR 0.47, p=0.04).Our RW results support outpt bsAb SUD as a safe and viable option with the use of structured protocols, with PT emerging as the most effective strategy to reduce CRS and facilitate SUD completion in the outpt setting.

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Table 1

Baseline characteristics of patients (n=86)	
Age, median (range)	71 (34-85)
Previous lines of therapy, median (range)	4 (2-8)
Triple-class exposed, n (%)	84 (98%)
Triple-class refractory, n (%)	68 (79%)
Exposed to T-cell redirecting therapy, n (%)	27 (29%)
Refractory to previous line of therapy, n (%)	65 (76%)
Presence of CRAB criteria, n (%)	57 (66%)
Presence of extramedullary disease, n (%)	17 (20%)
Patients with creatinine clearance < 60 ml/min, n (%)	26 (28%)
Patients with ECOG 2 or worse, n (%)	15 (17%)
Patients with Charlson Comorbidity Index 2 or worse, n (%)	64 (74%)

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LONG-TERM PROGRESSION-FREE SURVIVAL BENEFIT WITH CILTACABTAGENE AUTOLEUCEL IN STANDARD-RISK RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Introduction. CARTITUDE-4 (NCT04181827) enrolled patients (pts) with lenalidomide-refractory multiple myeloma (MM) after 1–3 prior lines of therapy (pLOT) and showed a significant benefit of ciltacabtagene autoleucel (cilta-cel) over established triplet regimens. However, the benefit of cilta-cel for pts with standard-risk cytogenetics is less defined. Here, we report outcomes in pts with standard-risk cytogenetics in CARTITUDE-4.

Methods. Pts randomized to cilta-cel underwent apheresis and bridging therapy followed by lymphodepletion and subsequent single cilta-cel infusion. The intent-to-treat (ITT) population included 208 pts; 32 progressed or died on bridging therapy and 176 were included in the as-treated (A-T) population. Pts with high-risk cytogenetics (del(17p), t(14;16), t(4;14), gain/amp(1q), n=105), or unknown cytogenetics (n=12) were excluded. Minimal residual disease (MRD)-negative complete response (CR) was defined per the International Myeloma Working Group criteria. PFS rates were determined from time of cilta-cel infusion for A-T pts.

Results. In the ITT population, pts with standard-risk cytogenetics had a 30-mo PFS rate (95% CI) of 71.0% (58.8–80.2) with cilta-cel (N=69) vs 43.2% (31.3–54.5) with standard of care (N=70). Pts with standard-risk cytogenetics in the A-T population (n=59) had a 30-mo PFS rate of 80.5% (95% CI, 67.2–88.8). In CARTITUDE-1 (NCT03548207), evaluating cilta-cel in pts with heavily pretreated RRMM (≥3 pLOT), the 30-mo PFS rate in pts with standard-risk cytogenetics (n=68) was 59.9% (95% CI, 47.2–70.5). The CARTITUDE-4 A-T population with standard-risk cytogenetics experienced 8 PFS events within 1 yr and 4 PFS events beyond 1 yr of cilta-cel infusion. 26 pts achieved MRD-negative CR at 12 mos after cilta-cel, all were progression-free at 30 mos.

Conclusions. The PFS rate at 2.5 yrs for pts with standard-risk RRMM was higher in CARTITUDE-4 compared with CARTITUDE-1, supporting use of cilta-cel as early as second line. Among A-T pts in CARTITUDE-4, 80.0% of those with standard-risk cytogenetics were progression-free and off treatment at 2.5 yrs; this rate increased to 100.0% in pts with standard-risk disease who attained MRD-negative CR at 1 yr. The low rate of progression events in cilta-cel-treated pts with standard-risk cytogenetics shows the profound benefit of a single cilta-cel infusion in this population. © *American Society of Hematology (2025). Reused with permission.*

Myeloma and other monoclonal gammopathies

PHASE 1 DOSE ESCALATION SAFETY AND EFFICACY OF ETENTAMIG IN PATIENTS WITH RELAPSED OR REFRACTORY LIGHT CHAIN AMYLOIDOSIS

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Background. Etentamig is a patient-centric, next generation differentiated BCMA x CD3 bispecific T-cell engager composed of a bivalent BCMA-binding domain with high avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life enabling convenient dosing from the start. Recent data from M24-209 (NCT06158854), demonstrated promising efficacy, with an 82% hematologic complete response (CR) rate and manageable safety profile.

Aims. We report updated safety and efficacy results from M24-209.

Methods. The Phase 1 dose escalation enrolled BCMA-targeted therapy-naïve pts with RR AL amyloidosis with ≥1 prior line of therapy (LoT). Eligible pts had a difference in involved/uninvolved serum free light chain of ≥50 mg/L, and pts with high cardiac risk (stage IIIb) disease were excluded. Three dose groups were explored in DE (etentamig 20 mg, 40 mg, and 60 mg, all Q4W), with 1 step-up dose from 40 mg onward. Treatment duration is fixed for 24 months, and pts will be followed until disease progression. Primary objectives are to determine safety/tolerability, pharmacokinetics/pharmacodynamics, and recommended Phase 2 dose.

Results. As of 22 November 2025, all doses in DE have been enrolled (N=34): 12, 11, and 11 pts have been treated with etentamig 20 mg, 40 mg, and 60 mg, respectively. Median (range) duration of follow-up in all pts was 10.1 (5.9–18.6) months; 88% of pts continued treatment. Median (range) number of prior LoT was 2 (1–8), and median (range) time from initial diagnosis was 4.5 (0–21) years. At baseline, 85% and 39% of pts had cardiac or renal involvement, respectively. Treatment-emergent adverse events were reported in 97% (53% Grade [G] ≥3) of all pts. No new CRS or ICANS events occurred compared with the previous data readout (Figure). With longer safety follow-up, the manageable safety profile was maintained, with G≥3 infections in 2 (6%) pts and G≥3 neutropenia in 3 (9%) pts. Hypogammaglobulinemia occurred in 10 (29%, all G1/2) pts; all pts received ≥1 dose of IVIG. All pts achieved ≥very good partial response and 91% achieved CR. Median (range) time to CR was 1.0 (0.2–14.1) months. Renal responses were maintained at 54% with an increase in cardiac responses to 43% of evaluable pts.Summary/Conclusion: etentamig monotherapy in pts with RR AL amyloidosis leads to 91% of CRs while maintaining its promising and manageable safety profile.

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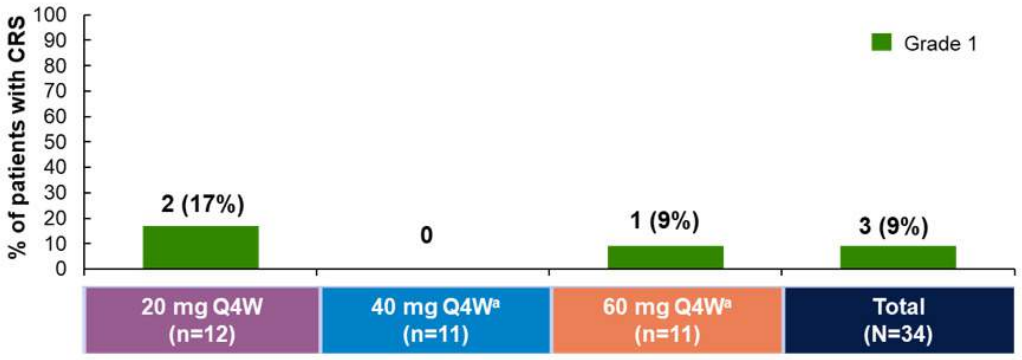
Figure. Incidence of CRS



Infections

INFECTION BURDEN IN MYELOFIBROSIS ON RUXOLITINIB: THE IMPACT OF TRANSFUSIONS, IRON OVERLOAD AND INFLAMMATION

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Background. Infections are a leading cause of morbidity and mortality in patients (pts) with myelofibrosis (MF). Red blood cell (RBC) transfusions, iron overload (IO), and systemic inflammation, reflected by a high neutrophil to lymphocyte ratio (NLR), have been associated with higher infectious risk.

Methods. To assess their impact in a uniform treatment setting, we performed a sub analysis of 968 ruxolitinib (RUX) treated MF pts included in the RUX MF study with data on infections. Transfusion dependency (TD) was defined as ≥3 RBC units (RBCU) in the 12 weeks pre RUX; transfusion requirement (TR) as ≥1 RBCU in the prior year not meeting TD criteria. Normal NLR was ≤3.53. IO was defined as ferritin >1000 ng/mL and/or >20 RBCU. Competing risk regression was applied to identify predictors of infection; IO replaced TR/TD due to collinearity and broader clinical relevance.

Results. At RUX initiation, 39.6% of pts had Hb <10 g/dL and 75.3% had elevated NLR; 50.0% had DIPSS int 2/high risk. Prior infections were reported in 163 pts (respiratory 39.9%, latent TB 21.5%). TR and TD occurred in 6.4% and 17.5% of pts; mean pre RUX RBCU was 10, mean ferritin 775 ng/mL, and 11.5% had IO.After a median of 2.5 years on RUX, 29.0% of pts developed ≥1 infection (370 events; incidence rate [IR] 11.4% pt years), mostly grade 1–2 (62.4%); infection was the ultimate cause of death in 28 pts. Infections were mainly respiratory (45.4%), followed by gastrointestinal (13.5%), urinary tract (12.7%), zoster (12.4%), sepsis (5.7%), skin/soft tissue (4.3%), and opportunistic/atypical (3.8%). At 5 years, cumulative incidence of first infection (by Fine-Gray model with death as competing risk) was 43.5% in TD, 36.8% in TR, and 29.4% in non TR pts (sub distribution hazard ratio, SHR 1.3, p<.001).In univariate analysis, IO (SHR 1.9, p=.003), DIPSS int 2/high (1.4, p=.002), NLR >3.53 (1.4, p=.04), and prior infections (2.37, p<.001) predicted higher risk; all remained significant in multivariate analysis. Notably, the 229 pts achieving an IWG MRT spleen response at 6 months had a lower IR compared with non responders (8.5 vs 11.6% pt years, p=.02).

Conclusions. Infectious risk on RUX was driven by prior infections, inflammatory burden, and transfusion related IO, while early spleen response was protective. Elevated NLR and IO emerged as simple, independent markers of infectious vulnerability, potentially guiding therapeutic choices and targeted prophylaxis.

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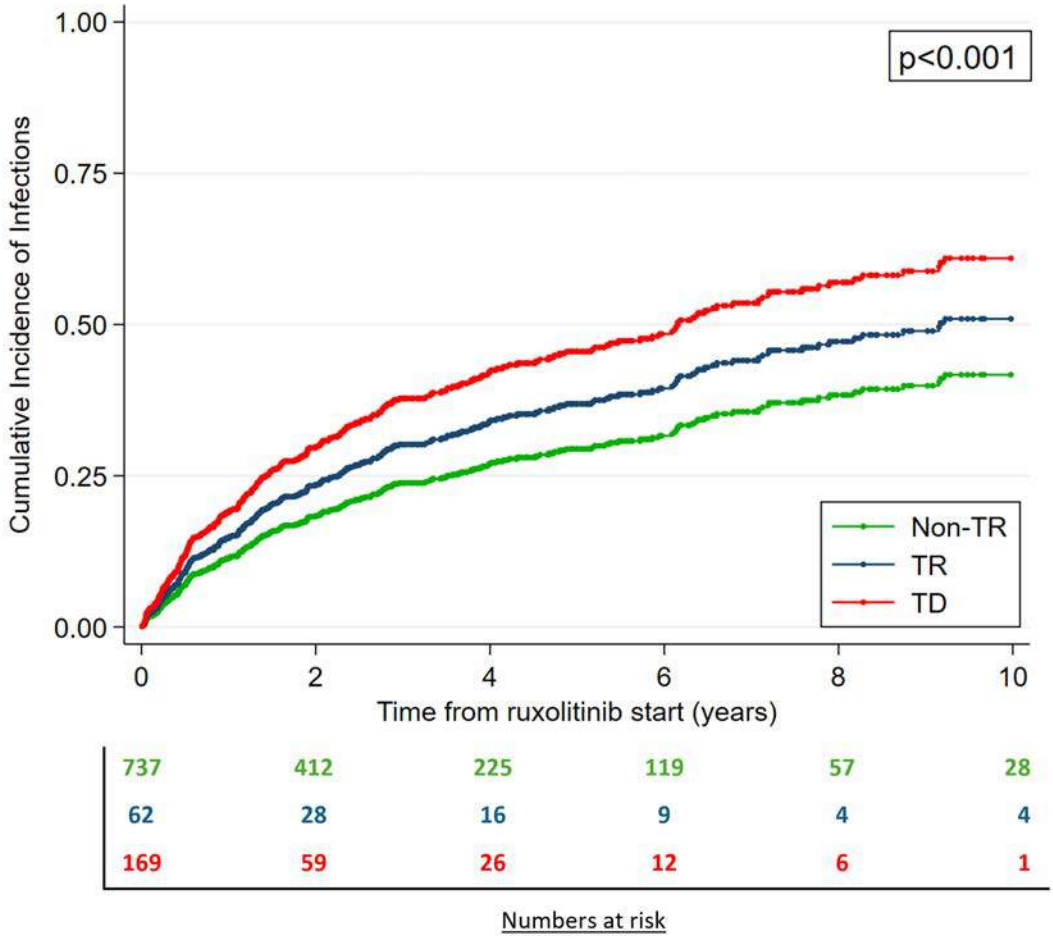
Figure: Cumulative Incidence Function of Infections estimated by Fine–Gray model (death as competing risk) by transfusion burden stratification



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MARIBAVIR FOR THE TREATMENT OF CMV INFECTION IN PATIENTS RECEIVING HEMATOPOIETIC STEM CELL TRANSPLANTATION: PRELIMINARY RESULTS OF THE SURVEY OF THE SEIFEM GROUP (SORVEGLIANZA EPIDEMIOLOGICA INFEZIONI NELLE EMOPATIE)

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Introduction. Patients with resistant/refractory (R/R) CMV infection (CMVi) following stem cell transplantation (HSCT) require prolonged anti-CMV treatment and therapeutic options are suboptimal due to toxicity and potential cross-resistance among the available anti-CMV agents. A phase 3 study showed that maribavir (MBV), an oral antiviral drug with multimodal activity, is effective and safe for the treatment of R/R CMVi in patients receiving HSCT and solid organ transplants.Aim of present retrospective study is to evaluate the preliminary results of MBV treatment in HSCT recipients in 9 italian centers on behalf of the SEIFEM Group.
Methods. Overall, 39 patients received MBV for CMVi, in 23 cases for refractoriness to GCV/VGCV (n=18), FOS (n=3) or both (n=2) and in 16 cases for intolerance to GCV/VGCV (n=11), FOS (n=2) or both (n=3); no patient was treated with MBV for resistant CMVi. All patients received letermovir (LTV) for CMV prophylaxis.
Results. Median age was 60.5 years (range 26-72); 30 patients had acute leukemias, 3 had myeloproliferative disorders and 6 lymphomas. HSCT donors were matched siblings (n=2), matched/mismatched unrelated (n=23), haplos (n=13) or CBU (n=1). In the majority of cases, GVHD prophylaxis included PTCy (n=23) or ATG (n=11). Among the 23 patients with refractory CMVi, the infection developed after LTV discontinuation (n=18), during LTV prophylaxis (n=4) and in 1 patient who did not receive LTV. R/R patients were treated with MBV 800 mg/d for 8 weeks obtaining the clearance of CMV in all 19 evaluable patients. One patient cleared the virus despite early MBV discontinuation, and four patients experienced further CMVi following the end of MBV treatment. Nausea and dysgeusia were the most common side effects reported by 3 patients; 1 patient with concomitant SARS-CoV2 infection required dose reduction. Renal insufficiency, cytopenias and GI sensitivity were the main causes of intolerance to GCV/VGCV/FOS leading to MBV treatment. Two of the 16 patients had CMVi progression while on therapy, 12 achieved virus clearance and 1 patient experienced CMV reactivation after the end of MBV course.
Conclusions. Results of this analysis in patients receiving MBV for R/R CMVi or intolerant to anti-CMV agents showed promising results in terms of safety and efficacy. Future prospective studies on a larger population are required to confirm these preliminary data.

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DURATION OF NEUTROPENIA IS THE ONLY RISK FACTOR FOR INVASIVE FUNGAL INFECTIONS IN PH-NEG ACUTE LYMPHOBLASTIC LEUKEMIA: PRELIMINARY RESULTS OF A MULTICENTRIC PROSPECTIVE SEIFEM STUDY (ALL-IFI)

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Incidence and outcome of invasive fungal infections (IFI) in acute lymphoid leukemia (ALL) are not completely defined. To describe incidence, clinical characteristics and predisposing factors of possible (poss) and proven/probable (p/p) IFI in Ph-negative ALL patients (pts) occurring during the first 3 courses, we carried out a prospective multicentric observational study within the SEIFEM (Sorveglianza Epidemiologica delle InFezioni nelle EMopatie). All consecutive adult Ph-negative ALL pts diagnosed since June 1st, 2022, and treated with curative intent were recorded. Data about age, gender, ALL type and biological characteristics, chemotherapy schedule, response to treatment, antifungal prophylaxis (AF), duration of neutropenia and mortality were also recorded. At the time of the analysis, 107 pts were enrolled in 17 centres. The median age of the whole cohort was 50y (range 18-82), M/F ratio 65/42. All the pts were evaluable for the first course, 85 for second and 71 for third; 74 (72.5%) pts were treated with pediatric-inspired protocols. Sixty-four (64%) pts received antifungal prophylaxis; in 51 (48%) cases it was mold active. Overall, 20 pts developed 21 IFI, 6 poss and 15 p/p, respectively. During the first course, IFI incidence was 17/107 (15.9%); p/p IFI were 12 (11.2%). Incidence was significantly lower during consolidation, as 4 pts developed IFI (1 poss, 3 p/p) during 156 courses (2.6%) ($p<0.0001$). Aspergillus spp was isolated in 11 out of the p/pIFI (Table 1). During induction, the only predisposing factor for IFI was the duration of neutropenia, higher in pts with IFI than in those without (18 vs 12 days, OR 1.12, CI 1.03-1.21, $p=0.005$). Age (OR 0.99, CI 0.97-1.03), gender (OR 1.53, CI 0.52-4.46), a pediatric-inspired protocol treatment (OR 0.54, CI 0.17-1.77), antifungal prophylaxis (OR 0.73, CI 0.25-2.14), antimold prophylaxis (OR 0.55, 0.18-1.64), refractory disease (OR 3.97, CI 0.49-32.09) had no impact on IFI event during induction. Three (15%) of 20 pts developing IFI at any time of observation deceased, but in only 1 (5%) case death was attributable to IFI (C. parapsilosis candidemia). IFI was high in ALL pts, particularly during induction, with aspergillosis the most common recorded. Only duration of neutropenia during induction was associated with IFI, whereas antifungal prophylaxis does not seem to be protective. However, attributable mortality was low, even if the impact on long-term survival needs a longer follow-up.

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Patient	Course number	Antifungal prophylaxis	Site of infection	Identification	Treatment	Outcome
1	1	micafungin	lung	*Aspergillus* spp	L-AmB → isavuconazole	resolved
2	1	micafungin	lung	*Aspergillus* spp	L-AmB	resolved
3	1	L-AmB	lung	*Aspergillus* spp	isavuconazole	resolved
4	1	L-AmB	lung	*Aspergillus* spp	voriconazole	resolved
5	1	no	lung	*Aspergillus* spp	L-AmB+isavuconazole	resolved
6	1	fluconazole	lung	*Aspergillus* spp	L-AmB	resolved
7	1	fluconazole	Lung+paranasal sinuses	*A.flavus*	L-AmB	resolved
8	1	no	blood	*C.tropicalis*	L-AmB	resolved
9	1	no	blood	*C.krusei*	caspofungin	resolved
10	1	caspofungin	blood (CVC)	*C.parapsilosis*	caspofungin	deceased
11	1	no	Liver and spleen	*Candida* spp	L-AmB+caspofungin	resolved
12	2	no	lung	*Aspergillus* spp	voriconazole	resolved
13	3	no	lung	*Aspergillus* spp	L-AmB → isavuconazole	resolved
14	3	fluconazole	lung	*Aspergillus* spp	L-AmB → voriconazole	resolved

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INFECTION PATTERNS AND IMMUNE RECONSTITUTION FOLLOWING THIRD LINE CAR T-CELL THERAPY IN PATIENTS WITH HIGH GRADE LYMPHOMA

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Patients (pts) with LBCL treated with chimeric antigen receptor T (CART)-cell therapy, frequently develop complications, including prolonged cytopenia, persistent CD4 T-cell depletion, B-cell aplasia, and hypogammaglobulinemia, particularly in the late follow-up, which are associated with an increased risk of long-term infections. We assessed the incidence, severity, and pattern of infections and relative immune recovery.We identified pts with LBCL consecutively treated with CART after 2 or more previous lines of therapy, between 2020-2025 at our institution. Data on infections were collected post CART infusion and classified according to the time of onset [short (0-30 days - d), medium (31-90 d) and long term (>90 d)], the etiology, the site of infection, and disease characteristics including data on immune reconstitution. The severity of infectious events was classified according to CTCAE v5.0.70 pts were included with a median age of 61 yrs (range 20-73), 7 (10%) were older than 70. 54/70 (77%) pts received Tocilizumab and 33/70 (47%) received steroid for CRS or ICANS management. 31% of pts had Late G>2 N-ICAHT. 12 months (mo) PFS and OS of the 70 pts were 57% and 71% respectively. Among survivors at 12 mo post CART infusion, 26/43 (60%) pts had persistent hypogammaglobulinemia, 15/43 (35%) had a B cell recovery and 17/43 (40%) had a CD4 recovery, with a median number of CD4 at 12 mo of 379/mmc.With a median f-up of 18 mo, 25 pts (35%) presented at least 1 infectious complication, 6/25 (24%) of them had recurrent infections, with a total of 33 events registered. Short, medium, and long-term infections occurred in 5/70 (7%), 5/70 (7%), and 15/70 (21%) pts, respectively. Microbiological isolates were bacterial, viral, and fungal in 55%, 33%, and 12% of cases, respectively (Table 1). The most common site of infection were lung and upper respiratory tract. 17/70 (24%) of pts had a severe event (G>2), 1 pts died for infection and 7 pts died from infectious complications in the setting of progressive disease. Global non relapse mortality was of 7% (5/70). Infections were significatively related with Late G>2 N-ICATH (p=0.007), Ig recovery (p= 0.023) and age > 70 yrs, p=0.03.Our study confirms the high incidence of infectious events after CART, mostly in the medium and long term period.Further analysis, also in earlier lines, would be useful to identify and manage pts with higher risk of post CART infection.

Table 1: Infection Patterns in CART patients

TIME of infection	N pts with infections	N total infections	Severity (G≥2)*	Bacterial*	Viral*	Fungal* §	Microrganism*°	Site*
Short term	5/70 (7%)	5	5/33 (15%)	4/33 (12%)	0	1/33(3%)	E.Coli + Stenotroph. maltophilia (n1) Bacillius cereus+Ent VRE (n1) Pseudom. aeruginosa (n1) Klebsiella Pneumoniae (n1)	Lung (n2) Blood (n3)^
Medium term	5/70 (7%)	5	3/33 (9%)	2/33 (6%)	3/33 (9%)	0	SARS-Cov2 n3	Lung/Upper resp tract (n5)
Long term	15/70 (21%)	23	13/33 (39%)	12/33 (36%)	8/33 (24%)	3/33 (9%)	S.pneumoniae(n1) E.Coli (n1) SARS-Cov2 (n5) Rhinovirus (n1) Respiratory syncytial virus (n1) Aspergillus spp (n1)	Lung/Upper resp tract (n20) Blood (n3)^
Total events	**25/70 (35%)**	**33**	**21/33 (63%)**	**18/33 (55%)**	**11/33 (33%)**	**4/33 (12%)**		

* Data based on the total number of recorded infectious events (n=33)
° etiologic microrganism was identified in 18 pts
§Fungal events were: proven1, probable 3
^ a total of 2 pts had a sincronous urinary tract infection and sepsis

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IMPACT AND MANAGEMENT OF LATENT TUBERCOLOSIS INFECTION IN CHRONIC LYMPHOCYTIC LEUKEMIA A CLL CAMPUS STUDY

A Visentin [1], I Angeletti [2], L Arletti [3], L Ballotta [4], E Benedetti [5], A Bosi [6], G Cancemi [7], M Cantelli [8], Mc Caparello [9], G Catania [10], M Cavallari [11], S Ciofini [12], M Criscuolo [13], L De Padua [14], A Di Francesco [15], L Farina [16], I Ferrarini [17], A Giordano [18], I Innocenti [13], E Lovato [19], M Maccaferri [20], A Mancini [21], S Mancuso [22], Ea Martino [23], N Maschio [24], L Morello [25], M Motta [19], R Murru [26], M Nicolosi [27], A Nunzi [28], J Olivieri [29], R Pasquale [29], S Pepe [30], F Perutelli [21], P Picardi [22], B Pocali [33], M Porazzo [34], G Quaresmini [35], C Riemma [36], I Romano [37], F Russo [28], C Salvetti [39], A Sanna [40], G Santuccio [41], L Schiattone [42], I Scortechini [43], A Tamburini [44], M Varettoni [45], F Vozella [46], S Zoli [47], F Angotzi [1], A Cellini [1], A Serafin [1], A Bevilacqua [1], M D'Antiga [1], N Danesin [1], L Scarfò [48], A Frustaci [49], L Laurenti [13], M Gentile [23], A Broccoli [50], Gm Rigolin [51], R Moia [52], C Vitale [31], P Sportoletti [21], R Marasca [20], V Gattei [53], G Gaidano [52], P Ghia [48], M Coscia [54], A Cuneo [51], L Trentin [1]

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Background. Latent tuberculosis infection (LTBI) affects up to 15% of the European population, and patients with hematologic malignancies have an increased risk of developing active tuberculosis (TB). However, LTBI screening is not currently recommended in chronic lymphocytic leukemia (CLL).

Aims. To evaluate the relevance of LTBI and TB in CLL by integrating data from clinical trials, pharmacovigilance databases, and real-world practice.

Methods. The Italian CLL Campus conducted: i) a random-effects meta-analysis of trials published in PubMed up to January 2026 including ≥50 CLL patients treated with BTK inhibitors (BTKi), venetoclax (VEN), or combinations, assessing LTBI screening (TST or IGRA) and TB incidence; ii) an analysis of TB cases reported in EudraVigilance database (January 31, 2026); iii) a survey among CLL Campus members on LTBI management.

Results. We analyzed 46 trials (9,404 patients; 6,065 treatment-naïve, 3,339 relapsed/refractory, RR) since 2014. No trial included LTBI screening. Only 2 active TB cases (0.02%) were reported, both in RR patients.In EudraVigilance database, 57 TB cases were identified among 43,096 adverse drug reaction reports (0.13%); 60% were male and half ≥65 years. TB was disseminated in 12% and exclusively

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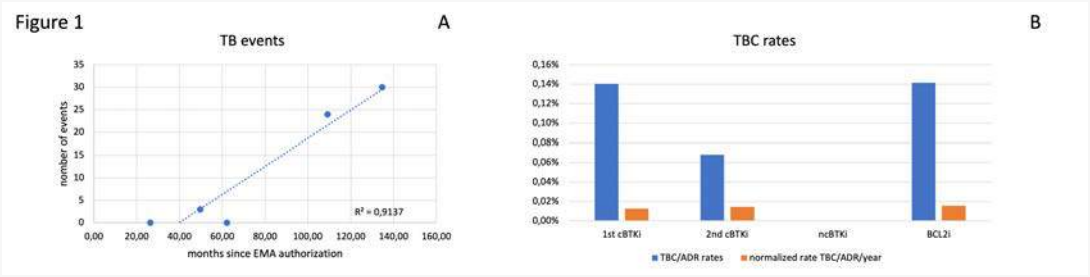
extrapulmonary in 7%. Outcomes were resolved in 8.8%, recovering in 14%, not recovered in 17.5%, fatal in 7%, and unknown in 52.6%. TB events correlated with time since EMA authorization (R^2=0.91, Fig. 1A). Incidence was higher with ibrutinib and VEN (0.14%), lower with second-generation BTKi (0.07%), and absent with non-covalent BTKi.Among 32 Italian centers, LTBI screening is routinely performed at diagnosis by 12% and before treatment by 31% of physicians. Among IGRA-tested patients, ~4% were positive (0–20% across centers). In these cases, 25% delayed CLL therapy until prophylaxis completion, while 72% started both concurrently. Prophylaxis mainly included isoniazid alone (44%) or with rifampicin (47%) for 6–9 months. Among 5,700 patients treated outside trials, 216 were IGRA positive: no TB cases occurred in those receiving prophylaxis, whereas 4/7 without prophylaxis developed TB (p<0.0001).

Conclusions. Despite notable mortality, LTBI screening is neglected in trials and inconsistently applied in practice. Given relevant drug–drug interactions between TB prophylaxis and CLL therapies, our findings support routine LTBI screening at CLL diagnosis as a preventive strategy.



Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

PLATELET RESPONSE KINETICS WITH IANALUMAB PLUS ELTROMBOPAG VS ELTROMBOPAG ALONE IN SECOND-LINE PRIMARY IMMUNE THROMBOCYTOPENIA: A RANDOMIZED, DOUBLE-BLIND, PHASE 3 VAYHIT2 STUDY

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Background. The primary analysis of the study VAYHIT2 (NCT05653219) demonstrated that in patients with primary immune thrombocytopenia (ITP) with insufficient response to or relapse after first-line corticosteroids, ianalumab plus eltrombopag prolonged time-to-treatment-failure and increased the proportion of patients with stable response at 6 months versus eltrombopag alone.[1]

Aim. To further characterise kinetics of response to ianalumab in primary ITP.

Methods. In this phase 3, randomized, double-blind trial patients were randomized (1:1:1) to four monthly infusions of ianalumab 9 mg/kg (n=50), ianalumab 3 mg/kg (n=51), or placebo (n=51), plus daily eltrombopag.[1] Patients with responses at Weeks 15 and 17 were eligible for eltrombopag tapering with discontinuation by Week 25. Response and complete response rates (platelet count [PC] ≥50 × 10^9/L and ≥100 × 10^9/L, respectively, without rescue or new ITP therapy), and PCs, were secondary endpoints.

Results. Data cutoff was June 20, 2025. PC (× 10^9/L) increased as early as the first post-baseline assessment (Week 2, Day 1); the median (interquartile range [IQR]) absolute increase from baseline was 149.0 (59.0–179.0) with ianalumab 9 mg/kg, 98.5 (42.0–172.0) with 3 mg/kg, and 52.0 (21.0–130.0) with placebo. Median time (months) to first response was 0.3 with ianalumab 9 mg/kg, and 0.5 with either ianalumab 3 mg/kg or placebo. PCs within a safe range were observed, particularly for ianalumab-treated patients through the end of eltrombopag tapering and discontinuation (Week 25, Day 1), when median (IQR) absolute PC was 145.5 (72.5−237.0) with ianalumab 9 mg/kg, 100.5 (39.5−168.0) with 3 mg/kg, and 67.0 (42.0−154.0) with placebo. Generally, higher response and complete response rates were observed with ianalumab versus placebo (Table 1). During eltrombopag tapering and discontinuation (Weeks 17−25), response and complete response rates were sustained in ianalumab-treated patients. Among responders, Kaplan-Meier-estimated median (95% confidence interval) duration of response (months) was 14.5 (4.9-not reached [NR]) with ianalumab 9 mg/kg, NR (4.9−NR) with 3 mg/kg, and 4.4 (3.5−5.3) with placebo.

Conclusions. Addition of ianalumab to eltrombopag was associated with rapid, robust, and durable responses in patients with ITP who had insufficient response or relapse after first-line corticosteroids.1. Cuker A, et al. N Engl J Med. 2025.Disclosure: This study was Funded by Novartis.

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Table 1. Response and complete response rates over time

Timepoint	Ianalumab 9 mg/kg + eltrombopag (n=50)	Ianalumab 3 mg/kg + eltrombopag (n=51)	Placebo + eltrombopag (n=51)
Week 2*			
n (%)	50 (100)	51 (100)	51 (100)
Response, n (%)	30 (60.0)	23 (45.1)	20 (39.2)
Complete response, n (%)	22 (44.0)	18 (35.3)	14 (27.5)
Week 11			
n (%)	50 (100)	51 (100)	51 (100)
Response, n (%)	40 (80.0)	39 (76.5)	36 (70.6)
Complete response, n (%)	31 (62.0)	24 (47.1)	25 (49.0)
Week 17†			
n (%)	50 (100)	51 (100)	51 (100)
Response, n (%)	41 (82.0)	37 (72.5)	37 (72.5)
Complete response, n (%)	32 (64.0)	24 (47.1)	27 (52.9)
Week 25‡			
n (%)	49 (98.0)	50 (98.0)	50 (98.0)
Response, n (%)	36 (73.5)	27 (54.0)	24 (48.0)
Complete response, n (%)	27 (55.1)	20 (40.0)	13 (26.0)
Week 33			
n (%)	44 (86.3)	43 (84.3)	44 (86.3)
Response, n (%)	21 (47.7)	20 (46.5)	12 (27.3)
Complete response, n (%)	18 (40.9)	11 (25.6)	8 (18.2)
Week 41			
n (%)	37 (74.0)	37 (72.5)	37 (72.5)
Response, n (%)	17 (45.9)	17 (45.9)	8 (21.6)
Complete response, n (%)	14 (37.8)	11 (29.7)	5 (13.5)

*After the first ianalumab or placebo infusion

†Start of eltrombopag tapering for eligible patients, i.e., patients who had ≥2 consecutive assessments with a platelet count ≥50 × 10^9/L at the end of the combination treatment period (from Week 15, Day 1, to Week 17, Day 1) without treatment failure by the end of the 16-week treatment period with both ianalumab and eltrombopag

‡End of eltrombopag tapering

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REDUCED-DOSE DOACS IN EXTENDED TREATMENT OF CANCER-ASSOCIATED THROMBOSIS (RED-CAT): INTERIM ANALYSIS FROM A MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY (COORDINATING CENTER DATA)

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Background and Aims. Cancer patients have a 4–7-fold increased risk of venous thromboembolism (VTE); guidelines recommend anticoagulation beyond 6 months in patients with VTE and active cancer. API-CAT showed non-inferiority of apixaban 2.5 mg twice daily (BID) vs 5 mg BID in preventing VTE recurrence with less bleeding. The ReD-CAT study aims to confirm these findings in a real-world setting and extend them to rivaroxaban. Primary endpoint was VTE recurrence; secondary endpoints were bleeding and comparison between drugs.

Methods. Multicenter retrospective study across 6 Hemostasis Centers in Piedmont, with ethics committee approval. Data from 2233 patients treated with rivaroxaban or apixaban (2017–2026) were analyzed, extracted from the AIFA registry of the coordinating center; 569 had cancer and 247 met inclusion criteria (≥18 years, proximal VTE and/or non-subsegmental pulmonary embolism, ≥6 months full-dose anticoagulation, active malignancy, no progression). Patients were stratified into four groups: apixaban 5 mg BID (C-AP) or 2.5 mg BID (P-AP), rivaroxaban 20/15 mg (C-RI) or 10 mg (P-RI). Outcomes were assessed by Kaplan–Meier analysis.

Results. 334 exposures were analyzed (93 C-RI, 67 C-AP, 87 P-RI, 87 P-AP). Median follow-up was 13 months. Baseline characteristics, including age, sex, weight, thrombotic and bleeding risk factors, cancer stage, and duration of prior anticoagulation, were well balanced across groups. Bleeding incidence was higher in full-dose groups (C-AP: 10% at 12 months, 65% at 30–36; C-RI: 13% and 35%) vs reduced-dose (P-AP: 1.5% and 10%; P-RI: 5.5% and 14%). Ten major bleeding events (of 37) occurred, 6 in C-AP. VTE recurrence was similar: at 12 months, 8% C-AP, 4% C-RI, 4% P-AP, 5% P-RI, remaining <10% at 36 months *(Figure 1)*.

Conclusions. This is the first real-world head-to-head comparison of rivaroxaban and apixaban in cancer-associated VTE. Overall, while efficacy was comparable across all groups, safety emerged as the main clinical discriminator, favoring reduced-dose regimens. These findings are consistent with the API-CAT trial, with similar results observed for rivaroxaban. Among full-dose regimens, a trend toward lower bleeding risk was observed with rivaroxaban compared to apixaban. Despite the retrospective design, the good balance of cohorts and consistency with existing literature support the reliability of these findings. Results will be further strengthened with data from the remaining centers.

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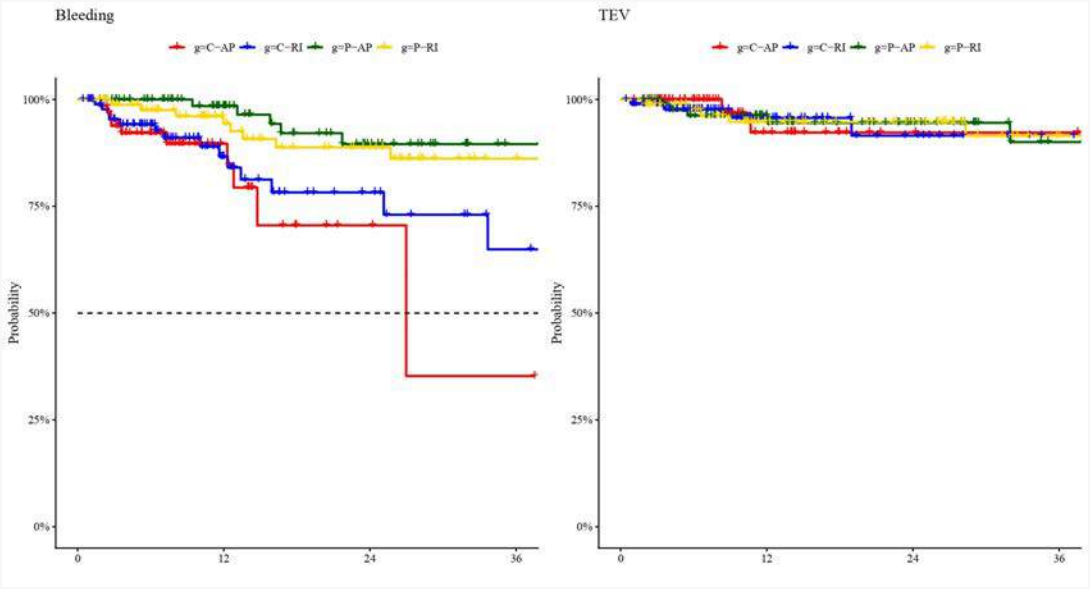

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ITALIAN REGISTRY ON ACTIVE ADULT IMMUNE THROMBOCYTOPENIA -GIMEMA ITP0918 STUDY: COMBINATION THERAPIES WITH A FOCUS ON TPO-RA BASED ASSOCIATIONS

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Background. Combination therapy (CT) for ITP is an emerging option, particularly in refractory patients, also given the progresses in pathophysiological understanding and availability of new treatments. Current guidelines do not address CT, and real-world data on its spread are very limited.

Methods. From October 2018 to March 2026, 29 hematology centers joined the Italian ITP Registry, recruiting adults with primary ITP on active treatment at the time of enrolment. CT was considered if maintained for at least 30 consecutive days. Historical data were collected retrospectively at study entry and prospectively at each annual visit. The study is sponsored by GIMEMA Foundation (Rome). Data collection and analysis were carried out by Hematology Project Foundation (Vicenza).

Results. As to March 25, 2026, 1203 patients (pts) were recruited, of which 467 were evaluable for this analysis. Pts with at least one CT were 141 (30.2%), 39 (8.4%) reporting two or more type of CTs. Male were 58 (41.1%) and female 83 (58.9%). Median age at the first CT was 62 (IQR: 49–75) and the median time from diagnosis to first CT was 10.4 (IQR: 4.1–50.0) months.The most common of all CTs was eltrombopag (ELT)+corticosteroids (CS) (36.7%) followed by TPO-RA+immunosuppressor (16.3%), romiplostim (ROM)+CS (15.8%), CS+immunosuppressor (CSA/MMF/AZA-/CTX/RTX) (15.8%), fostamatinib+TPO-RA or immunosoppressor (4.6%), avatrombopag (AVA)+CS (4.1%) and fostamatinib+CS (3.5%) (Fig. 1).Among all pts receiving at least one TPO-RA, the percentage treated with TPO-RA in combination was 29.7% for ELT, 37.3% for ROM and 30% for AVA. The most common TPO-RA-based CT was with CS: 79.1%, 60.8%, 80% with ELT, ROM and AVA respectively. Three patterns of CS administration emerged: bridging, continuous and intermittent. The median CS exposure for these three patterns was respectively 65, 551 and 325 days in ELT combinations, 99, 341 and 122 days in ROM combinations and 53, 355 and 166 days in AVA combinations. Less frequent TPO-RA-based CT were with immunosuppressor (14.3%, 33.3%, 20.0% with ELT, ROM and AVA respectively) and TPO-RA -fostamatinib (5.5% for ELT and 5.9% for ROM).

Conclusion. These preliminary data show a high use of CT in real life. TPO-RA-based CT was the most common one, particularly in association with CS. Interestingly, CT have also been reported in a considerable number on patients combining TPO-RA with older immunosuppressant agents or most recent agents like fostamatinib.

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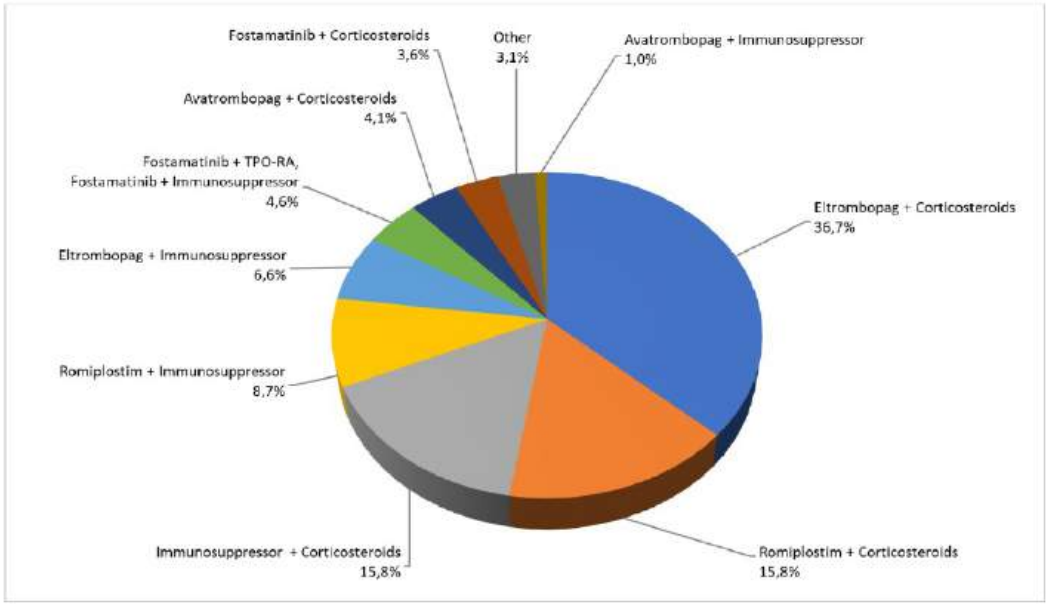

Fig. 1, distribution of CT.

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

EFFICACY AND SAFETY OF SPLENECTOMY IN PRIMARY ITP IN THE MODERN ERA: A GIMEMA STUDY

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Background. Splenectomy is mainly reserved for selected patients (pts) with primary immune thrombocytopenia (ITP) in chronic phase. Most reports derive from historical cohorts, with limited contemporary real world evidence. We evaluated efficacy and safety of splenectomy performed after 2010.

Methods. The GIMEMA ITP1324 is a multicenter retrospective observational study including adult ITP pts who underwent splenectomy between 2010-2022. Pts were longitudinally assessed for platelet (PLT) response (complete, CR: PLT≥100×10^9/L; partial, PR: PLT≥30×10^9/L with a ≥2 fold increase, overall response rate (ORR): CR+PR), post splenectomy treatments and incidence of adverse events (AEs). Longitudinal PLT trends and response durability were analyzed by generalized estimating equation (GEE) models.

Results. Among 69 splenectomized pts, 68 were eligible for analysis (60% female). Median age at splenectomy was 38 years; median pre operative PLT count was 89×10^9/L. Comorbidities were present in 32%, including prior thrombosis in 4.5% and G≥3 infections in 18%. Vaccination coverage was 96%, antithrombotic and antibiotic prophylaxis were used in 17% and 3.2%. ITP therapy was administered in all pts, mostly corticosteroids (CS) (86%), IVIG (49%), TPO RAs (30%) and rituximab (12%). As a bridge to splenectomy, 72% of pts received therapy including CS (48%), IVIG (32%) and TPO-Ras 26%).At 1 mo, 73% of pts achieved CR, with rates of 75%, 71%, and 65% at 3, 6, and 12 mos; ORR were 81%, 88%, 85%, and 83%, respectively. GEE analyses showed a borderline decline in CR probability over time (OR=0.96 per step) and a modest reduction in PLT counts (Figure). Among responders, 9%, 10.8% and 12.3% lost the R after 3, 6 and 12 mos respectively.Post splenectomy therapies were required in ~1/3 of pts (27–36% across timepoints). Use of rescue therapies declined over time: CS from 48% to 16–22% and IVIG from 32% to 6.5%. TPO RAs were the most common agents (16–22%), rituximab use (1.5%) and PLT transfusions were uncommon (1–3%).Peri operative AEs occurred in 13%, mainly G2 infections and bleeding. Over follow up, AEs were infrequent (3–11%), mostly mild infections or mucocutaneous bleeding, with 1 mesenteric vein thrombosis.Further efficacy and safety data will be reported at the congress.

Conclusions. This contemporary Italian real world cohort confirms that splenectomy achieves high response rates with a low incidence of complications, supporting its continued role in selected pts with ITP.

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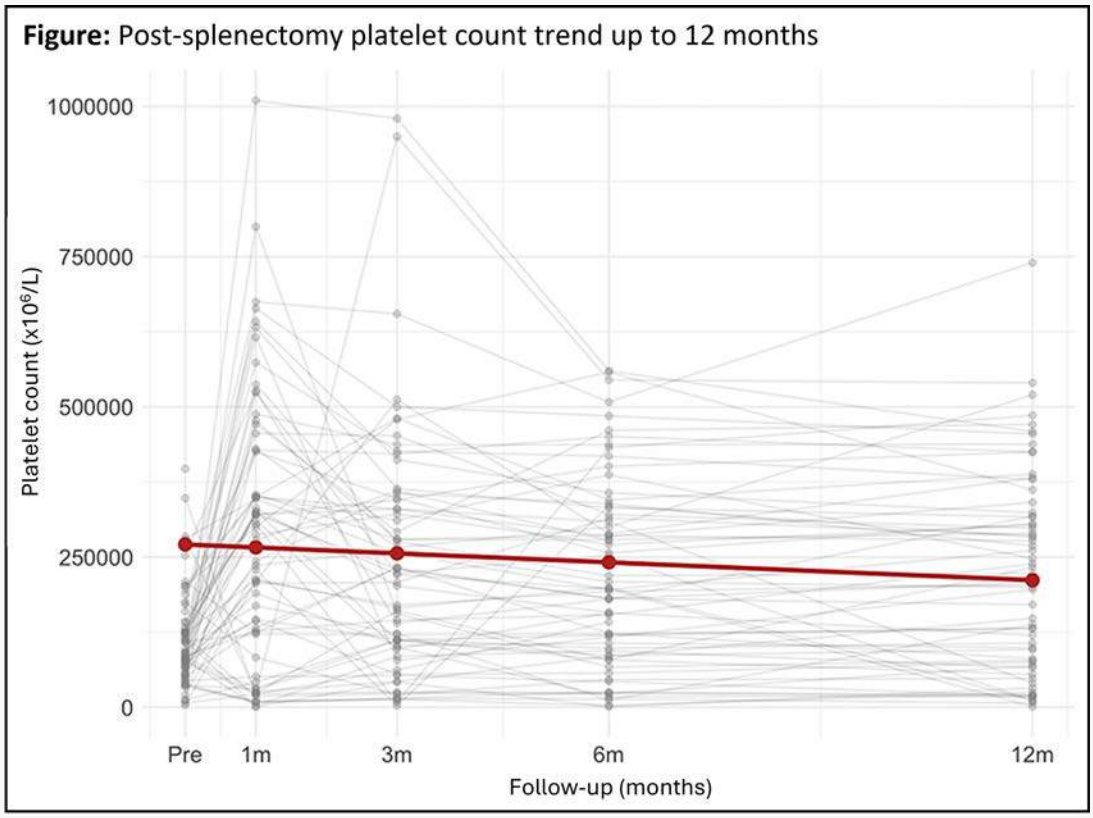
Figure: Post-splenectomy platelet count trend up to 12 months
1000000
750000
500000
250000
0
Platelet count (x10⁶/L)
Pre
1m
3m
6m
12m
Follow-up (months)

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

BIOLOGICAL CHARACTERIZATION OF PATIENTS WITH PRIMARY ITP: THE GIMEMA ITP1222 STUDY

I. Fortunati[1], E. Lucchini[2], V. Carrai[3], E. Rossi[4], C. Santoro[5], F. Palandri[6], A. Borchiellini[7], U. Consoli[8], M. Ballerini[1], E. Simeone[9], G. Carli[10], A. Poloni[11], J. Agnelli Giacchello[12], B. Toffoletto[13], M. Granzotto[13], F. Sirianni[13], L. Gorreo Renzulli[14], A. Piciocchi[14], S. Soddu[14], F. Zaja[1|2]

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Different pathogenic mechanisms, including B-cell–mediated autoantibody production and T-cell–driven cytotoxicity, may variably contribute to the pathogenesis of primary ITP. Despite advances in treatment, no validated predictive biomarkers are available, and therapeutic decisions remain mainly guided by clinical features.The prospective GIMEMA ITP1222 study aims to biologically characterize adult patients with primary ITP by collecting longitudinal blood and bone marrow samples at diagnosis, before each line of treatment and during follow-up, and to correlate them with treatment response. Laboratory assessments included platelet parameters, antiplatelet antibodies (anti-GPIIb/IIIa, GPIb/IX and GPIa/IIa, detected by indirect MAIPA), thrombopoietin (TPO) serum levels by ELISA, lymphocytes flow cytometry, cytokine levels, B and T-cell clonality, complement markers, genetic panel for autoimmune-associated lymphoproliferative disorders, fecal microbiota. Response to treatment is evaluated according to International Working Group criteria.Out of 77 enrolled patients by 10 Italian centers, 53 were evaluable at this cut-off. Median age was 59 years (range 20–88), 62% were female, median platelet count was 10×109/L (range 1-86) with a median immature platelet fraction of 19.1% (range 2.4-51.6). Median TPO level was 61pg/mL (range: undetectable - 1533).Antiplatelet antibodies were detected in 20 patients (38%): 10 tested positive for all 3 antibodies, 5 for two, and 5 for one. The most frequently detected was anti-GPIIb/IIIa, in 15 patients.All patients received steroids as first-line therapy (51% prednisone and 49% dexamethasone). At day +30, 49 patients were evaluable: 17 (35%) were in complete response, 11 (22%) in response, and 21 (43%) were non-responders.Analysis of biological parameters at day +30 are currently ongoing. Additional results, particularly those concerning baseline cytokine profiles, B- and T-cell clonality and fecal microbiota, as well as the correlation of these parameters with response at day +30 will be presented at the meeting.

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Non-Hodgkin's Lymphoma

LARGE B-CELL LYMPHOMA TREATMENT WITH LONCASTUXIMAB TESIRINE IN AN ITALIAN REAL-LIFE EXPERIENCE

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Loncastuximab tesirine (LT), an anti-CD19 pyrrolobenzodiazepine-conjugated monoclonal antibody, is approved for the treatment of large B-cell lymphoma (LBCL) patients from third line. The phase 2 registration trial showed rapidly occurring responses lasting for more than a year in patients with least 2 previous treatment lines.This is an Italian real-life observational study with LT aimed at assessing its effectiveness in terms of response rate and time to response in a cohort of patients with LBCL relapsing after or refractory to at least 2 previous treatments. Progression-free, overall survival, response duration and safety are secondary endpoints. LT was administered in accordance with prescribing indications until disease progression or unacceptable toxicity.Thirty-seven patients (25 males and 12 females) with LBCL (including 4 cases of double-hit diffuse LBCL) received LT for a median number of 3 cycles (range: 1-16) and after a median of 3 (range: 2-12) previous lines of therapy. Median age was 69 years (range: 26-90). Disease stage was II-I-IV in 89.2% of the cases, with extranodal disease in 78.4% and bulky masses in 21.6%. ECOG performance status ≥ 2 was reported in 43.2% of the cases. Three patients already received autologous transplant and 12 (32.4%) CART cells. Eighteen (48.6%) were refractory to the latest treatment. A complete response was obtained in 32.4% of patients and a partial response in 10.8%; median time to response was 3.3 months. The remaining 51.4% of the patients progressed with no response; 5.4% remained stable. At a median follow-up of 17.1 months, median progression-free and overall survival were 2.7 and 5.5 months, respectively (Figure). Median duration of complete response was 5.4 months. Seven patients developed 17 drug-related hematologic adverse events (AEs), including grade 3 anemia, neutropenia and thrombocytopenia in 3, 1 and 3 cases, and grade 4 neutropenia and thrombocytopenia in 1 and 3 cases, respectively. Twenty-five extra-hematologic AEs were reported in 19 patients; 4 AEs were grade ≥ 3: grade 3 skin toxicity and edema in one case each, and 2 grade 3 infections. No treatment-related deaths occurred.LT displays rapid disease control in a population of highly pretreated LBCL patients with severe presentation. More disappointing survival results were seen in the current population compared to registration study due to much more unfavorable disease characteristics.

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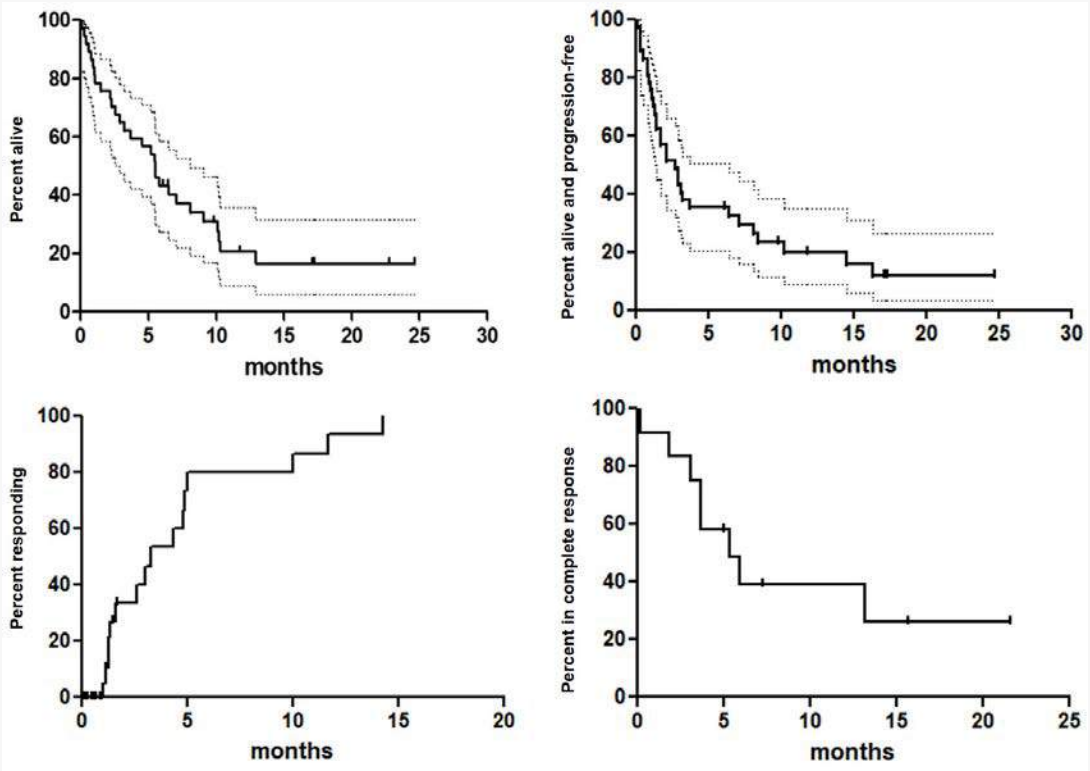
Non-Hodgkin's Lymphoma



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Non-Hodgkin's Lymphoma

INTEGRATED MOLECULAR AND METABOLIC PROFILING IDENTIFIES DETERMINANTS OF OUTCOME WITH LONCASTUXIMAB TESIRINE IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

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Relapsed or refractory large B-cell lymphoma (LBCL) remains associated with poor prognosis. Loncastuximab tesirine (Lonca) is a CD19-directed antibody-drug conjugate with demonstrated clinical activity in heavily pretreated disease; however, treatment benefit is heterogeneous and no validated biomarkers currently enable biological stratification or prediction of outcome, underscoring the need to define determinants of response. We conducted a single-center retrospective analysis of 41 R/R LBCL patients treated within the LOTIS-1 (n=16) and LOTIS-2 (n=25) trials at Humanitas Research Hospital. ctDNA was assessed by CAPP-Seq at baseline (BL), cycle 3 (C3), and end of treatment (EoT), expressed as haploid genome equivalents per mL (hGE/mL); copy number variations were derived from ctDNA using CNVkit. TMTV was calculated using an SUV threshold of 4.0. Biomarker cutoffs were defined by ROC analysis; PFS by Kaplan-Meier with HSCT censoring. The overall response rate was 53.7% (CR 17.1%, PR 36.6%), with median PFS of 3.3 months (95%CI 2.8-5.4) and median OS of 5.8 months (95%CI 4.7-10.7).Baseline ctDNA and TMTV emerged as strong independent predictors of outcome. Using Youden-optimal cutoffs (ctDNA 244.8 hGE/mL; TMTV 134.8 mL), high ctDNA and high TMTV were associated with shorter PFS (2.7 vs 5.9 months, p=0.001; and 2.7 vs 5.9 months, p=0.0004, respectively). A composite ctDNA+TMTV risk score identified three groups with markedly different PFS (7.8, 3.7, and 2.5 months; p=0.0001) and ORR ranging from 75% to 31%. On multivariable analysis, TMTV (HR 2.62, p=0.016) and ctDNA (HR 2.54, p=0.029) were independent predictors of PFS. MRD negativity at C3, achieved in 51.5% of evaluable patients, identified a subset with markedly prolonged PFS (7.8 vs 3.6 months, p=0.018). TP53 mutation was detected in 48.8% of patients; the biallelic subgroup (mutation + del17p, n=4) had the highest baseline ctDNA and no MRD clearance at C3. No de novo CD19 mutations emerged during treatment. No gene mutation independently predicted PFS; conversely, specific copy number gains were significant predictors: 7q21.3 (HR 7.45, p=0.0007), 7q11.2 (HR 6.04, p=0.004), 1p12 (HR 4.76, p=0.004), and 11q (HR 2.88, p=0.038).These data demonstrate that integrated liquid biopsy and metabolic imaging enables prognostic stratification in R/R LBCL treated with Lonca, with chromosomal instability emerging as a novel potential determinant of resistance to CD19-directed ADC therapy.

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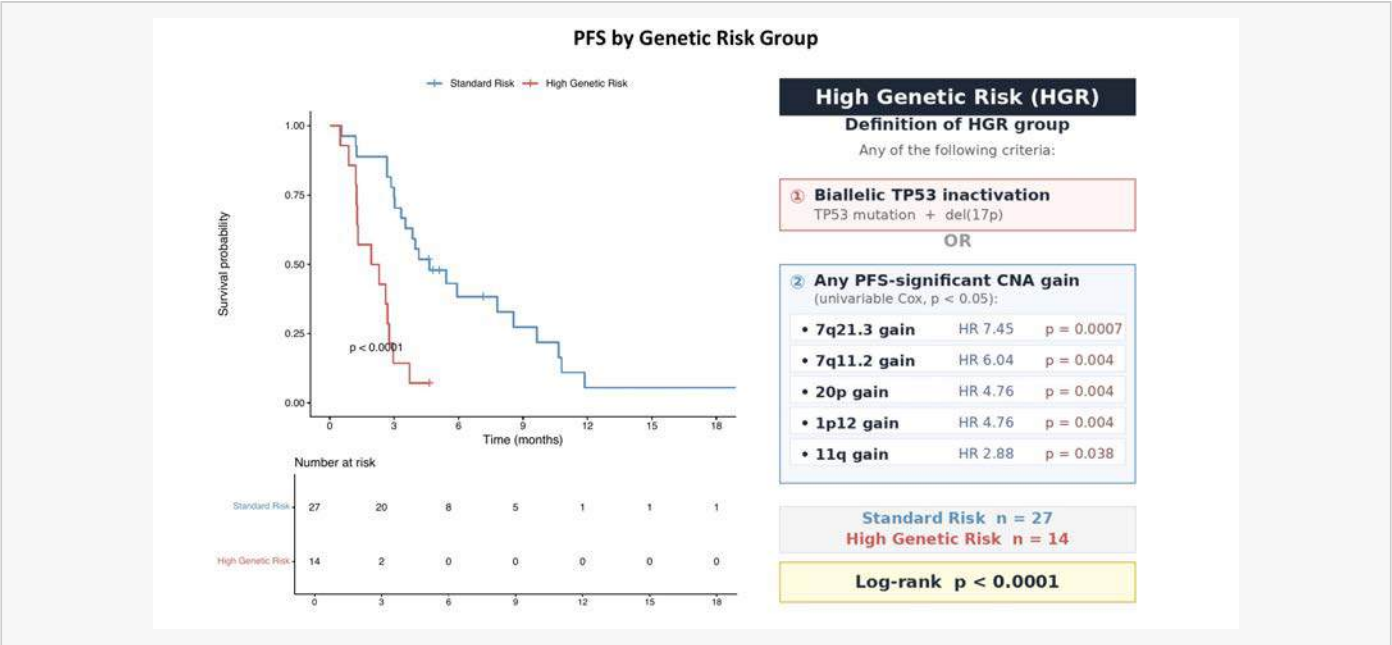
PFS by Genetic Risk Group
Standard Risk
High Genetic Risk
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
3
6
9
12
15
18
Time (months)
Number at risk
Standard Risk 27 20 8 5 1 1 1
High Genetic Risk 14 2 0 0 0 0 0
High Genetic Risk (HGR)
Definition of HGR group
Any of the following criteria:
① Biallelic TP53 inactivation
TP53 mutation + del(17p)
OR
② Any PFS-significant CNA gain
(univariable Cox, p < 0.05):
• 7q21.3 gain HR 7.45 p = 0.0007
• 7q11.2 gain HR 6.04 p = 0.004
• 20p gain HR 4.76 p = 0.004
• 1p12 gain HR 4.76 p = 0.004
• 11q gain HR 2.88 p = 0.038
Standard Risk n = 27
High Genetic Risk n = 14
Log-rank p < 0.0001

Non-Hodgkin's Lymphoma

BGB-16673, A BRUTON TYROSINE KINASE DEGRADER, IN PATIENTS WITH RELAPSED/REFRACTORY WALDENSTRÖM MACROGLOBULINEMIA: A PHASE 1 CADANCE-101 STUDY UPDATE

A. M. Frustaci[1], J. Trotman[2], C. Cheah[3], J. Seymour[4], C. Tam[5], R. Parrondo[6], D. Roos-Weil[7], E. Tausch[8], A. Michallet[9], G. Hess[10], F. Bach[11], H. Eradat[12], Y. Zhang[13], L. Xu[13], K. Hua[13], S. Fabre[13], M. Takai[13], S. Rose[13], M. Shadman[14]

[1]Niguarda Cancer Center, Division of Hematology; [2]Concord Hospital; [3]Linear Clinical Research; [4]Peter MacCallum Cancer Centre; [5]Alfred Hospital; [6]Mayo Clinic; [7]Assistance Publique Hôpitaux de Paris; [8]Ulm University; [9]Centre Léon Bérard; [10]Klinikum der Johannes Gutenberg-Universität Mainz; [11]University Hospital of Cologne; [12]UCLA Santa Monica Cancer Care; [13]BeOne Medicine Ltd; [14]Fred Hutchinson Cancer Center

Background. BGB-16673 is a novel BTK degrader that induces proteasomal degradation of BTK, inhibiting signaling and promoting tumor regression. The ongoing phase 1/2 CaDAnCe-101 study (NCT05006716) is evaluating BGB-16673 monotherapy in patients (pts) with B-cell malignancies.

Aims. To report updated safety and efficacy results for phase 1 of CaDAnCe-101 in pts with R/R WM.

Methods. Eligible pts had R/R WM, ≥2 prior treatments (tx) including anti-CD20 antibody and a covalent BTK inhibitor (BTKi), and ECOG performance status 0-2 (0/1 in the EU). BGB-16673 was administered orally once daily. Primary objectives were safety/tolerability, maximum tolerated dose, and recommended expansion dose. Secondary objectives included overall response rate (ORR; ≥minor response per IWWM-11); the major response rate (MRR) was defined as ≥partial response.

Results. As of Dec 15, 2025, 43 pts received BGB-16673 (100 mg, n=15; 200 mg, n=15; 350 mg, n=13). Median age was 72 years; median number of prior tx was 3. Prior tx included anti-CD20 antibody (100%), covalent BTKi (100%), noncovalent BTKi (16.3%), BCL2 inhibitor (23.3%), chemotherapy (93.0%), and proteasome inhibitor (32.6%); 83.7% discontinued prior BTKi due to progressive disease (PD). Median follow-up was 14.3 months, and 60.5% remained on tx. Any-grade tx-emergent adverse events (TEAEs) occurred in 95.3% of pts (grade ≥3, 60.5%). The most common were neutropenia/neutrophil count decreased (37.2%), diarrhea (30.2%), and contusion (27.9%). Grade ≥3 TEAEs included neutropenia/neutrophil count decreased (34.9%) and anemia (14.0%); 8 pts had a grade ≥3 infection. No atrial fibrillation occurred. Febrile neutropenia and major hemorrhage (grade 3 hematemesis) occurred in 1 pt each. TEAEs that led to tx discontinuation in 11.6%, and dose reduction in 7.0% of pts; as previously reported, 3 pts died due to TEAEs. The ORR was 85.7%, the MRR was 76.2%, and the very good partial response rate was 31.0%. Median time to first response was 1.0 months and 2.8 months to best overall response. Responses were observed in high-risk pts, including 82.9% who discontinued a prior BTKi due to PD. At a median follow-up was 16.6 months, the estimated 15-month PFS rate was 70.4% (95% CI, 52.6%-82.5%).

Conclusions. BGB-16673 demonstrated a manageable safety profile with durable and early evidence of antitumor activity in heavily pretreated pts with R/R WM, including pts with BTK, CXCR4, and TP53 mutations. The phase 2 portion is actively enrolling.

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Table. ORR (defined as PR-L or better) according to prior therapy and mutation status

Characteristic	Patients, n/N (%)	ORR, n/N (%)
Prior therapy		
cBTKi and BCL2i	43/67 (64.2)	40/43 (93.0)
cBTKi, BCL2i, and ncBTKi	12/67 (17.9)	9/12 (75.0)
Mutation status		
BTK mutation	25/66 (37.9)	19/25 (76.0)
del(17p)/*TP53* mutation	44/67 (65.7)	35/44 (79.5)
PLCG2 mutation	10/66 (15.2)	9/10 (90.0)
IGHV unmutated	37/48 (77.1)	32/37 (86.5)
Complex karyotype (≥3 abnormalities)	23/43 (53.5)	17/23 (73.9)

BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; IGHV, immunoglobulin heavy-chain variable region; ncBTKi, noncovalent BTK inhibitor; PR-L, partial response with lymphocytosis.

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Non-Hodgkin's Lymphoma

EFFICACY AND SAFETY OF LONG-TERM ODRONEXTAMAB TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: 3-YEAR FOLLOW-UP FROM THE PHASE 2 ELM-2 STUDY

S. Luminari[1|2], J. Villasboas[3], D. Jagadeesh[4], D. Stevens[5], M. Taszner[6], J. Cai[7], A. Uppala[7], J. Brouwer-Visser[7], H. Mohamed[7], M. Namuduri[7], G. Chong[8]

[1]Azienda Unità Sanitaria Locale – IRCCS of Reggio Emilia; [2]University of Modena and Reggio Emilia; [3]Mayo Clinic, Rochester; [4]Cleveland Clinic Main Campus; [5]Norton Cancer Institute; [6]Medical University of Gdańsk; [7]Regeneron Pharmaceuticals, Inc; [8]Olivia Newton-John Cancer Wellness & Research Centre

Background Odro (CD20×CD3 bispecific antibody) showed compelling efficacy and generally manageable safety in heavily pretreated pts with R/R FL in the Phase 2 ELM-2 study (NCT03888105). We report 3-year outcomes in the global R/R FL population of ELM-2, including pts who switched to once every 4 weeks (Q4W) dosing.

Methods. Details of the ELM-2 R/R FL cohort were reported previously (Kim et al. *Ann Oncol* 2024). Odro step-up dosing was given in Cycle (C)1 to help mitigate cytokine release syndrome (CRS) risk, followed by 80 mg in C2–4, then 160 mg once every 2 weeks (Q2W) maintenance. Pts with complete response (CR) for ≥9 months (mos) switched from Q2W to Q4W dosing. Endpoints reported here include duration of response (DOR) and progression-free survival (PFS) by independent central review, overall survival (OS), and safety.

Results. At data cutoff (Aug 15, 2025), 128 pts were evaluable for efficacy/safety (overall global population). Median duration of Odro exposure was 42.9 weeks (range 0.4–264.0) and median duration of follow-up was 39.2 mos (95% CI 35.8–39.9). Median duration of follow-up from time of switching in pts who switched to Q4W dosing (n=48) was 27.0 mos (95% CI 22.4–31.9). Baseline characteristics were similar between the overall population and pts who switched to Q4W dosing.In the overall population, median DOR was 26.0 mos and median duration of CR was 35.2 mos. In pts who switched to Q4W dosing, median DOR from time of switching was 31.9 mos. In the overall population, median PFS was 24.1 mos (36-mo PFS rate 40.8%) and median OS was not reached (NR; 36-mo OS rate 64.3%). In pts with CR, median PFS was 38.0 mos and median OS was NR.All 128 pts had treatment-emergent adverse events (TEAEs), with Grade ≥3 TEAEs in 112 pts (87.5%). Discontinuation due to TEAEs occurred in 30 pts (23.4%) and 5 pts died due to treatment-related adverse events. With 0.7/4/20 mg step-up dosing, CRS occurred in 34/60 pts (Grade 3 in 1 pt); no new CRS events occurred after switching to Q4W dosing. Infections occurred in 81.3% of pts; most common were COVID-19 (39.8%), pneumonia (20.3%), and upper respiratory tract infections (17.2%).

Conclusions. Odro demonstrated durable responses, with prolonged PFS/OS, particularly in pts with CR. The long-term safety profile was generally consistent with previous reports, with no new safety signals. In ELM-2 with ~3 years' follow-up, Odro continued to show efficacy benefits and manageable safety in heavily pretreated pts with R/R FL.

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Non-Hodgkin's Lymphoma

THE PREDIC-TO STUDY: AN INTERNATIONAL, REAL-WORLD COHORT STUDY OF VENOUS THROMBOEMBOLISM RISK MODEL STRATIFICATION IN DLBCL PATIENTS ACROSS ASIA, EUROPE AND UNITED STATES OF AMERICA

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality in diffuse large B-cell lymphoma (DLBCL). Several models, including Khorana, ThroLy, and Model IX, have been developed to stratify thrombotic risk, but their comparative performance in DLBCL remains unclear. This study aimed to compare the discriminative ability of Khorana, ThroLy, Model IX, and R-IPI for predicting VTE and overall survival (OS) in a large international real-world cohort. We retrospectively analyzed 1,504 consecutive DLBCL patients diagnosed between 2004 and 2024 across five centers in Europe, Asia, and the United States (NCT06694779). VTE was defined as objectively confirmed deep vein thrombosis or pulmonary embolism after diagnosis. VTE occurred in 219 patients (14.6%), with a 1-year cumulative incidence of 3.3% (95% CI 2.4–4.2) and a median time to event of 72 days. VTE independently predicted inferior OS (38.5 vs 172.3 months). In univariate analysis, hemoglobin, leukocytosis, hypoalbuminemia, BMI>30, bulky disease, and deep vein compression were associated with increased VTE risk ($p<0.05$), while central venous catheter placement was not (HR 1.00, 95% CI 0.71–1.42). Patients not receiving anthracycline-based chemotherapy had higher thrombotic risk (HR 2.53, 95% CI 1.68–3.83), likely reflecting frailty. All models stratified VTE risk, with higher incidence in high-risk groups for Model IX (HR 2.73, 95% CI 1.88–3.95), Khorana (HR 2.54, 95% CI 1.91–3.37), and ThroLy (HR 2.54, 95% CI 1.80–3.58). Model IX showed the best discrimination for VTE (c-index 0.63, 95% CI 0.59–0.66), followed by Khorana, ThroLy, and R-IPI (Table 1). LASSO Cox analysis identified additional predictors, including deep vein compression, BMI>30, hemoglobin, neutrophils, and R-IPI, while albumin showed a protective role, suggesting residual risk not captured by Model IX. For OS, Model IX again performed best (c-index 0.67, 95% CI 0.65–0.69), outperforming other scores (Table 1). While R-IPI retained prognostic value for survival, its ability to predict VTE was limited. Conversely, VTE-oriented models, especially Model IX, captured prognostic information relevant to both thrombosis and survival. In conclusion, VTE is a frequent early complication in DLBCL associated with worse survival, and Model IX represents the most informative tool for risk stratification.

Models	Variables included	OS (c-index, 95% CI)	OS (ΔAIC)	VTE (c-index, 95% CI)	VTE (ΔAIC)
Model IX	Lymphoma subtype (FL or DLBCL), albumin concentration (g/L), WBC count>11x10⁹/L, bulky disease	**0,6749** (0.6516 - 0.6982)	-120	**0.6304** (0.5949 - 0.6659)	- 34
Khorana	Cancer type, PLT count ≥350x10⁹/L, Hb <10 g/dL or use of red-cell growth factors, WBC count >11x10⁹/L, BMI ≥35	0,5998 (0.5757 - 0.6240)	- 86	0,6276 (0.5916 - 0.6636)	- 49
Throly	Previous VTE/IMA/stroke, ECOG 2-4, BMI > 30, Extranodal localization, Mediastinal involvement, ANC <1 × 109/L, Hb <10 g/dL	0,6652 (0.6419 - 0.6885)	- 141	0.6083 (0.5698 -0.6469)	-35
R-IPI	Age >60y, Serum LDH > URL, ECOG ≥2, Ann Arbor Stage (III-IV), Extranodal Involvement	0,6553 (0.6355 - 0.6751)	**- 180**	0,5938 (0.5604 - 0.6273)	**- 76**

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Acute myeloid leukemia

NEWER AML RISK SCORES IMPROVE RISK STRATIFICATION IN CPX-351 TREATED S_AML PATIENTS COMPARED TO ELN2022, BUT A TAILORED PROGNOSTIC MODEL IS STILL NEEDED

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The increasing use of novel agents highlights the need for treatment-specific prognostic models in acute myeloid leukemia (AML). For unfit patients receiving hypomethylating agents plus venetoclax (HMA-VEN) new scores have been proposed. CPX-351 has replaced standard 7+3 chemotherapy as the preferred regimen for fit patients with secondary AML (sAML), a high-risk entity characterized by high-risk mutations. In this setting, ELN 2022 classification provides limited prognostic discrimination, as most sAML patients are classified as adverse risk, and no dedicated score exists for CPX-351–treated patients. We evaluate whether newer HMA-VEN risk scores improve prognostic stratification compared to ELN 2022 in sAML patients treated with CPX-351.96 s-AML patients (median age 69, range 38-77) received CPX-351. NGS was performed on bone marrow using a 34-gene panel (SOPHiA Genetics), Illumina platform, SOPHiA DDM® software. Patients were stratified by ELN 2022 and 2024, the Mayo Clinic genetic risk model (Gangat N. Am J Hematol 2025), and the Beat-AML 2024 model (Hoff FW. Blood Adv 2024).With ELN 2022 most patients were classified as adverse risk (79/96, 82.3%), whereas 10 (10.4%) and 7 (7.3%) as favorable and intermediate. ELN 2024 criteria classified 54 (56.3%), 17 (17.7%) and 25 (26%) as low, intermediate and high risk, respectively. The Mayo model identified 9 (9.4%), 31 (32.3%) and 56 (58.3%) as low, intermediate, and high risk, respectively, while Beat--AML stratified 17 (17.7%), 40 (41.7%) and 39 (40.6%) into the same categories. After cycle 1, 77/96 patients (80.2%) achieved CR. ELN 2022, Mayo, and Beat-AML did not correlate with CR, whereas ELN 2024 favorable risk predicted higher CR rates (91.8% vs 62.5% and 75.0%; p=0.019). Median follow-up was 43 months and median overall survival (OS) was 14 months. ELN 2022 and Mayo did not stratify OS, while ELN 2024 and Beat-AML discriminated outcomes (median OS 20 vs 10 vs 8 months with ELN 2024 and 43 vs 12 vs 10 months with Beat-AML, for low, intermediate and high risk group, $p<0.05$, Fig.1). Allogeneic hematopoietic stem cell transplantation (HSCT) was performed in 29/77 CR patients (37.7%) and was the strongest predictor of OS ($p<0.05$). No model stratified OS among HSCT patients, whereas ELN 2024 and Beat-AML retained prognostic value in non-HSCT patients (median OS 28 vs 13 vs 8 months in the ELN 2024 and 38 vs 17 vs 9 months in the Beat AML model, for low, intermediate and high risk group, $p<0.05$, Fig.1).

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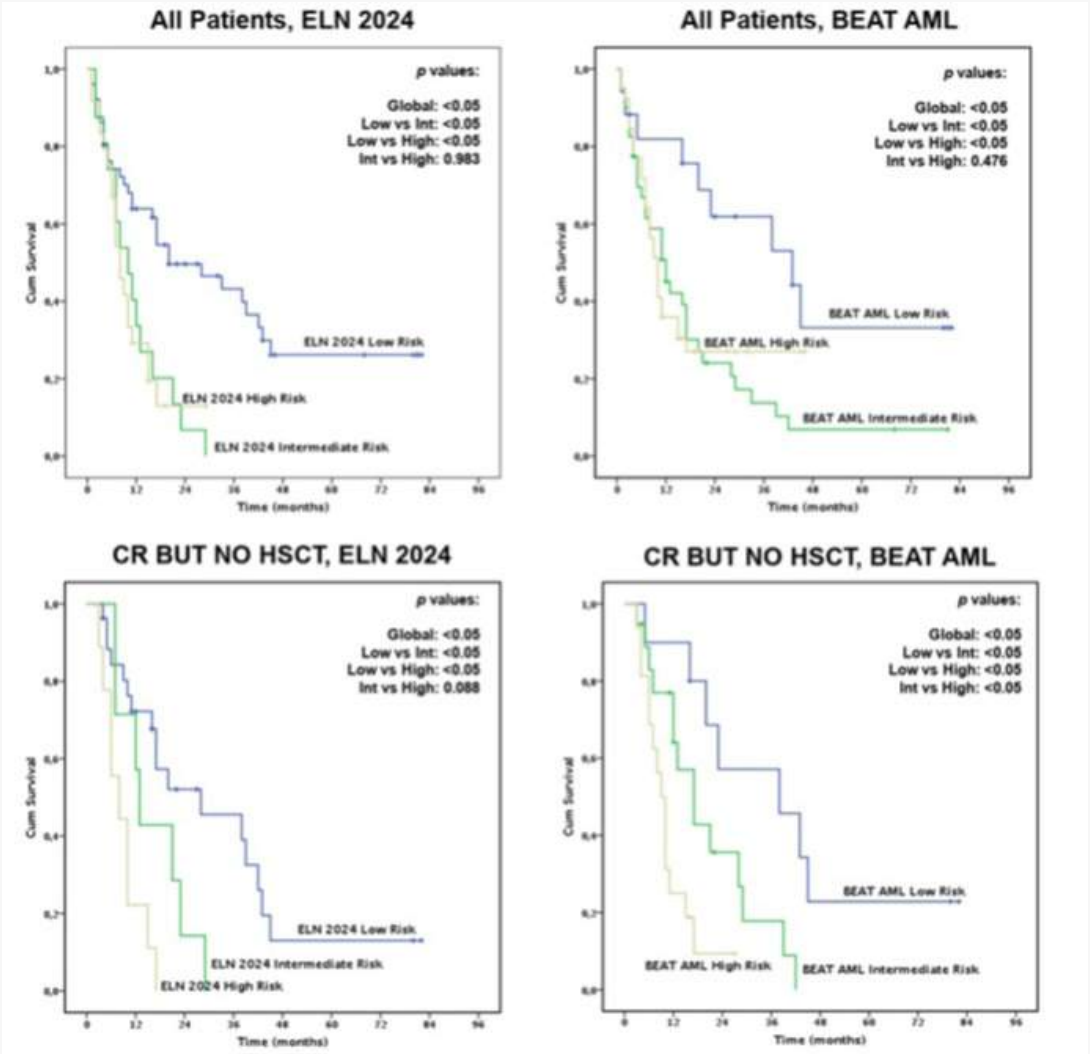

Figure 1: Overall Survival According to ELN 2024 and BEAT AML risk score in all patients (panel A and B) or in CR patients not receiving HSCT (panel C and D)

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Acute myeloid leukemia

ABSOLUTE LYMPHOCYTE COUNT AFTER INDUCTION CHEMOTHERAPY IS A PREDICTIVE BIOMARKER IN ACUTE MYELOID LEUKEMIA PATIENTS AND RELATES WITH POST-THERAPY CHANGES IN IMMUNE TRANSCRIPTOMIC BONE MARROW PROFILE

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Background. Recently, interest in the bone marrow (BM) microenvironment (ME) of acute myeloid leukemia (AML) has been growing. Absolute lymphocyte count (ALC) is an independent prognostic factor in neoplasms; in AML, enhanced ALC recovery after intensive chemotherapy (IC) is associated with superior overall survival (OS). Data correlating ALC recovery and immune-related prognostic factors are still lacking.AimsTo evaluate ALC recovery as an outcome predictor in AML patients achieving complete response (CR) to IC and to explore the role of ME in mediating ALC.

Methods. We evaluated 188 AML patients who achieved CR after IC. From IC start, 4 ALC time-points (TPs) were established and ALC cut-off was 500/mm3.ALC kinetics was analysed at single TPs and also in 2 groups: group A ALC≥500/mm3 at all 4 TPs and group B ALC<500/mm3 in at least one TP. PanCancer Immune NanoString panel were used in BM samples of 35 patients to explore transcriptomic variation during IC.

Results. Among 188 patients, 97 (51.6%) received "3+7" and 91 (48.4%) fludarabine-based IC. Median age was 55. No significant differences were observed among patients regarding biology. Median follow-up was 51.4 months.In "3+7" cohort, a significant correlation with OS in group A (25,5% of all) vs group B (26%) was observed (p=0.02). Notably, within "3+7" patients who achieved measurable residual disease (MRD) negativity (neg), group A had superior OS. When stratifying all patients into those who received allogeneic transplant (HSCT; 66%) and those who did not (34%), OS was not affected by ALC in HSCT cohort, whereas, in non-HSCT patients, it resulted inferior in group B, but group A performed as transplanted ones.As for NanoString analysis, 13 patients (37%) and 22 (63%) belonged to group A and group B, respectively, with no significant differences at baseline between the two groups. After IC, BM of patients in group A was enriched in T-cell activation mediators and immune checkpoints while Group B exhibited inflammatory and myeloid genes (Figure 1A). Gene set enrichment analysis showed a structured T-cell immune reconstitution in Group A whereas ALC failure was associated with uncontrolled immune activation (Figure 1B).

Conclusions. Our study demonstrates that ALC kinetics during IC is a promising biomarker to refine prognostic stratification of AML. The immune transcriptomic profile of BM samplesvaries according to ALC and supports a biological significance of immune ME in guiding ALC recovery.

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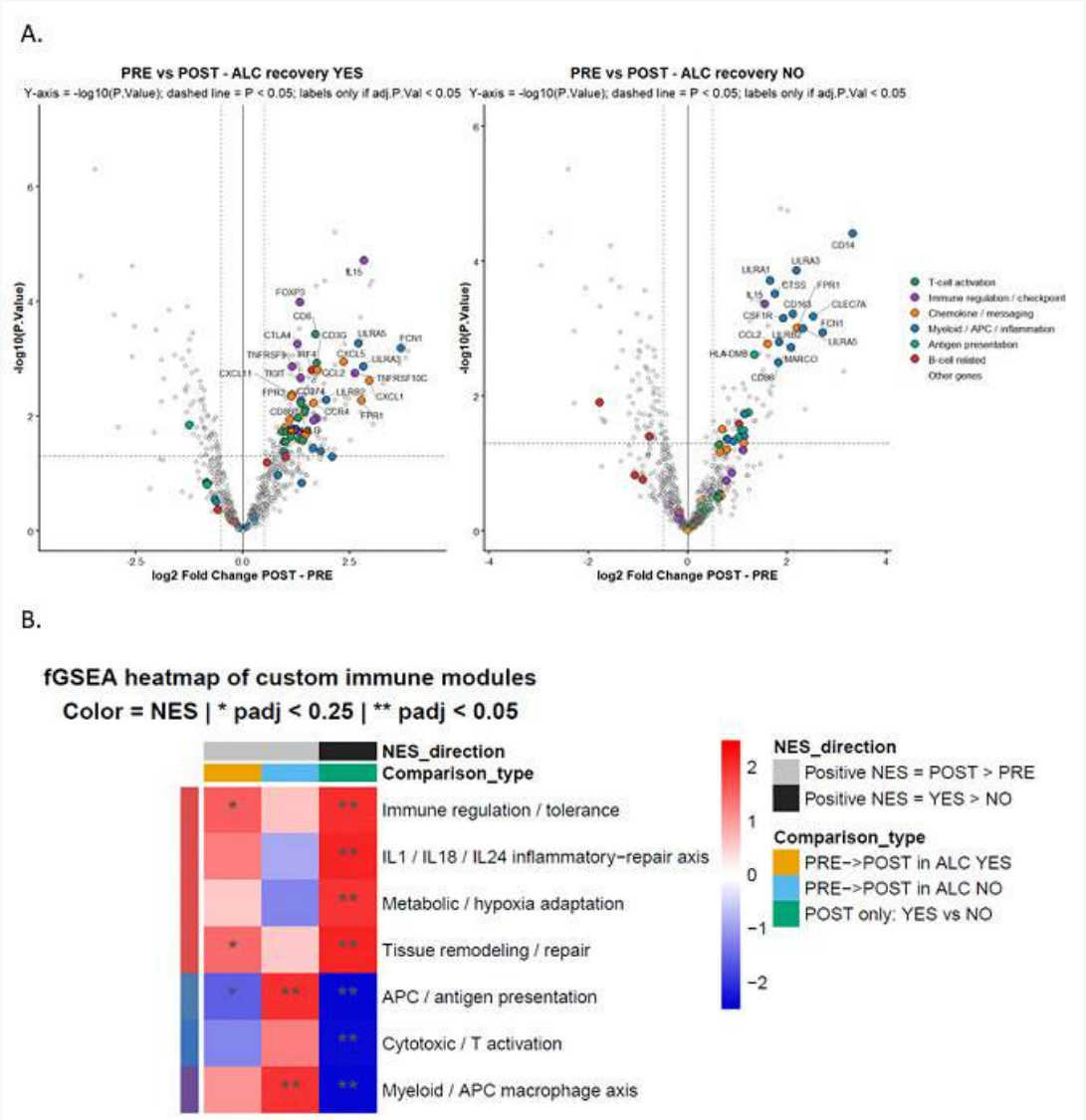

Figure 1: (A.) Volcano plots (POST vs PRE) comparing ALC recovery YES (Group A) and ALC recovery NO (Group B) patients show distinct immune trajectories after induction therapy. Labeled genes represent significantly differentially expressed transcripts (adjusted $P < 0.05$). ALC recovery in group A is characterized by induction of immune regulatory and checkpoint programs (including CTLA4, CD274, TIGIT, and FOXP3), consistent with progressive restoration of immune homeostasis and peripheral tolerance. In contrast, ALC recovery in group B shows predominant activation of myeloid/APC, antigen-presentation, and cytotoxic inflammatory programs, indicating persistent and poorly controlled immune activation. **(B.)** fGSEA of manually curated immune modules confirms enrichment of immune regulation/tolerance, inflammatory-repair (IL1/IL18/IL24 axis), metabolic adaptation, and tissue remodeling in ALC recovery (Group A), whereas ALC recovery (Group B) is enriched for APC/antigen-presentation, cytotoxic T-cell activation, and myeloid inflammatory pathways. Overall, ALC recovery is associated with structured immune reconstitution, while ALC failure reflects sustained dysregulated immune activation.

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Acute myeloid leukemia

RAMD: A RAPID THIRD GENERATION SEQUENCING BASED METHOD FOR ACUTE MYELOID LEUKEMIA RISK ASSESSMENT

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Identification of a well-characterized set of prognostically informative chromosomal aberrations and mutations is required at diagnosis of acute myeloid leukemia (AML) to comply with European Leukemia Net 2022 (ELN22) guidelines for risk assessment and to guide treatment choices, including referral to allogeneic stem cell transplantation. However, the heterogeneity of gold standard assays (GSA) often results in long turnaround times, requiring 4 to >30 days to obtain a complete picture. To overcome this, we developed Rapid AML Mutations Detection (RAMD), a third-generation sequencing-based assay that enables simultaneous screening of ELN22–relevant molecular and cytogenetic alterations within 72 hours. To develop the assay, 88 bone marrow samples at diagnosis of AML were retrospectively collected; matched GSA test results were available for all. 200ng of patient's cDNA was amplified to obtain amplicons of known hot spot mutational regions and potential fusion transcripts originated by known recurrent translocations by 5 parallel multiplex-PCRs. PCR products were barcoded and sequenced via long-read sequencing. Average sequencing depth per amplicon ranged between $1x10^4$ and $1.2x10^6$X. WGS was subsequently performed on the same flow cell (average depth 29.7X ±10.9) to detect chromosomal abnormalities such as structural variants and copy number alterations. Raw data were processed through an automated real-time bioinformatic pipeline, generating full-comprehensive reports for both targeted and whole-genome approach. Using RAMD on the cohort of 88 samples, we detected 21/21 gene fusions, 19/19 *FLT3*-ITD and 150/154 SNVs/InDels with a VAF ≥3%, all previously identified by GSA. Notably, all gene fusions, from canonical AML1-ETO, inv(16) (including types D and E), and *PML::RARA* to rarer events such as *KAT6A::CREBBP* and *MLL::ELL*, were identified within 6–8 hours thanks to real-time analysis. WGS further revealed rare rearrangements involving *KMT2A* (including MLL^{PTD}), *RARA*, *MECOM*, and *RUNX1* among others. RAMD's primary value lies in its remarkable speed, low cost, and a single-method approach utilizing simple wet preparations and automated real-time pipeline. RAMD is an ideal candidate for clinical laboratory integration with minimal financial burden and basic staff training. Furthermore, the ability to generate a patient's full mutational profile and whole-genome data within a 72-hour window marks a definitive advancement toward truly personalized precision medicine.

Acute lymphocytic leukemia

VENETOCLAX ALONE AND IN COMBINATION WITH PONATINIB OR BLINATUMOMAB TARGETS HIGH-RISK ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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Intro. Despite advances, including targeted immunotherapies (inotuzumab, blinatumomab [blina]), outcomes in adult acute lymphoblastic leukemia (ALL) remain poor. Venetoclax (Ven), a selective BCL2inh, has shown activity in B-/T-ALL and AML. Ponatinib (Pona), a potent TKI used in Ph+ and some Ph− B-ALL, represents a rational combination partner.

Methods. A preclinical panel included 18 cell lines (4 AML, 2 T-ALL, 12 B-ALL) and 47 primary samples (43 B-ALL, 5 T-ALL, 1 MPAL) were treated with Ven and Pona for viability/proliferation evaluation. Co-culture with healthy donor $CD3^+$ T cells assessed blina activity (24h). RNA-seq was performed in 32 B-ALL pts and 19 donors; digitalMLPA-ALL CNA analysis in 25 samples. Results: Ven exhibited heterogeneous activity across AL cell lines, with 13/19 classified as sensitive (72h; see Fig. 1A). Importantly, marked sensitivity to ven was observed across multiple B-ALL subgroups (Fig 1A), including high-risk subtypes. Importantly, the Ven–Pona combo showed synergistic effects in SUP-B15 cells and additive effects in other B-ALL subgroups. BCL2 B-ALL expression identified distinct high- (n 7) and low-expressing subsets (n 12). No correlation was observed between BCL2 expression and Ven response. dMLPA-ALL showed enrichment of 20q13.12/13 deletions in responders, while non-responders were enriched for large chr17 CNAs. 43 primary B-/T-ALL samples were stratified into 3 groups by Ven sensitivity; IC50 was lower in C1 ($p<0.01$; Fig 1B), indicating a clear response gradient. Interestingly 5/9 relapses were classified as sensitive (3 Ph−, including 1 BCL2r case, and 2 Ph+/ABL1T315I) and 4 (Ph-like, MPAL KMT2Ar, Ph+, CEBPEr) were non-resp and exhibited marked resistance (IC_{50}16 to 99μM). Importantly, the Ven–Pona combo (n=4) showed evidence of synergistic/additive interactions in 3/4 pt samples (2 Ph-,1 Ph+), with the higher syn score in a relapsed Ph-like case. In preliminary co-culture experiments using NALM-6 and healthy $CD3^+$ T cells, the addition of Ven enhanced NALM-6 sensitivity to T $CD3^+$ cytotoxicity. Remarkably, the ven-blina combo further potentiated T-cell killing. Conclusion: Ven showed broad activity across AL subgroups. In B-ALL, distinct sensitive/resistant subsets emerged at diagnosis and relapse. Ven remained active in relapsed high-risk cases, supporting its potential and need for stratification. Combo with Pona/Blina showed promising synergy, warranting further study. PNRR-M-R1-2023-12377495 MULTIDIMENSION-ALL

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Acute lymphocytic leukemia

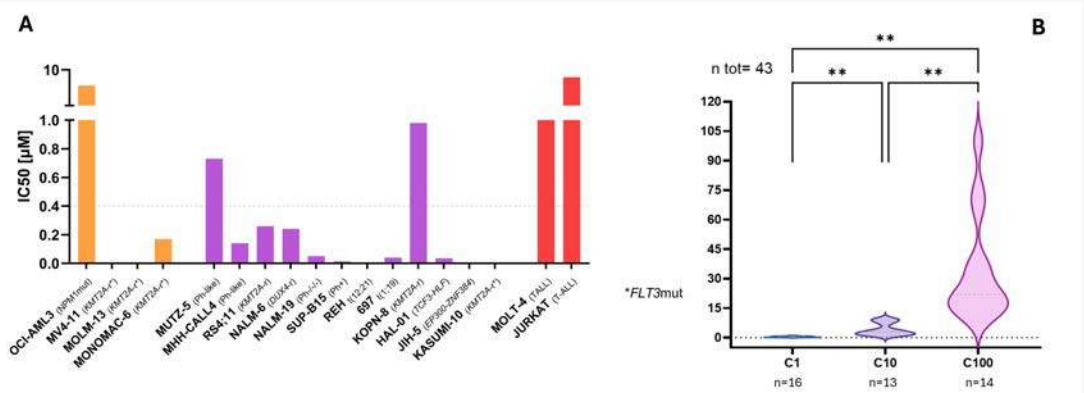

Fig.1. (A) *In vitro* 72h response to venetoclax in **19** acute leukemia cell lines [4 AML (orange), 2 T-ALL (red), and 12 B-ALL (purple)]. Cell lines with an IC_{50} lower than 0.4 µM (grey dashed line) were classified as sensitive. Among AML cell lines (blue), MV4-11 and MOLM-13 were the most sensitive, both harboring *KMT2A*-r and *FLT3*-mut, followed by MONOMAC-6 (acute monocytic leukemia, *KMT2A*-r and *FLT3*-mut). OCI-AML3, carrying *NPM1* and *DNMT3A* mutations, was the most resistant AML cell line, with an IC_{50} of 6.5 µM. B-ALL cell lines (red) showed a more heterogeneous response: KASUMI-10, REH, and JIH-5 were the most sensitive (IC_{50} range 0.001-0.0001 µM), whereas MUTZ-5 and KOPN-8 were particularly resistant, with IC_{50} values of 0.73 and 0.98 µM, respectively. The two T-ALL cell lines (green), MOLT-4 and JURKAT, were both highly resistant to venetoclax, with IC_{50} values of 1.06 and 8.37 µM, respectively. * *FLT3*-mutated cell lines. **(B)** *In vitro* 72h response to venetoclax in **43 B-ALL** patient primary cells and divided according to their IC50 [C1: IC50 < 1 µM; C10: 1–10 µM; C100: > 10 µM. IC50. * p<0.05 ** p<0.01, *** p<0.001].

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Acute myeloid leukemia

PROGNOSTIC PERFORMANCE OF THE NEW ELN 2024 CLASSIFICATION IN UNFIT PATIENTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH NON-INTENSIVE THERAPIES A MULTICENTRIC STUDY OF RETE EMATOLOGICA LOMBARDA

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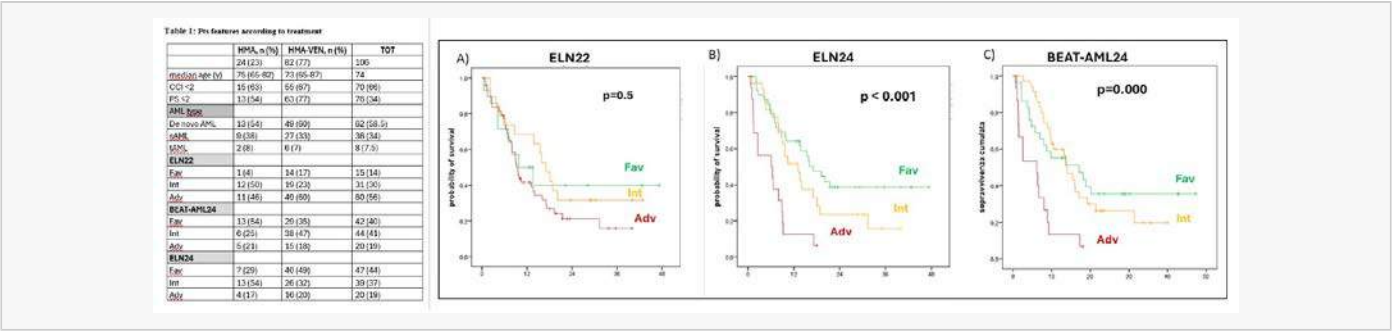
The European LeukemiaNet (ELN) recommendations represent the gold standard for risk stratification in Acute Myeloid Leukemia (AML). Two new models, ELN24 and BEAT-AML24, have been proposed for patients (pts) eligible for non-intensive therapies (n-IT).We retrospectively evaluated 106 elderly AML pts (median age: 74 y), unfit according to SIE/SIES/GITMO criteria, diagnosed within REL between 2020 and 2022, to assess the prognostic impact of ELN22, ELN24, and BEAT-AML24 in a real-world setting. Overall survival (OS) was estimated with the Kaplan–Meier method-.Twenty-four pts (23%) received hypomethylating agents (HMA) alone, while 82 (77%) HMA plus venetoclax (VEN). Clinical features were similar, although a higher rate of pts with PS <2 received the VEN-HMA (77% vs 54%, p = 0.03).According to ELN22, ELN24, and BEAT-AML24, 14%, 44%, and 40% of pts were classified as favorable (fav); 30%, 37%, and 41% as intermediate (int); and 56%, 19%, and 19% as adverse (adv), respectively (Table 1).The median OS was 9 months (m). ELN22 did not significantly stratify OS (median: 9.8 vs 13.5 vs 8.9 m in fav, int, and adv risk groups, respectively; p=0.6), with no differences by treatment (HMA p=0.3; VEN-HMA p=0.5; Fig1A).Using ELN24, median OS of the whole cohort was 15.9, 9.8, and 6.1 m in fav, int, and adv risk groups, respectively (p < 0.001), discriminating between int and adv-risk (p = 0.055) although not in a significant way. According to treatment received, the ELN24 failed to discriminate OS in HMA group (p=0.44; median OS: 3.8 m). Conversely, in the VEN-HMA group, ELN24 model showed strong stratification (p<0.001), particularly between int and adv-risk groups (10.3 vs 6.1 m; p=0.008). Fav-risk pts had a median OS of 17 m, significantly superior to int (p=0.038) (Fig1B).According to BEAT-AML24, median OS was 13.6, 8,7 and 6.1m in fav, int, and adv risk groups, respectively (p=0.01), without discrimination between fav and int-risk pts (p=0.8). Like ELN2024, it stratified OS only in VEN-HMA (median: 17, 13.8, and 6.1 m in fav, int, and adv risk, respectively; p=0.000), mainly between int and adv-risk group (p=0.002) (fav vs int-risk group; p=0.08) (Fig1C).In this real-life setting, none of the models allowed prognostic stratification in HMA-monotherapy pts.The ELN24 classification provides robust prognostic stratification only in VEN-HMA treated pts, outperforming BEAT-AML24 model, whereas ELN22 was not suitable for prognostic assessment in pts receiving n-IT.



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Allogeneic, Autologous transplant

REPORT ON THE EARLY EFFICACY AND SAFETY OF MESENCHYMAL STROMAL CELLS (MSCS–OBNITIX™) IN RELAPSE/REFRACTORY ACUTE AND CHRONIC GVHD WITHIN A COMPASSIONATE USE PROGRAM: AN ITALIAN MULTICENTER EXPERIENCE

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Background. Graft versus host disease (GvHD) remains a major complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and patients with steroid- and ruxolitinib-refractory (SRR-GVHD) GvHD have limited treatment options. Clinical management in this setting remains poorly defined. In this context, mesenchymal stromal cells (MSCs) have emerged as a promising therapeutic strategy because of their immunomodulatory and anti-inflammatory properties.

Methods. We conducted a retrospective multicentre analysis of patients with acute and chronic GvHD treated with third-party mesenchymal stromal cells (MSCs- Obnitix™) under compassionate use in Italy. Early response was assessed according to EBMT criteria after the last MSCs infusion.

Results. 14 patients from 8 Italian Centres were included. Median age was 59 years, and the main indication to allo-HSCT was acute leukaemia (both myeloid and lymphoid). In this case series we had mainly skin and gastrointestinal tract involvement.aGvHD was grade 3 in 10/12 (84%) and grade 4 in 2/12 (16%) cases, whereas cGvHD included one moderate and severe case (Table 1 A and B, respectively). The median number of prior therapy lines was 3 (range 2-3).Immunosuppressive therapy before MSCs mainly included ruxolitinib in aGvHD (8/12, 66%) and various combinations in cGvHD. Most patients received four MSC infusions (10/14, 71%). The overall response rate after the last MSCs infusion was 7/12 (58%) in aGvHD, with CR being achieved in 4/12 (34%) and PR in 3/12 (25%) patients. Refractory cases were 5/12 (42%). Both cGvHD patients achieved PR. In aGvHD, immunosuppressive therapy was discontinued in 2/12 (17%) of patients. No adverse events were ever detected. Five patients (42%) in the aGvHD group died, 80% from infectious causes and 20% as consequence of GvHD.

Conclusions. Our data show that MSCs cell therapy provides an improvement in heavily pretreated GvHD, including both gastrointestinal and cutaneous manifestations, allowing discontinuation or reduction of immunosuppressive therapy in about 6/14 (43%)% of cases, and without adverse events. These results encourage further and earlier exploration of MSCs either alone or in combination for GvHD prophylaxis and treatment.

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A

Italian Experiences on Compassionate use of MSCS (Obnitix) for R/R acute-GVHD

aGvHD N = 12	Organ Invol N (%)	Prior Therapy lines	MSCs-cycles N	IST at MSC	Response @ last cy N (%)	Side-Ef N (%)	IST – post N (%)	Outcome Aliv/Dead N (%)
Grade								
G3 10 (84%) G4 2 (16%)	Skin 3 (25%)	1 S-1; Rux+ECP; Etanr 2 S-2; Rux, Etanr 3 S-1; Rux, Etanr	3 3 4	Rux+CsA+S Rux+CsA+S Rux+CsA+S	SD CR CR	0 0 0	Rux+FK+S CsA+S Rux+CsA+S	A A A
	GI 4 (33%)	1 S-2; Rux 2 S-2+CsA;Rux 3 S-2;Rux; Vedolizumab 4 S-2; Rux; ECP	4 4 4 2	Rux+S S Rux+S CsA+S	SD CR CR SD	0 0 0 0	Rux S Rux+S CsA+S	A D D D
	Skin+GI 5 (42%)	1 S-2; Rux 2 S-2; Rux; ECP 3 S-2; Rux; ECP 4 S-2; Rux; ECP 5 S-2; Rux; ECP	3 4 4 4 4	Rux S S Rux+ECP+S Rux+ECP+S	PR PR SD SD PR	0 0 0 0 0	- - S Rux+S ECP	A A D D A
		Median prior lines= 3 (2-3)	≥4 = 8 (66%)		CR 4 (34%) PR/SD 8 (66%)	0	10 (83%)	A 7 (58%) D 5 (42%) Death cause Infec. 4 (80) GvHD 1 (20)

B

Italian Experiences on Compassionate use of MSCS (Obnitix) for R/R chronic-GVHD

CGvHD N = 2	Organ Invol N (%)	Prior Therapy lines	MSCs-cycles N (%)	IST at MSC	Response @ last cy N (%)	Side-Eff N (%)	IST – post N (%)	Outcome Ali/Dead N (%)
Severity								
Moderate 1 (50%)	Skin +lung =1 (50%)	1 S-2, CSA, ECP, FK, Rux, belumosudil, MTX, imatinib	4	MTX+imatinib+S	PR	0	MTX+imatinib+S	A
Severe 1 (50%)	Skin+eye+GI=1 (50%)	2 S-2, CSA, ECP, MTX, Rux, ibrutinib, belumosudil, MMF	4	MMF+S	PR	0	MMF+S	A
Enrolling Italian Centres ➢ AOU delle Marche, Ancona ➢ ASST Spedali Civili, Brescia ➢ IRCCS Ospedale Policlinico San Martino, Genova ➢ A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo ➢ Fondazione IRCCS Policlinico San Matteo, Pavia ➢ Policlinico Universitario A. Gemelli IRCCS, Roma ➢ Ospedale Universitario S. M. M., Udine ➢ Ospedale dell'Angelo, Venezia M			≥4 = 2/2		PR 2/2	0 0		A 2 (100%) D 0

Table 1. Abbreviations: GI=gastrointestinal tract; S=corticosteroids; S-1=methylprednisolone 1mg/Kg; S-2= methylprednisolone 2mg/Kg; Rux=ruxolitinib; ECP=extracorporeal photopheresis Etanr=etanercept; CSA= cyclosporine; FK=tacrolimus; MTX=methotrexate; MMF=mycophenolate mofetil; Infec=infection; CR=complete response; PR=partial response; SD=stable disease; A=alive; D=dead

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POST-TRANSPLANT IMMUNOTHERAPY WITH ALLOGENEIC DONOR-DERIVED CIK CELLS AFTER HLA-MISMATCHED TRANSPLANTATION

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Background. Cytokine-induced killer (CIK) cells are expanded CD3+, CD8+ and CD56+ T cells combining T and NK cell features, mediating graft versus leukemia effect with low risk of inducing graft versus host disease (GvHD). Our previous phase I/II studies showed feasible production, low GvHD and antileukemic activity, particularly in molecular relapse after allogeneic hematopoietic cell transplantation (alloHCT)(Introna M. BBMT 2017). A recent German study further supported this approach (Rettinger E, JCO 2026). We conducted a phase I/II trial using haploidentical or HLA-mismatched donor-derived CIK cells for post alloHCT relapse (NCT03821519), followed by a compassionate use.

Methods. CIK cells were generated from haploidentical (67.9%) or mismatched unrelated donor (36.1%) using OKT3, IFN-gamma and IL-2 for 18-25 days. Three infusions were planned every 21 days (5x10^6, 5x10^6 and 10x10^6 cells/kg). From Dec 2018 to Jan 2025, 47 patients were enrolled; production was successful in 44 patients and target dose was reached in 36 (81.8%). Fourteen patients were not infused due to progression (n=7), GvHD (n=4), infection (n=2) or withdrawal (n=1). We analyzed 28 patients receiving at least one infusion with >=21 days' follow-up.

Results. Median age was 61.9 years (range 54.1-65.3). Diagnoses were AML (75%), myelofibrosis (17.8%), ALL (3.6%) and MDS (3.6%). Median time from HCT to relapse was 5.3 months. At enrollment, 8 patients (28.6%) had active disease (AD), 16 (57.1%) were in MRD positive CR or mixed chimerism (MC), and 4 (14.3%) received prophylactic CIK cells in MRD-negative CR and full chimerism (FC) for high relapse risk. Bridging therapy was used in 9 patients (34.6%) with 44% response; DLI was used in 3. At CIK cell infusion, 5 patients (17.9%) had AD, 17 (60.7%) MRD positive CR or MC, and 6 (21.4%) MRD negative CR and FC. Median follow-up was 9.6 months. Median OS and PFS were 31.2 and 10.1 months, respectively. Outcomes were better in CR with MRD/MC than AD: OS not reached vs 9.8 months and PFS 13.6 vs 4.7 months. Toxicity was limited to one grade 1 skin acute GvHD and one mild chronic GvHD; the latter after prior DLI.

Conclusions. Donor-derived CIK cells after post-HCT relapse were feasible and safe in haploidentical and HLA-mismatched settings, with promising activity, especially in MRD relapse or MC. These findings support earlier prophylactic evaluation of CIK cells in high risk patients after HCT.

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SARCOPENIA ASSESSMENT BY BIOELECTRICAL IMPEDANCE AND FUNCTIONAL TESTS PREDICTS CLINICAL OUTCOMES AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background. Allogeneic hematopoietic stem cell transplantation's outcomes are influenced by patients' nutritional and functional status, with sarcopenia—defined by reduced muscle mass, strength, and physical performance—being potentially associated with increased treatment toxicity, longer hospitalization and poorer survival, although its prognostic role remains insufficiently explored.

Methods. We retrospectively analysed adult patients allografted in our Unit for any diagnosis between November 2018 and February 2025. Data collection included demographics, transplant-related risk scores, functional tests (handgrip strength, chair stand test, gait speed), and body composition by bioelectrical impedance analysis. Sarcopenia was defined using European criteria, such as appendicular skeletal muscle mass (ASM, ASM/height^2), strength (handgrip), physical performance. Outcomes included OS, mortality, and relapse incidence. Associations between sarcopenia and outcomes were assessed by descriptive statistics and univariate/multivariate analyses.

Results. 182 patients were included: 110 (60.4%) were alive and in CR, 38 (20.9%) relapsed, and 34 (18.7%) died. Sarcopenia was absent in 67% of patients, while 33% met at least one criterion. Median OS was 30 months (16–49). On univariate analysis, OS was lower in patients with at least one sarcopenia criterion (14 months, 3–24) versus those without sarcopenia criteria (30 months, 16–43); p=0.015 (figure 1). Lower handgrip strength and ASM/height^2 were associated with mortality (p=0.008), while relapse correlated with lower handgrip strength (p=0.008), percentage muscle mass (p=0.047), ASMM/height^2 (p=0.039), and BMI (p=0.043). Multivariate analysis showed that patients who relapsed or died had lower lean, cellular, and muscle mass (p=0.020). Female sex and handgrip strength were protective factors (HR=0.21, p=0.013 and HR=0.91, respectively - p=0.017).

Conclusions. This study underscores the prognostic relevance of sarcopenia in transplant candidates. Muscle strength, rather than anthropometric indices, appears to drive post-transplant outcomes and can be measured by a practical marker such as handgrip test. Pre-frail and frail patients may benefit from a multidisciplinary prehabilitation approach combining exercise and nutritional support, in order to improve survival and enhance quality of life.

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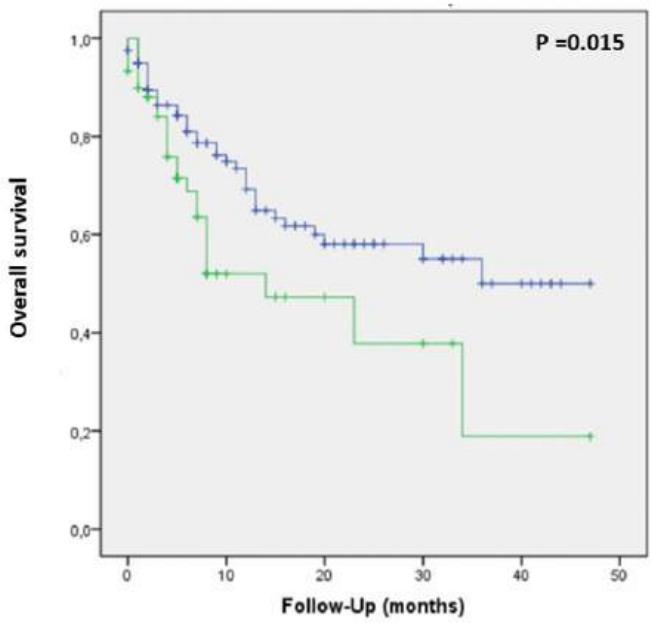

Figure 1. Overall survival in patients without sarcopenia criteria versus those with at least one sarcopenia criterion.

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CHGVHD IMMUNE RECONSTITUTION-SCORE: INTEGRATING IMMUNOLOGICAL AND CLINICAL FEATURES TO PREDICT OUTCOMES IN CHRONIC GVHD

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Background. Chronic-GvHD (chGvHD) is a clinically relevant late complication in long-term survivors of allogeneic HSCT, exerting a substantial impact on patients' quality of life as well as on overall morbidity and mortality. Previously, we demonstrated how a composite score based on post-transplant immune reconstitution (IR) and clinical parameters is effective in predicting chGvHD outcomes.Aim: to validate the chGvHD IR-score in a contemporary cohort of patients and its ability to predict free survival from chGvHD and recurrence, 5 years after the onset of chGvHD itself.

Methods. chGvHD IR-score was calculated using a previously published algorithm, stratifying patients into low-, intermediate-, and high-risk groups. We prospectively analysed 180 patients undergoing allogeneic HSCT (2016–November 2023) who developed chGvHD; the IR-score was available in 166 cases (median follow-up 1132 days, range 386–2648). We assessed the association between IR-score risk and the probability of being alive, in remission, and free from active GvHD or immunosuppressive therapy at 5 years from chGvHD onset, including patients from both historical (n=127) and contemporary (n=78) cohorts with potential 5-year follow-up.

Results. 65 out of 166 patients were classified as low-risk, 73 as intermediate, and 28 as high-risk at the time of chGvHD diagnosis. The 3 years-OS was 92%, 86%, and 60% for low-,intermediate-, and high-risk respectively (p=0.0006). Overall, 127 patients in the historical cohort and 78 in the contemporary cohort were evaluable for the 5-year response. Eighty-nine patients (43%) were alive, in complete remission and off-immunosuppressive treatment, 76 patients (37%) were dead or relapsed while 40 patients (20%) were still under immunosuppressive treatment due to active chGvHD at 5 year after chGvHD onset. Probability of being alive, in complete remission and off immunosuppressive treatment was higher among low-risk patients, while, high-risk patients showed higher probability of death. This confirms the 5-year prognostic value of chGvHD IR-score (p<0.0001).

Conclusions. ChGvHD IR-score is a valid predictor tool of both short and long-term outcomes in chGvHD, effectively stratifying overall survival at 3 and regarding immunosuppressive therapy on long-term. Integration of immunological and clinical parameters into this composite score provides a practical and prognostic tool for a personalized, risk-adapted management strategy for chGvHD

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EARLY INFECTIOUS BURDEN AFTER ALLOGENEIC HSCT IS DIFFERENT ACCORDING ANTI-THYMOCYTE GLOBULIN OR POST-TRANSPLANT CYCLOPHOSPHAMIDE GVHD PROPHYLAXIS

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Anti-thymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) are distinct in vivo T-cell depletion strategies associated with different patterns of immune reconsti-tu-tion, so their overall infectious burden remains poorly defined.The aim of study was to assess whether GVHD prophylaxis platform influences post-transplant infectious burden.We performed a retrospective single-centre study including 146 adult patients undergoing first allo-HSCT (2023–2025) for hematologic malignancies, receiving peripheral blood grafts across donor types and analyzed according to GVHD prophylaxis (ATG-based 5 mg/kg days −2/−1 or PTCy-based 100/80 mg/kg) to evaluate infectious burden.The primary endpoint was 100-day cumulative infectious burden, defined as the cumula-tive number of bacterial, viral and fungal infections and fever of unknown origin (FUO), modelled as time-dependent infection exposure and expressed as area-under-the-curve (AUC). The conventional cumulative incidence (CI) of different infections was reported. In PTCy recipients, FUO between day 0 and +3 were excluded to avoid non-infective fever. Antimicrobial prophylaxis was uniform across cohorts, with fluconazole prophylaxis, acy-clovir and letermovir. Antibacterial prophylaxis was not used.The AUC analysis demonstrated a higher overall infectious burden in PTCy recipients compared with ATG (median AUC 0.17 vs 0.07; p=0.037) (figure), while no significant dif-ferences were observed when AUC was analyzed separately for bacterial, viral or fungal burden.The 100-day CI of bacteremia, viremia and fungal infections were numerically higher in PTCy cohort: 65.2% vs 49.1% (p=0.143), 38.3% vs 24.6% (p=0.265), and 12.4% vs 5.3% (p=0.224), respectively. In univariable competing-risk analysis, PTCy was associated with a higher risk of bacteremia (SHR 1.59, 95% CI 1.01–2.51; p=0.046), and confirmed in multi-variable analysis (SHR 1.56, 95% CI 0.99–2.47; p=0.055), whereas no significant associa-tion emerged for viral or fungal infections. OS, PFS, relapse incidence, NRM and GVHD were comparable between groupsOur findings suggest that cumulative burden assessment by AUC may reveal clinically rel-evant differences in infectious risk not captured by conventional cumulative incidence analyses. This approach may be particularly informative when evaluating intensified GVHD prophylaxis platforms, including multi-agent combinations under investigation in clinical trials.

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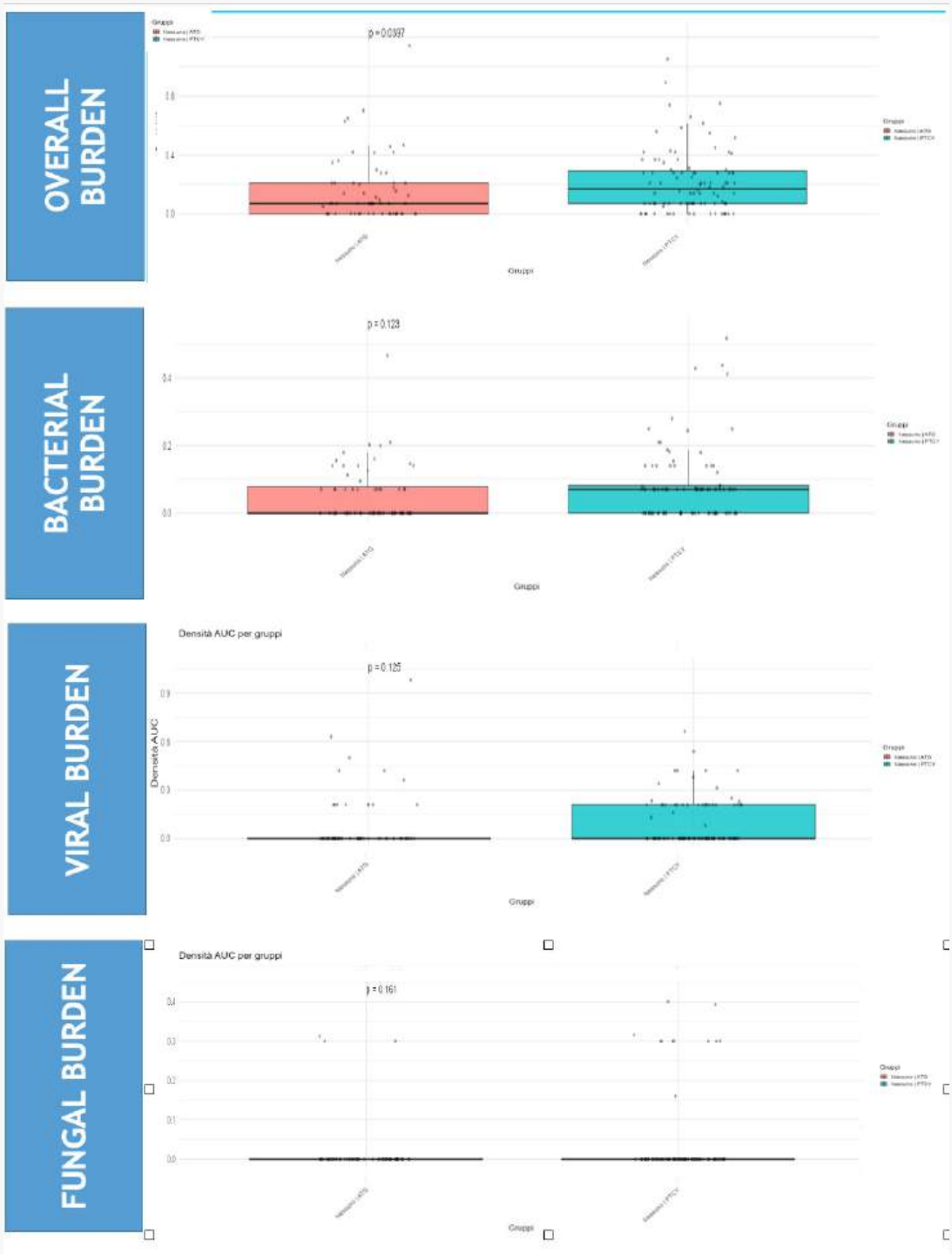

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Myeloma and other monoclonal gammopathies

EFFECTIVENESS OF BRIDGING THERAPY AND IMPROVED OUTCOMES AFTER CILTACABTAGENE AUTOLEUCEL IN CARTITUDE-4

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Introduction. In CARTITUDE-4, single cilta-cel infusion significantly improved progression free survival (PFS) and overall survival (OS) vs standard of care in relapsed and lenalidomide-refractory multiple myeloma after 1–3 prior lines of therapy. We examine how bridging-therapy responses pre cilta-cel relate to post-infusion outcomes in CARTITUDE-4.

Methods. Pts receiving cilta-cel underwent apheresis, bridging therapy (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]), lymphodepletion, then single cilta-cel infusion 5–7 days after lymphodepletion initiation.

Results. 196 pts received cilta-cel: 172 (87.8%) received DPd and 24 (12.2%) PVd while bridging (median 2 [range, 1–6] cycles). After bridging, 42 (21.4%) pts had very good partial response or better (≥VGPR), 70 (35.7%) had partial response (PR), 61 (31.1%) had minimal response/stable disease (MR/SD), 20 (10.2%) had progressive disease (PD), and 3 (1.5%) were not evaluable. Based on responses after bridging, 30-mo PFS rates with cilta-cel were 75.9% for pts with ≥VGPR, 72.9% for pts with PR, 56.5% for pts with MR/SD, and 30.0% for pts with PD. The corresponding 30-mo OS rates were: 85.1%, 91.4%, 74.8%, 40.0%, respectively.In pts with ≥VGPR or PR, no movement or neurocognitive treatment-emergent adverse events (MNTs) occurred, while 2 cases were reported in the remaining pts. In pts with ≥VGPR, PR, MR/SD, and PD, cranial nerve palsy occurred in 11.9%, 7.1%, 8.2%, and 5.0%, and fatal infections in 2.4%, 4.3%, 13.1%, and 15.0%, respectively. Prolonged (grade 3/4 not recovering to grade 2 by day 60 post cilta-cel) thrombocytopenia was lower in pts with ≥VGPR (9.5%) and PR (11.4%) or MR/SD (11.5%) after bridging, as compared with those with PD (50%). Prolonged neutropenia was lower in pts with ≥VGPR pre cilta-cel (2.4%) vs 9.8–15.7% with PR or lower. Non-relapse mortality was 7.1%, 8.6%, 18.0%, 30.0%, in pts with ≥VGPR, PR, MR/SD, and PD, respectively.

Conclusions. In CARTITUDE-4, better bridging-therapy responses correlated with longer PFS and OS. Moreover, no MNTs were observed in pts with ≥PR after bridging, while poorer responses were linked to higher probability of fatal infections, prolonged thrombocytopenia/neutropenia, and higher rates of non-relapse mortality post cilta-cel. These data highlight the importance of optimizing bridging therapy for disease control pre cilta-cel.© *American Society of Hematology (2025). Reused with permission*.

Myeloma and other monoclonal gammopathies

REAL-WORLD EVIDENCE ON THE COMBINATION OF SELINEXOR WITH BORTEZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: A GRUPPO ITALIANO MALATTIE EMATOLOGICHE DELL'ADULTO (GIMEMA) MULTIPLE MYELOMA WORKING GROUP STUDY

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Selinexor, bortezomib and dexamethasone (SVd) is a regimen approved in Italy for relapsed/refractory multiple myeloma (RRMM) patients (pts) treated with 1-3 prior lines and refractory to lenalidomide (R), but most evidence comes from clinical trials, where pts refractory to R- and anti-CD38 agents are underrepresented, while real-world (RW) data are scarce. Therefore, the Gruppo Italiano Malattie EMatologiche dell'Adulto Multiple Myeloma Working Group sponsored a national, non-profit, multicenter observational study to collect RW data on SVd efficacy and safety.At present, 19/26 centers are active, with 43 pts enrolled (39 included in this analysis). Median age was 76 years (range 58-87); based on available data, 4/30 (13%) had ECOG≥2, 7/30 (23%) were frail per the IMWG index; 2/20 (10%) had extramedullary disease. Median time from diagnosis was 3 years (range <1-19), median prior therapies 1 (range 1-3); all were R-refractory, 31/32 (97%) refractory to anti-CD38 agents, 7/32 (22%) triple-class exposed.Median starting doses of S and d were 80 mg/week (range 20-100) and 20 mg/week (range 8-50), respectively; all received 1.3 mg/mq/week of V; 31/39 (80%) received antiemetic prophylaxis.After a median follow-up of 9.3 months (range 0.6-27.7), pts received a median of 4 cycles (range 1-10); 21/39 (54%) discontinued SVd, mainly due to progression (15/21, 71%) or toxicity (2/21, 9%). The overall response rate was 25/35 (71%) (14 [40%] partial responses [PR], 8 [23%] very good partial responses, 3 [8%] complete responses). 12-month overall survival rate was 67%, and median progression-free survival (PFS) 8.3 months (95% confidence interval, 4.2-not reached), with no significant differences based on number of prior lines but with a trend towards a better PFS in pts achieving ≥PR (12 vs 5.3 months, p=0.05).Data on adverse events were available in 19 pts: thrombocytopenia was the most common hematological one, recorded in 15/19 (79%), with 3 (16%) grade (G) 3 cases; 14/19 (74%) reported gastrointestinal events (nausea, vomiting, diarrhea, constipation, dysgeusia), with 1 G3 diarrhea; 5/19 (26%) reported neuropathy, all G1-2. 11 infections were recorded, with 4 G3 and 1 G5 events.Data collection is still ongoing, and updated results will be presented at the meeting. Based on our results, SVd provides a valuable treatment option, primarily as a second-line therapy for older, frailer pts, not eligible for immunotherapy, with a favorable safety and tolerability profile.

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Myeloma and other monoclonal gammopathies

PREDICTORS OF INFERIOR PROGRESSION-FREE SURVIVAL IN TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH DARATUMUMAB-BASED REGIMENS IN THE PHASE IV REAL MM TRIAL

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Introduction. Daratumumab-based regimens are standard therapies for transplant-ineligible (NTE) patients (pts) with newly diagnosed multiple myeloma (NDMM). However, impact of emerging prognostic biomarkers and frailty on outcomes remains unclear.

Methods. REAL MM is a randomized, multicenter, phase IV trial (NCT03829371), comparing bortezomib-melphalan-prednisone (VMP) ± daratumumab (DVMP) vs. lenalidomide-dexamethasone (Rd) ± daratumumab (DRd) in real-life NTE NDMM pts. In the first part, pts were randomized 1:1 to 9 VMP cycles vs continuous Rd; from July 2022, to DVMP vs DRd. This analysis focuses on the daratumumab cohort. Stratification included IMWG frailty score and cytogenetic (CG) risk [high risk: del(17p), t(14;16) or t(4;14)]. The primary endpoint was progression-free survival (PFS). This analysis aimed to identify patient related (IMWG frailty score) and disease related prognostic factors associated with PFS at current follow-up. Frail and ultra-frail pts were defined as IMWG scores 2 and ≥3 respectively. CG risk was reclassified according to the IMS-IMWG consensus genomic staging (CGS) definition, except for TP53 mutations and biallelic del(1p32), which were not included (modified CGS, mCGS). High circulating tumor cells (CTCs) were defined as >0.07%.

Results. At data cut-off (February 26, 2026), 170 pts were randomized (DVMP n=87, DRd n=83), median age was 76 years. After 23.7 months of median follow-up (FU), no PFS differences were observed (DVMP vs DRd HR 1.12, p=0.73). Regarding patient and disease-related prognostic factors, 65%, 22% and 14% of the pts were fit/unfit, frail, and ultra-frail, while 29% had high risk mCGS and 32% high CTC levels. In univariate analysis, ultra-frail status (HR 4.22, p<0.001 vs fit/unfit) and high CTCs (HR 1.94, p=0.045 vs low) were associated with inferior PFS, while frail pts (HR 2.18, p=0.051 vs fit/unfit) and high risk mCGS (HR 1.87, p=0.09 vs standard risk) showed only a trend of poorer PFS. In multivariate analysis, only ultra-frail status remained independently associated with worse PFS (HR 2.86, p=0.027, fig).

Conclusions. In this population, frailty, particularly ultra-frailty, was the main driver of early PFS events, at the current FU. Patient-related factors appeared to have a greater impact on outcomes than disease ones, supporting their role in guiding treatment. These data support frailty integration into risk stratification and identify ultra-frail as a subgroup requiring tailored approaches.

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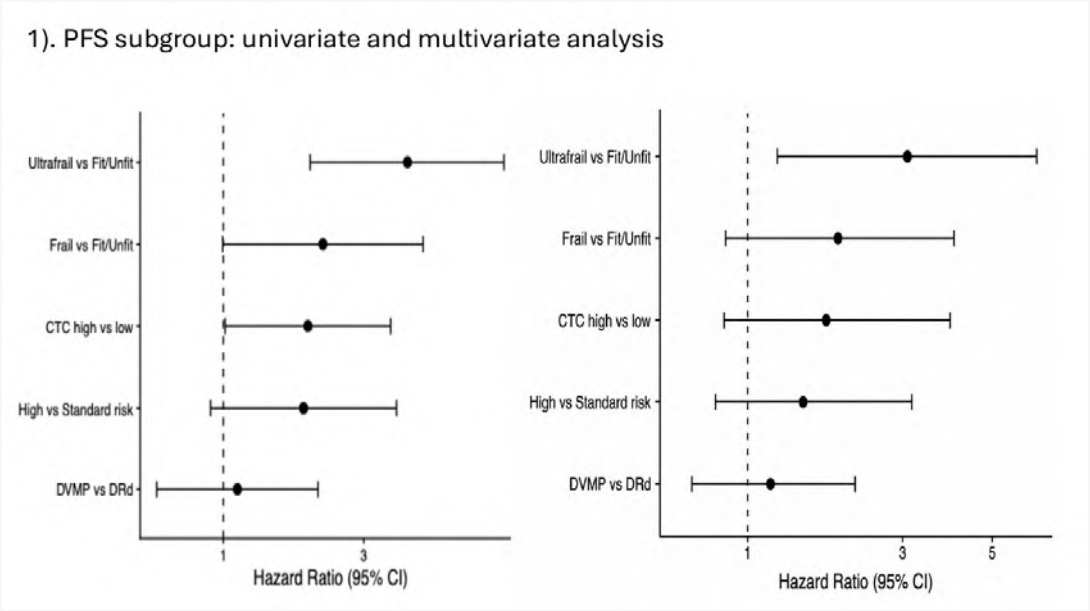

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Myeloma and other monoclonal gammopathies

PROGNOSTIC ROLE OF STANDARDIZED (18)F-FDG-PET/CT AND WB-DW-MRI IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS RECEIVING T CELL-REDIRECTING THERAPIES

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Background. CAR T-cells and bispecific antibodies (BsAbs)(T cell-redirecting therapies, TCRT) have revolutionized treatment of relapsed/refractory multiple myeloma(RRMM). The prognostic role of functional imaging(FDG-PET/CT and WB-DW-MRI), both at baseline and in defining imaging MRD, has been widely validated in newly diagnosed MM but is less explored in the setting of RRMM. Preliminary studies have shown a significant role of PET response at 3 months(-mos) after CAR-T infusion.

Aims and methods. Herein we present a single-center retrospective/prospective study aimed at assessing the prognostic role of functional imaging in the setting of TCRT. Patients(pts) underwent PET/CT and WB-DW-MRI (the latter since August 2024) prior to TCRT and every 3 mos thereafter until negative or PD. Interpretation of the imaging techniques was based on IMPeTUs and MY-RADS criteria. Pts also underwent NGS MRD assessment at achievement of ≥VGPR.

Results. 73 pts were enrolled until September 2025. 40 received anti-BCMA CAR-T, 15 anti-BCMA BsAbs and 18 anti-GPRC5D BsAbs. After a median follow-up of 17 mos, median PFS(mPFS) was 21 mos and median OS was NR(86% alive at 24 mos). At baseline, all pts underwent PET and 40 pts underwent WB-DW-MRI. Baseline presence of paraskelatal disease(28 pts=38%), extramedullary disease (11 pts=15%) and >10 focal lesions by PET(20 pts=27%) or MRI(14 pts=35%) were not associated with PFS(p>0.05). Among 55 pts undergoing PET after 3 mos, 29(53%) achieved metabolic CR(CMR), with improvement of mPFS(27 vs 10 mos,p=0.01). Among 35 pts undergoing MRI after 3 mos, 28(80%) achieved RAC1, with improvement of mPFS(NR vs 9 mos,p=0.003). Only 2 and 1 pt achieved CMR and RAC1 at later timepoints respectively. Among 31 pts repeating both imaging techniques after 3 mos, concordance was good in defining presence of response(k=0.64) and fair for imaging MRD(k=0.31). 16 pts(52%) achieved both CMR and RAC1, with improvement of mPFS compared to pts achieving CMR or RAC1 and pts achieving neither(NR vs 10 vs 3 mos,p=0.006). All 14 pts with available NGS MRD data achieved negativity, thus preventing correlation analyses with outcome.

Conclusions. This study supports standardized assessment of imaging MRD by IMPeTUs and MY-RADS criteria in the setting of TCRT. 3 mos after CAR-T infusion or BsAb initiation is a significant early time-point for response assessment. Updated data with larger number of enrolled pts and longer follow-up will be presented at the meeting.

Myeloma and other monoclonal gammopathies

MEZIGDOMIDE, CARFILZOMIB, AND DEXAMETHASONE *VS.* CARFILZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: RESULTS FROM THE PHASE 3 SUCCESSOR-2 TRIAL

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Background. Mezigdomide (Mezi) is a potent oral CELMoD that induces rapid, maximal Ikaros/Aiolos degradation, enhancing MM cell death and immune stimulation vs IMiDs®. We report initial results from SUCCESSOR-2 (NCT05552976), the first phase 3 study of MeziKd vs Kd only in RRMM.

Methods. In this phase 3, 2-stage, inferentially seamless trial, adults with RRMM and ≥1 prior line of therapy (LOT), including an anti-CD38 monoclonal antibody (mAb) and lenalidomide (LEN), were randomized 3:3:3:2 (Mezi 0.3, 0.6, 1.0 mg+Kd, or Kd) in stage 1 to select optimal Mezi dose, and 3:2 in stage 2 to compare efficacy/safety of MeziKd vs Kd. MeziKd was given in 28-day (D) cycles of Mezi (D1–21), carfilzomib (CFZ) 56 mg/m^2 QW, and dexamethasone (DEX) 40 mg QW; Kd arm received CFZ 56 mg/m^2 BIW or 70 mg/m^2 QW+DEX. Primary endpoint was progression-free survival (PFS). Secondary endpoints included selected Mezi dose, overall response rate (ORR), deaths, and safety.

Results. Mezi 1.0 mg was selected for stage 2. In total, 479 pts (pts; 288 MeziKd at 1.0 mg Mezi; 191 Kd) were included in the analysis. Median age was 68 y. Median number of prior LOTs was 2; 92.1% of pts were triple-class-exposed, with 85.8% refractory to anti-CD38 mAb and 75.8% to LEN; 37.2% were exposed to pomalidomide and 7.3% to anti-BCMA tx. At data cutoff, median follow-up was 10.6 mo; 52.4% of MeziKd and 31.4% of Kd pts remained on tx. Median tx duration was 8.9 mo for MeziKd vs 6.2 mo for Kd.MeziKd significantly improved PFS vs Kd (Table), with consistent benefit across subgroups, including pts with >2 prior LOTs, prior tx exposure/refractoriness, high-risk cytogenetics, extramedullary disease, and age ≥75 y. ORR and rates of complete response or better were higher with MeziKd vs Kd (Table). Fewer deaths were reported with MeziKd vs Kd (Table), mostly due to progressive disease. Grade 3–4 TEAEs were more frequent with MeziKd vs Kd, mainly due to neutropenia and infections; grade 5 infections were uncommon in both arms (Table).

Conclusions. MeziKd showed a clinically meaningful PFS benefit from first relapse in a predominantly triple-class-exposed, anti-CD38 mAb- and LEN-refractory RRMM population with high unmet need. These data support Mezi as a potent oral tx with a predictable, manageable safety profile and potential new standard of care across RRMM settings.
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Table. Summary of primary and secondary endpoints by treatment arm

	MeziKd (n=288)	Kd (n=191)
Primary endpoint		
PFS, median (95% CI), months	18 (14.5-22.1)	8.3 (5.6-10.7)
HR (95% CI)	0.48 (0.36-0.63)	
P-value	<0.0001	
Secondary endpoints, %		
Overall response rate	80.2	53.4
Complete response or better	26.7	8.9
Deaths	21.5	26.7
Safety, %		
Grade 3-4 TEAEs	83.7	56.5
Neutropenia	61.1	9.1
Infections	34.0	15.6
Grade 5 infections	2.4	1.1

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CONGRESSO NAZIONALE SIE

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POSTERS

Allogeneic, Autologous transplant

PLASMA EXTRACELLULAR VESICLES (ORIGINATED FROM PLATELETS, ENDOTHELIAL CELLS, LEUKOCYTES) AS BIOMARKERS OF ACUTE GVHD FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION

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Background. Validated biomarkers for acute Graft-versus-Host Disease (aGVHD) remain elusive despite its high impact on post-SCT mortality. Having previously identified a link between aGVHD and CD146+ extracellular vesicles (EVs), we employed a patented polychromatic flow cytometry (PFC) method to analyze post-transplant EV dynamics. This study characterizes the cellular origin of these EVs and evaluates the predictive value of CD146+ subsets for aGVHD.

Methods. This study enrolled 80 SCT recipients, 19 of whom developed aGVHD (grade II: n=10; grades III-IV: n=9). Peripheral blood was collected before SCT and at multiple post-transplant time points (days 0-180). For absolute EV quantification, fresh whole blood was analyzed via PFC using BD Trucount™ Tubes. The panel included phalloidin-FITC, APC lipophilic dye, anti-CD31-PECy7, anti-CD45-V500, anti-CD41a-PE, and anti-CD146-BV786. EV subsets were categorized as leukocyte-derived (CD45+, LK), platelet-derived (CD41a+/CD31+/CD45-), and endothelial-derived (CD41a-/CD31+/CD45-, EC), including CD146+ activated fractions. Associations with aGVHD were assessed using logistic regression models (LRM), estimating odds ratios (OR) on absolute values and changes from baseline. Analyses were performed with STATA 15 and SPSS 25.

Results. Platelet-derived extracellular vesicles (EVs) demonstrated a strong correlation with platelet counts (rho=0.75; p<0.001). While total leukocyte (LK) EVs and CD146+ LK EVs did not exhibit a significant increase following stem cell transplantation (SCT), CD146+ LK EVs stayed higher than those observed in healthy donors and showed no association with acute graft-versus-host disease (aGVHD). Conversely, total EC EVs and CD146+ EC EVs both rose within the first two weeks post-SCT. CD146+ EC EVs showed a significant association with the onset of aGVHD (absolute levels: OR 1.11, p=0.038; change from baseline: OR 1.094, p=0.043). Notably, the ratio of CD146+ EC EVs to total EC EVs increased prior to clinical disease manifestation, suggesting endothelial activation. This specific ratio was significantly associated with aGVHD (absolute ratio: OR 1.248, p=0.043; change: OR 1.183, p=0.033).

Conclusions. Early post-SCT expansion of endothelial-derived EV reflects endothelial dysfunction. CD146+ EC EV, and particularly their proportion among EC EV, are associated with aGVHD onset and may represent predictive biomarkers. Prospective validation using a standardized PFC assay (MACSPlex EV Kit) is ongoing.

Allogeneic, Autologous transplant

FLUDARABINE–TREOSULFAN (FT10) CONDITIONING IN OLDER AML PATIENTS UNDERGOING HAPLOIDENTICAL TRANSPLANTATION: A PROSPECTIVE ITALIAN STUDY WITH EXTERNAL COMPARISON TO THE HAPLO-UK REDUCED-INTENSITY CONDITIONING COHORT

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Allogeneic haematopoietic stem cell transplantation (allo-HSCT) remains the only curative strategy for high-risk acute myeloid leukemia (AML), but its applicability in elderly and comorbid patients is limited by conditioning related toxicity. Haploidentical HSCT with post transplant cyclophosphamide (PTCy) has expanded access to transplantation, yet the optimal reduced intensity conditioning regimen in this setting remains undefined. Treosulfan-fludarabine conditioning (FT10) has demonstrated a favourable toxicity profile in matched donor, but prospective data in the haploidentical platform are scarce. We conducted a prospective, multicentre feasibility study, enrolling patients with intermediate or high risk AML, aged≥65 years, with HCT-CI≥2, lacking an HLA identical donor and undergoing FT10 based haplo-HSCT between June 2019 and December 2023. Conditioning consisted of treosulfan (30 g/m^2) and fludarabine (150 mg/m^2), followed by GVHD-prophylaxis with PTCy, cyclosporine and mycophenolate-mofetil. Primary-endpoint was cumulative incidence of non relapse mortality (NRM). Transplant outcomes were descriptively compared with an external reduced-intensity conditioning from the phase II Haplo-UK study. Thirty five AML patients were included in the FT10 (median age 69 years); 80% were transplanted in complete remission (CR), including 58% in CR/MRD negative. Median neutrophil and platelet engraftment occurred at days +14 and +22, with full donor chimerism achieved in 94% of evaluable patients and one case of graft failure (2.8%). Cumulative incidence of NRM was 18% at day +100 and 28% at 1 year, with infections representing the leading cause of NRM. Outcomes were strongly influenced by disease status at transplant: 1-year OS and LFS were 79% and 70% in patients transplanted in CR/MRD-negative, compared with 42% and 38% in those transplanted with active disease. Acute grade II–IV and chronic GVHD occurred in 13% and 40% of patients, respectively. When restricted to patients transplanted in CR, survival and relapse outcomes were within the range of those observed in the Haplo-UK cohort, despite the substantially older age and higher comorbidity burden of FT10 patients (Fig). FT10 haplo-HSCT with PTCy proved feasible and effective in elderly, comorbid AML patients. These findings support the potential role of FT10 as a conditioning option for a population traditionally excluded from transplant and support further validation in larger comparative studies.

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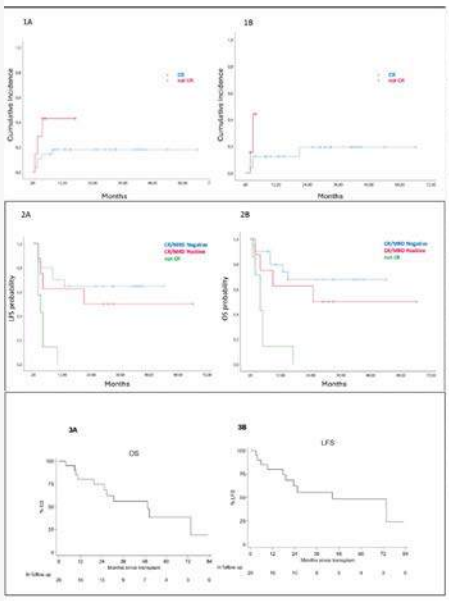

FIGURE LEGEND

Figure 1A shows non-relapse mortality according to disease status at the time of transplant. Red line= active disease; blu line= complete remission. There is a trend for a higher mortality within patients with active disease, although the difference is not statistical significant (p-value 0.18).

Figure 1B shows cumulative incidence of relapse according to disease status at the time of transplant. Red line= active disease; blu line= complete remission. There is a trend for a higher cumulative incidence of relapse within patients with active disease, although the difference is not statistical significant (p-value 0.15).

Figure 2A shows leukaemia-free survival according to disease status at time of transplant. Green line= active disease; red line= complete remission with positive measurable residual disease (CR-MRD+); blu line= complete remission with negative measurable residual disease (CR-MRD-). 1-year LFS is 70% and 62% for CR-MRD+ and CR-MRD-, respectively. For patients with active disease, 6-month LFS is 38% (p-value 0.0001).

Figure 2B shows overall survival according to disease status at the time of transplant. Green line= active disease; red line= complete remission with positive measurable residual disease (CR-MRD+); blu line= complete remission with negative measurable residual disease (CR-MRD). 1-year OS is 79% and 62% for CR-MRD+ and CR-MRD-, respectively. For patients with active disease, 6-month OS is 42% (p-value 0.0001).

Figure 3A shows overall survival within the haplo-UK cohort.

Figure 3B shows leukaemia-free survival within the haplo-UK cohort.

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GUT MICROBIOTA DIVERSITY IN TRANSPLANT AND CAR-T RECIPIENTS: A COMPARATIVE STUDY

M. Bergnach[1], G. Tomadini[1], M. L. Battista[1], M. Isola[2], M. De Martino[2], A. Geromin[1], G. Facchin[1], M. Moratti[1], R. Plos[1], G. Battaglia[1], C. Pipan[3], S. Marzinotto[3], F. Curcio[2|3], L. Montanari[4], C. Tascini[2|4], R. Fanin[1|2], F. Patriarca[1|2]

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While there is a growing interest in the composition of gut microbiota of allogeneic stem cell transplant (SCT) recipients and its impact on GVHD and survival, its relevance in the setting of CAR-T therapy is less explored. We compared the gut microbiota composition of 27 recipients of allogeneic SCT, 14 autologous SCT and 23 CAR-T admitted to the Transplant Center of Udine. Fecal samples were collected at hospital admission (T0), on the day of cells infusion (T1) and 7 days after cells infusion (T2). Microbiota composition was assessed using biodiversity index, alpha diversity (according to Shannon Index) and Firmicutes/Bacteroides (F/B) ratio. Median age was 63 years without differences among groups (p=0.230). CAR-T patients were more heavily pretreated compared to SCT recipients (p<0.001). As expected, the prevalent hematological diseases were multiple myeloma for autologous SCT recipients (79%), acute leukemia and myelodysplastic syndrome for allogeneic SCT recipients (70%) and B lymphoma and multiple myeloma for CAR-T (57% and 39%, respectively). At admission, both biodiversity index and alpha diversity were significantly lower in allogeneic SCT and CAR-T patients than in autologous patients (p<0.001 and p=0.054), while F/B ratio was similar across groups (p=0.869). A significant decrease in alpha diversity over time was observed in all groups (p=0.015), with the lowest levels at T2 in allogeneic SCT and CAR-T recipients (Figure 1). F/B ratio did not change significantly in autologous SCT patients, while it showed a marked increase between T1 and T2 in both CAR-T and allogeneic SCT recipients. We conclude that at admission allogeneic SCT patients and CAR-T recipient had a lower gut microbiota biodiversity, that may reflect more recent and/or intensive chemotherapy in comparison with autologous SCT recipients. We confirm a significant progressive alteration of the gut microbiota following conditioning and SCT and observed a particularly pronounced impairment of gut biodiversity after CAR-T therapy.

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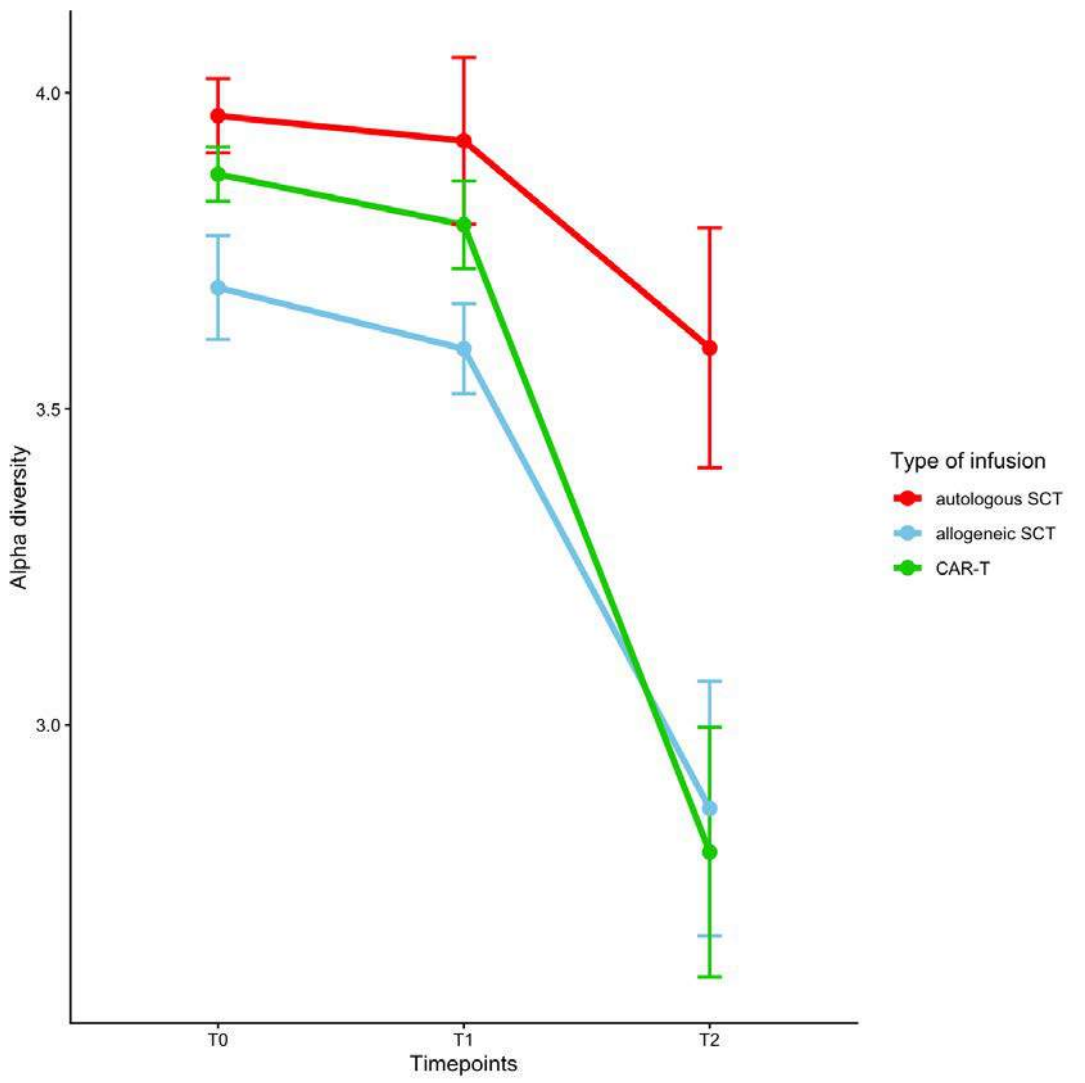

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LONG-TERM OUTCOME OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN FOLLICULAR LYMPHOMA

L. Meschia[1|3], L. Farina[1], G. Balestra[1|3], S. Ljevar[2], A. Guidetti[1|3], A. Dodero[1], A. Chiappella[1], A. Barone[1|3], M. Pennisi[1], F. Stella[1], L. Devizzi[1], P. Matteucci[1], P. Corradini[1|3]

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Autologous stem cell transplantation (ASCT) is an option for young fit patients with relapsed follicular lymphoma (FL), especially in case of progression within 24 months from the first-line (POD24). We performed a retrospective analysis on 122 FL patients autografted from 2000 to 2021 at Istituto Nazionale dei Tumori di Milano. Median age was 48.9 years (IQR 41.5-56.1). Histologic grade was I-II in 65.7% and grade III in 34.3% of the patients; 69% of the patients were in stage IV at diagnosis and FLIPI score was low in 24%, intermediate in 34% and high in 42% of the cases. POD24 was observed in 59% of the patients and 79% of them received Rituximab in first-line. Seventy-nine percent of the patients received ASCT in second-line. Forty-eight percent of ASCT were performed between 2000-2010 and 52% between 2011-2021. Eighty-three percent of the patients were in complete remission (CR) before ASCT. Positron Emission Tomography scan (PET) was performed in 71% of cases before ASCT and in 86% of them was negative. Forty-one percent of the patients were treated according to the high dose sequential chemotherapy protocol (HDS), 31% received R-DHAOX or DHAP before ASCT. Twenty-four patients received an allogeneic SCT (alloSCT) due to disease relapse.Median follow up was 159.6 months (IQR 96.8-228.9). Ten-year and 20-year progression-free survival (PFS) was 55.1% and 29.4%, respectively. Ten-year and 20-year overall survival (OS) were 79.8% and 43.8% respectively. One and 2-year non-relapse mortality (NRM) was 2.6% and 3.5%, respectively. In univariate analysis (including age, histologic grade, stage, FLIPI score, POD24, Rituximab in first-line, CR before ASCT, year of transplant, positive minimal residual disease before ASCT, number of previous lines, HDS versus R-DHAOX/DHAP) no-POD24 and R-DHAOX/DHAP before ASCT were significantly correlated with a better PFS (p=0.018 and p=0.032). Univariate analysis for OS including the same variables and alloSCT showed that only age was significant (p=0.024). In multivariable analysis including age, POD24, number of previous lines and disease status before ASCT, POD24 retained significance for PFS but not for OS. Five and 10-year second-tumour incidence was 9.3% and 14%, respectively, without any significant impact of variables included in the univariate analysis. Long-term results of ASCT in FL showed that one-third of the patients may be potentially cured and they should be used as ‘benchmark’ for new available therapies in young high-risk FL patients.

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MONITORING POST TRANSPLANT RELAPSE WITH CELL-FREE DNA IN PATIENTS WITH MYELOFIBROSIS

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Cell-free DNA (cfDNA) is an emerging biomarker for non-invasive diagnostics and disease monitoring. We performed 80 analyses of driver mutations and chimerism in peripheral blood from 37 patients with myelofibrosis undergoing post--transplant follow-up, comparing cfDNA-based assays with standard cellular methods cfDNA was isolated from plasma using a two-step centrifugation protocol and analyzed for chimerism by short tandem repeat (STR) profiling and for JAK2 V617F mutation by droplet digital PCR (ddPCR). All analyses were performed in duplicate, validated with appropriate controls, and systematically compared with conventional cellular chimerism from peripheral blood or bone marrow. Longitudinal monitoring was carried out to assess molecular dynamics over time and their clinical correlations.Overall, 70 samples showed concordant results between cfDNA and standard monitoring, while 10 samples were discordant. In three cases evaluated at day +30 post-transplant, standard analysis indicated complete donor chimerism with full clearance of the driver mutation, whereas cfDNA detected residual mixed chimerism; notably, these cases converted to complete chimerism by day +60. In two relapsed patients treated with donor lymphocyte infusion, restoration of complete chimerism was identified earlier by standard methods compared to cfDNA analysis. The remaining five discordant results derived from serial samples of a single patient, in whom cfDNA analysis showed a progressive decline in donor chimerism and the appearance of JAK2 signal despite persistently complete chimerism and negative minimal residual disease (MRD) by standard techniques, anticipating subsequent overt clinical relapse (Fig.1).In conclusion, although larger data are warranted, cfDNA-based MRD monitoring appears to be a reliable and minimally invasive approach, showing substantial concordance with standard methods and, in selected cases, increased sensitivity, as suggested by earlier detection of relapse and delayed clearance of driver mutations following transplantation or donor lymphocyte infusion.

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MULTI-TARGET SIRNA-MEDIATED INFLAMMATORY SILENCING IN A TRANSLATIONAL MODEL OF OCULAR GRAFT-VERSUS-HOST DISEASE AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

A. Cavalleri[1], F. Trenta[1], S. Mutti[1], H. Moreiras[2], H. Levis[2], G. Favero[3], S. Lancellotti[4], A. Leoni[1], B. Xhahysa[1], L. Garuffo[1], E. Morello[1], V. Romano[4|5], R. Rezzani[3], D. Russo[1], M. Malagola[1], M. Farina[1], S. Bernardi[1]

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Ocular chronic graft-versus-host disease (oGVHD) is a frequent and severe complication after allogeneic stem cell transplantation, characterized by epithelial damage driven by persistent inflammation and leading to refractory dry eye disease, for which current treatments are largely symptomatic and lack targeted control of local inflammatory pathways, highlighting the need for precision therapeutic strategies and translational models.In this context, we aimed to develop a translational inflammatory model of oGVHD and evaluate a multi-target RNA interference approach against 11 inflammatory mediators, with validation in patient tears.Human corneal epithelial cells (HCET) were stimulated with hyperosmolar medium and LPS (500-1000 ng/mL). IL8, IL6, TNFα, and IL1β were quantified by digital PCR to define inflammatory conditions. Eleven inflammatory genes were targeted using two siRNA sequences each, applied individually or in combinations of 2-4 targets. Uptake was confirmed by fluorescence microscopy and cytotoxicity assessed by LDH assay. A multilayer air–liquid interface (ALI) model on PET inserts was established to reproduce epithelial stratification and inflammation. Gene expression was analyzed in cell lysates. Translational validation was performed in tears from 44 subjects (16 healthy controls, 28 patients with inflammatory dry eye).LPS induced robust upregulation of IL8, IL6, TNFα, and IL1β in monolayers. Efficient intracellular delivery of siRNA was confirmed, with significant knockdown of IL8 and IL6 at 24-48 h (Fig.1A-B). Extension to all 11 targets resulted in sustained downregulation at 48 h. Combined silencing of 2–4 genes produced strong multi-target inhibition. The ALI model reproduced epithelial stratification and barrier dysfunction. Reduced inflammatory mediators in supernatants were observed after both single- and dual-target siRNA treatments, indicating functional modulation of secretion. In tears, a subset of the 11 markers was differentially expressed between healthy controls and dry eye patients, including immune-related mediators not detectable in monolayer cultures, supporting translational relevance.We established reproducible mono- and multilayer oGVHD models and showed that multi-target siRNA silencing is feasible, effective, and minimally cytotoxic. Concordance with patient tear profiles supports precision RNA interference for local immunomodulation and tear-based liquid biopsy in oGVHD.

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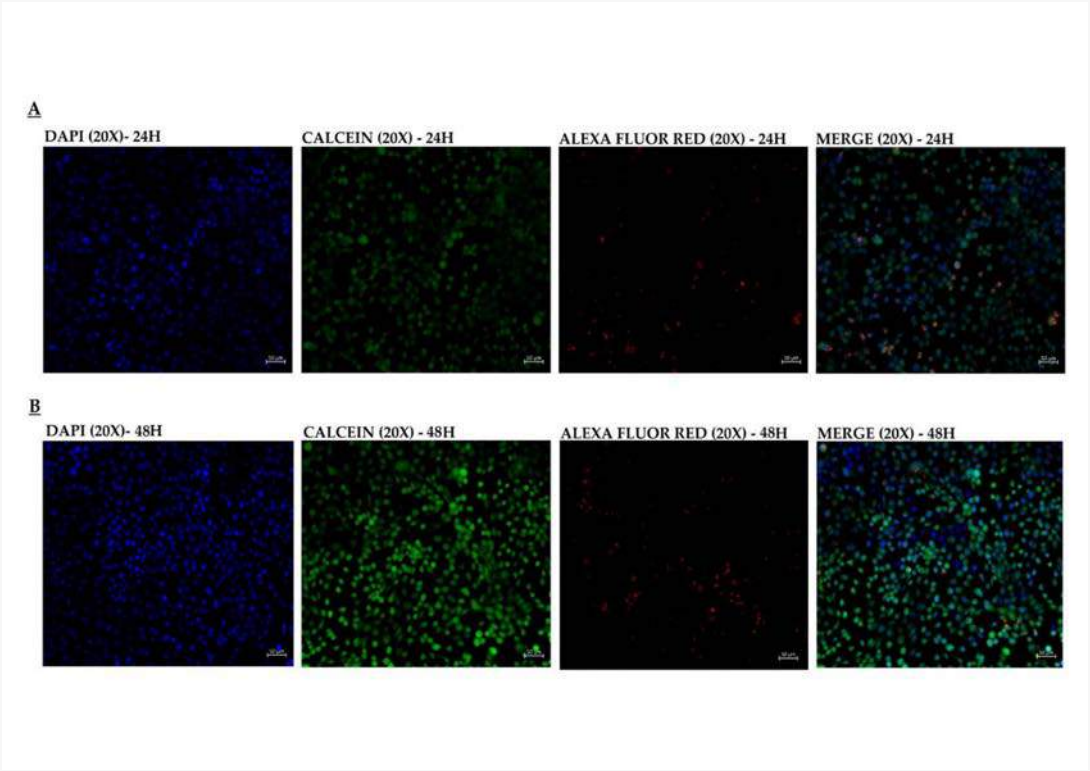

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ASSISTING PATIENTS DURING CAR-T THERAPY: A DYNAMIC SCORE-BASED ANALYSIS OF NURSING BURDEN, CLINICAL COMPLEXITY, AND FUNCTIONAL IMPAIRMENT

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CAR-T therapy for R/R B-cell malignancies offers high efficacy but causes severe toxicities—including CRS, ICANS, cytopenias, and functional decline—requiring intensive and highly specialized nursing care. Quantitative data on the dynamic evolution of nursing complexity along the treatment trajectory remain limited.This prospective study dynamically applied validated nursing assessment scales in 60 consecutive adult CAR-T recipients treated at our institution. Patients were assessed at admission, day −5/−4, day 0, day +7, day +14, and discharge, using six validated instruments: NRS-2002 (nutritional risk), Conley Scale (fall risk), Braden Scale (pressure injury risk), Barthel Index (functional independence), IDA (nursing workload), and MEWS (clinical instability).At admission, nursing burden was low: 92% of patients fully independent (Barthel Index), and mean Braden and Conley scores indicated minimal risk. However, 32% were already at nutritional risk (NRS-2002 ≥3), with significantly lower BMI compared to low-risk patients (22.1 vs 25.9; p0.001). After CAR-T infusion, all scores worsened significantly (p0.001 across all scales). Fall risk (Conley) rose from a mean of 0.7 at baseline to 1.7 at day +7 (52% at risk) and 1.9 at day +14 (62% at risk). Functional independence (Barthel) declined sharply from 98.5 at day 0 to 76.2 at day +7 and 74.0 at day +14, with 13–16% of patients reaching total dependency (Barthel ≤20). Pressure injury risk (Braden) followed a similar trajectory, declining from 21.9 to a nadir of 18.6 at day +14. Nursing workload (IDA) increased progressively, peaking at day +8 (mean 19.4), while MEWS-detected clinical instability peaked at day +5 (13% at risk), closely paralleling the established kinetics of CRS and ICANS. CRS occurred in 95% of patients (G ≥2: 56%) and ICANS in 33% (G ≥2: 13%). All scales except MEWS showed significantly higher complexity in patients experiencing clinically relevant CRS (grade ≥2) or any-grade ICANS. Although partial recovery was observed by discharge, scores did not fully return to baseline, with persistent functional impairment in a subset of patients.The period between day 0 and day +14 represents the peak of nursing burden and clinical vulnerability in CAR-T recipients. Systematic, score-based monitoring using validated multidimensional tools enables early identification of at-risk patients, optimized resource allocation, and coordinated interdisciplinary care throughout the acute CAR-T phase.

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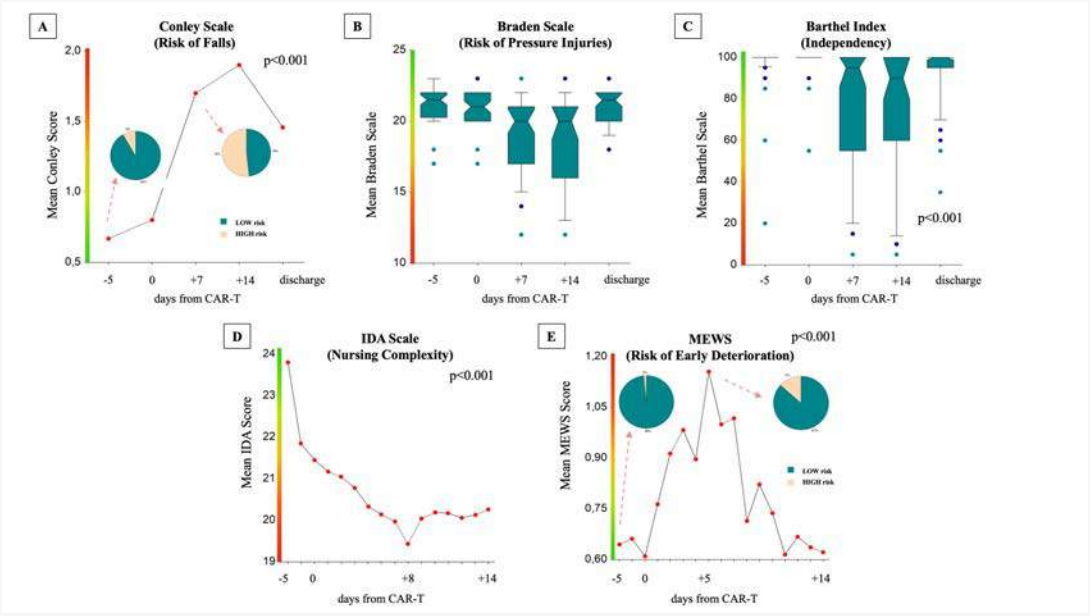

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PRELIMINARY BASIS FOR A PREDICTIVE ALGORITHM OF REHABILITATION REQUIREMENTS IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

G. Magliano[1], A. Arcangeli[2], S. Silvestri[2], G. Brambilla[1], M. Farina[1], V. Radici[1], D. Avenoso[1], A. Leoni[3], S. Bernardi[3], F. Re[3], M. Calonghi[2], M. Dossena[2], D. Corbo[4], D. Russo[1], M. Malagola[1], E. Morello[1]

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Background. Although the benefits of physical activity and rehabilitation are acknowledged in the field of allogeneic hematopoietic stem cell transplantation (allo-HSCT), comprehensive and individualized rehabilitative care is still lacking.
Materials and Methods. We aimed to identify key predictors of rehabilitative needs in HSCT patients to enable the development of an early detection algorithm. Clinical data from hospitalized patients allografted for any diagnosis in our Unit between November 2018 and February 2025 were retrospectively collected. Potential predictors analyzed included sex, age, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Patient-Generated Subjective Global Assessment (PG-SGA), 4-Meter Gait Speed, 30-Second Chair Stand Test, Handgrip strength, Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), non-invasive ventilation (NIV), neurological complications, high-dose steroid use, hospitalization length, and ICU admission. Surrogate endpoints considered indicative of rehabilitative need were relapse occurrence and post-transplant hospital readmission.
Results. Among 190 patients, 181 were included in relapse and 141 in readmission analysis. In relapse comparisons, relapsed patients had a higher median age (68.4 vs 65.5 years; p=0.032) and lower mean handgrip strength (27.9 vs 34.1 kg; p=0.005). In multivariate logistic regression with average marginal effects (AME), age >60 years was the strongest relapse predictor (OR: 17.76, CI: 2.83–362.3, p=0.011; AME: +0.243, p<0.001), while handgrip strength (OR: 0.86, CI: 0.78–0.93, p<0.001; AME: –0.019, p<0.001), female sex (OR: 0.23, CI: 0.05–0.90, p=0.042; AME: –0.166, p=0.015), and NIV (AME: –0.164, p=0.040) were associated with lower relapse risk. For readmission, prolonged hospitalization was the strongest predictor (OR: 3.43, CI: 1.30–9.83, p=0.016; AME: +0.251, p=0.010), whereas NIV (OR: 0.15, CI: 0.03–0.61, p=0.013; AME: –0.323, p=0.001) and gait speed (OR: 0.11, CI: 0.01–1.04, p=0.063; AME: –0.431, p=0.050) were associated with reduced readmission risk (figure 1).
Conclusions. Age, sex, handgrip strength, gait speed, NIV use, and hospital-stay duration emerge as significant predictors of rehabilitative needs in HSCT patients. Future prospective longitudinal studies are warranted to refine predictor selection, validate the rehabilitative impact of the identified variables, and develop a model suitable for clinical implementation.

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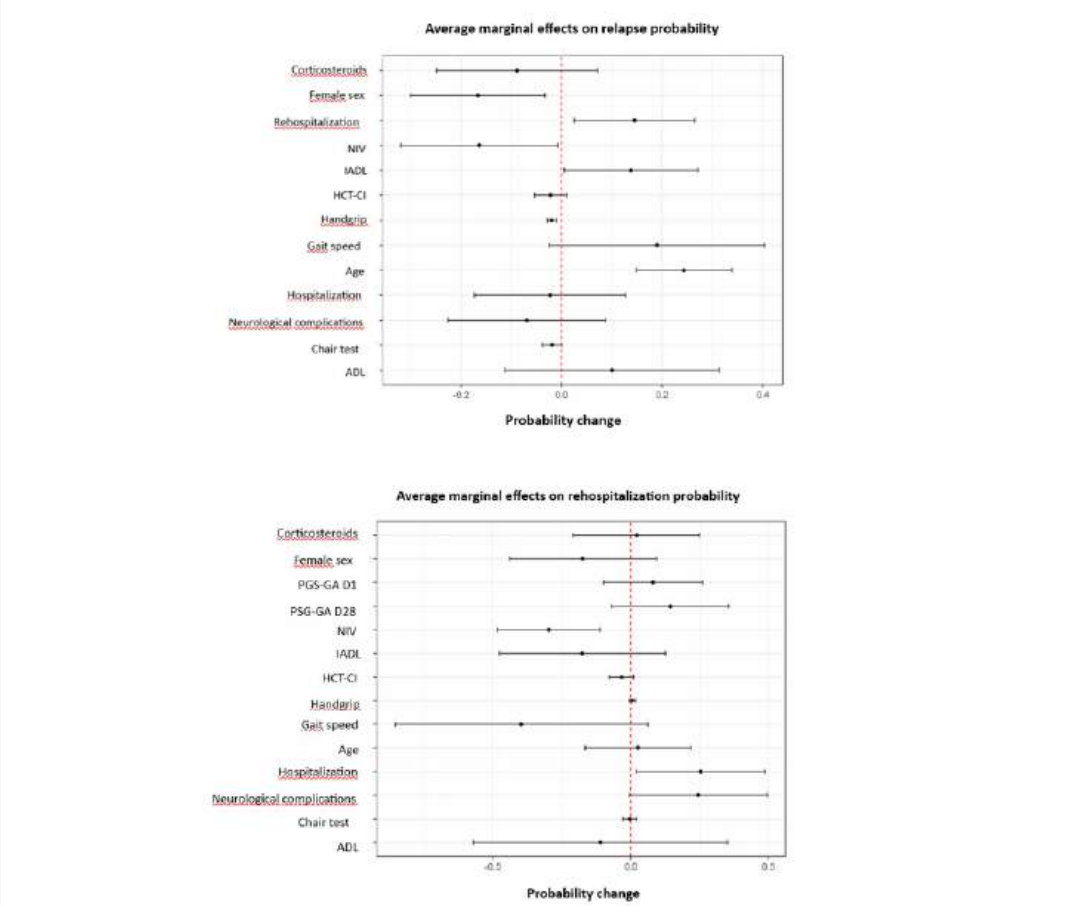

Figure 1. Abbreviations: NIV= non-invasive ventilation; ADL= Activities of Daily Living; IADL= Instrumental Activities of Daily Living; HCT-CI= Hematopoietic Cell Transplantation Comorbidity Index; PGS-GA D1= Patient-Generated Subjective Global Assessment on day +1 from HSCT; D28=on day+28 from HSCT

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IMPROVEMENTS OF CLINICAL OUTCOME IN AML/MDS PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANTATION THROUGH PERSONALIZATION OF CONDITIONING REGIMEN AND GVHD PROPHYLAXIS

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Disease-, patient- and procedure-related factors influence outcomes after allogeneic hematopoietic stem cell transplantation (allo-SCT) in acute myeloid leukemia (AML). Conditioning intensity is a key determinant. Busulfan (BU) shows inter-individual pharmacokinetic (PK) variability, leading to under- or overexposure. Another factor influencing outcome is GVHD prophylaxis. In vivo T-cell depletion with anti-thymocyte globulin (ATG/ATLG) is used in matched unrelated donor (MUD) and HLA-identical sibling transplants.This study evaluated the interaction between BU-based conditioning, with or without PK-guided dose adjustment, and ATG.-Between 2010 and August 2025, 111 patients were included: AML in complete remission, BU-based myeloablative conditioning (MAC) with or without PK-guided dosing, matched related (MRD) or matched unrelated donor (MUD), and GVHD prophylaxis with or without ATG.Patients received fixed-dose BU until October 2022; thereafter, dosing was adjusted to a predefined target area-under-the-curve (AUC). PK assessment was performed after the first BU dose (100 mg/m^2) and repeated after the third dose. Two target exposure levels were predefined: AUC16 for patients aged 65–70 years and/or with HCT-CI ≥3, and AUC20 for the remaining patients. GVHD prophylaxis for HLA-identical sibling transplantation consisted of cyclosporine A (CSA) plus short--course methotrexate (MTX). From 2021 onwards, patients undergoing matched related (MRD) or matched unrelated donor (MUD) transplantation received CSA+MTX+ATG (5 mg/kg on days −2 and −1).Patients were stratified into three cohorts according to exposure to BU-PK and ATG: no BU-PK/no ATG; ATG without BU-PK; and BU-PK plus ATG. Median follow-up was 60 months (range 2–190).Overall, 2-year OS, LFS, 100-day and 1-year NRM, 1-year CIR, and 1-year GRFS were 62%, 58%, 9%, 17%, 25% and 58%. The 6--month cumulative incidence of grade 2–4 and 3–4 acute GVHD, and 1-year moderate-to-severe chronic GVHD, were 28%, 9% and 14%. Outcomes by cohort are reported in Table. Clinical outcomes were numerically better in the BU-PK/ATG cohort, with significantly lower moderate-to-severe cGVHD. 1-year GRFS in the BU-PK/ATG cohort was 84%, without increased relapse risk.These findings confirm the protective effect of ATG in reducing moderate/severe cGVHD in CR AML. Moreover, BU-PK combined with ATG may further improve transplant tolerability, yielding 1-year GRFS of 84%. No NRM was observed in the BU-PK/ATG cohort.

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	No BU-PK/no ATG	ATG	BU-PK/ATG	pvalue
OS @2y	62%	56%	68%	0,58
LFS @2y	51%	54%	68%	0,52
NRM @100 days	7%	15%	0	0,35
NRM @1y	18%	24%	0	0,35
CIR @1y	20%	15%	11%	0,81
aGVHD 2-4	25%	36%	22%	0,4
aGVHD 3-4	11%	7%	6%	0,79
S/M cGVHD	34%	0	6%	0,005
GRFS @1y	42%	63%	84%	0.08

Myeloma and other monoclonal gammopathies

AGE AND FRAILTY ANALYSES OF TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA IN THE PHASE 3 MAIA AND CEPHEUS TRIALS OF DARATUMUMAB + LENALIDOMIDE-DEXAMETHASONE AND BORTEZOMIB-RD

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Background. MAIA and CEPHEUS trials demonstrated that daratumumab (Dara) with standard of care (SOC) VRd or Rd significantly improved clinical outcomes versus SOC in TIE NDMM. Here we describe efficacy and safety in TIE pts from both trials by age and baseline (BL) frailty using the latest data cuts.

Methods. Pts were randomized 1:1 to Dara-Rd (n=368) or Rd (n=369) in MAIA and 1:1 to Dara-VRd (n=144) or VRd (n=145) in CEPHEUS. Progression-free survival (PFS), complete response or better (≥CR), overall MRD negativity (neg) at 10^{-5} with ≥CR, sustained MRD neg with ≥CR (confirmed MRD neg ≥12 ± 1 months [mo] apart without MRD positivity in between), and safety were assessed by age (<70, 70–<75, or ≥75 years [y]) and BL frailty (assessed by IFM simplified frailty score: 0–1, non-frail; ≥2, frail).

Results. Median follow-up was 64.5 mo in MAIA and 76.0 mo in CEPHEUS. In MAIA, 155 (21%) pts were <70 y, 261 (35%) 70–<75 y, and 321 (44%) ≥75 y; 341 (46%) pts were frail, 88.0% of whom were ≥70 y. In CEPHEUS TIE pts, 70 (24%) pts were <70 y, 133 (46%) 70–<75 y, and 86 (30%) ≥75 y; 83 (29%) pts were frail, 86% of whom were ≥70 y.- Dara-Rd or Dara-VRd improved PFS, MRD neg rates, sustained MRD neg rates, and ≥CR rates vs Rd or VRd arms across age and frailty subgroups in both trials (Table). Safety was consistent with established individual drug profiles, and adverse event rates were generally comparable across treatment arms and subgroups within both trials. Additional data on patient-specific factors relevant to these subgroups will be presented.

Conclusions. Dara-based regimens improved efficacy outcomes across subgroups in MAIA and CEPHEUS trials, reinforcing Dara-based regimens as SOC in TIE NDMM regardless of age or frailty. These data offer clinically relevant insights to help guide treatment selection for TIE pts. *© 2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting.*

Table: PFS, ≥CR, MRD negativity, and sustained MRD negativity by age and frailty in MAIA and CEPHEUS

	PFS, hazard ratio (95% CI)		≥CR rate, %		MRD neg with ≥CR (10^{-5}) rate, %		Sustained MRD neg with ≥CR (10^{-5}) rate, %	
Age/ Frailty status	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**	MAIA*	CEPHEUS**
<70 y	0.35 (0.21–0.56)	0.60 (0.31–1.18)	56.4 vs 31.2	85.7 vs 68.6	35.9 vs 11.7	74.3 vs 42.9	25.6 vs 3.9	62.9 vs 28.6
70–<75 y	0.64 (0.45–0.89)	0.60 (0.37–0.99)	56.2 vs 31.3	77.9 vs 69.2	36.2 vs 12.2	55.9 vs 47.7	20.8 vs 5.3	45.6 vs 38.5
≥75 y	0.59 (0.44–0.79)	0.46 (0.22–0.94)	44.4 vs 28.6	80.5 vs 44.4	26.9 vs 9.9	58.5 vs 26.7	13.8 vs 3.1	43.9 vs 15.6
Frail	0.64 (0.48–0.85)	0.62 (0.32–1.18)	44.8 vs 33.1	72.9 vs 54.3	25.6 vs 13.0	56.3 vs 34.3	15.7 vs 4.1	39.6 vs 17.1
Non-frail	0.48 (0.36–0.64)	0.51 (0.34–0.78)	56.6 vs 27.5	84.4 vs 63.6	37.8 vs 9.5	63.5 vs 41.8	21.4 vs 4.0	54.2 vs 32.7

*MAIA: DRd vs Rd; **CEPHEUS: DVRd vs VRd

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Myeloma and other monoclonal gammopathies

REALITEC-2 SUBGROUP ANALYSIS: AN INTERNATIONAL OBSERVATIONAL RETROSPECTIVE STUDY OF TECLISTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA IN THE REAL WORLD

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Introduction. Teclistamab is a widely used anti-BCMA bispecific antibody for triple-class-exposed (TCE) RRMM. With median follow-up of 30.4 months in MajesTEC-1, teclistamab induced deep and durable responses across all patients, including those more difficult to treat such as penta-refractory, high-risk cytogenetics, and older than 75 years. The first REALiTEC cohort, an observational study including patients treated through pre-approval access programs, demonstrated clinical outcomes consistent with MajesTEC-1, including in subgroups associated with poor prognosis. We report a subgroup analysis of the second cohort, REALiTEC-2.

Methods. REALiTEC is a retrospective, non-interventional study based on data from patient medical records. Endpoints assessed included response rates, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results. 260 patients from 11 countries in Europe and Israel were assessed. Median age was 68 years; 67.6% of patients had high-risk cytogenetics. Extramedullary disease was reported in 19.1% of cases; 60% of patients would be ineligible for MajesTEC 1. Patients received median four prior lines of therapy. Overall response rate (ORR) was 66.5%, with 54.6% very good partial response or better (≥VGPR). At 12.7-month median follow-up, median DOR was not reached (NR) with a 12-month estimate of 64.4%; median PFS was 15.2 months, and median OS was NR with a 12-month estimate of 69.8%. No significant differences were found in ORR and ≥VGPR rates across clinically relevant subgroups compared with the overall cohort (Figure). DOR, PFS, and OS were similar between subgroups and the overall population with improved outcomes observed in elderly patients for DOR and PFS (both p=0.026), and in those with ISS I-II compared with ISS III for PFS and OS (p=0.022 and p≤0.001, respectively). Patients achieving ≥VGPR had significantly longer DOR, PFS, and OS (p<0.001).

Conclusions. REALiTEC-2 demonstrated comparable outcomes with MajesTEC-1 within a broader TCE RRMM patient population, with no significant differences in effectiveness observed across subgroups associated with poorer prognosis. These results further substantiate the role of teclistamab as an effective real-world standard of care for TCE RRMM. *Accepted and presented at the European Hematology Association (EHA) Annual Congress 2026*.

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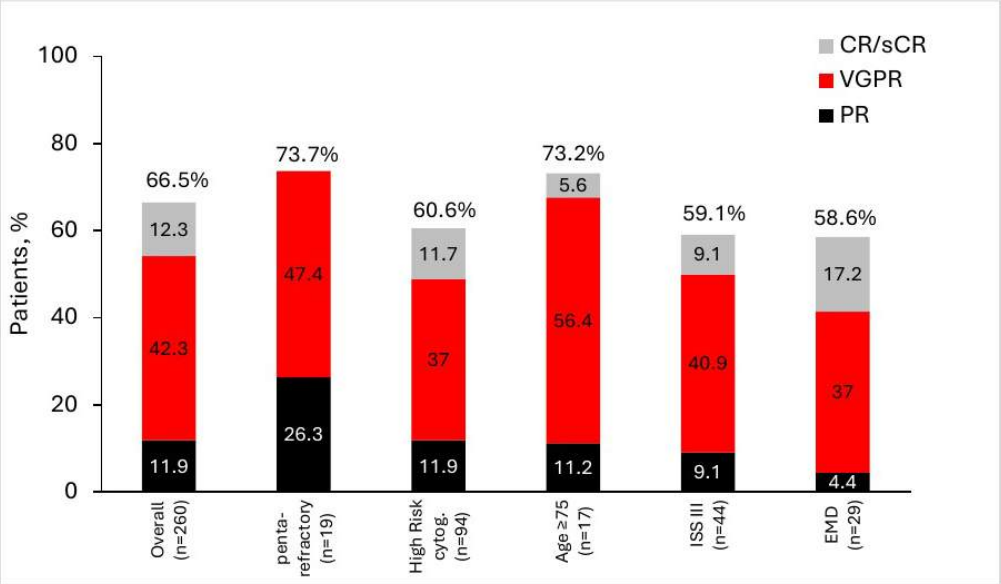
Figure: Response rates by subgroup



EMD, extramedullary disease; CR, complete response; ISS, international staging system; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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Myeloma and other monoclonal gammopathies

LINVOSELTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA IN THE LINKER-MM1 STUDY: LONGER FOLLOW-UP AND SUBGROUP ANALYSES

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Background Linvoseltamab, a BCMA×CD3 bispecific antibody, demonstrated durable efficacy and a generally manageable safety profile in pts with RRMM. We report longer-term FU of pts, including high-risk subgroups, receiving the FDA- and EMA-approved 200 mg dose, in the Phase (Ph) 1/2 LINKER-MM1 study (NCT03761108).

Methods. In Ph2, pts received linvoseltamab IV QW through Week 14, then Q2W; pts with ≥VGPR and ≥24 weeks of treatment switched to Q4W dosing. Ph2 primary endpoint was objective response rate (ORR) by IRC. Efficacy was assessed in prespecified subgroups defined by age; ISS stage; cytogenetic risk; baseline (BL) sBCMA concentration, BMPC % and EMP; and disease refractoriness. Efficacy by prior treatment was analysed *post hoc*.

Results. The analysis included 117 pts, and as of 23 Jul 2024, the median duration of FU was 21.3 months (mos).ORR was 71% (≥CR 52%) with median duration of response of 29.4 mos (95% CI 20.0–not evaluable [NE]). Median progression-free survival was not reached (17.3 mos–NE). Median overall survival was 31.4 mos (23.8–NE). Of 58 pts who transitioned to Q4W dosing at ≥24 weeks of treatment, 43 had disease that remained in response. Among 27 pts with VGPR at transition, 19 (70%) later achieved ≥CR.ORRs were high across subgroups of the overall 200 mg cohort, including by age (≥75 yrs 71%; ≥65–<75 yrs 76%; <65 yrs 66%), ISS stage (I 73%; II 71%; III 62%), cytogenetic risk (high 67%; standard 73%), BL sBCMA (≥400 ng/mL 57%; <400 ng/mL 83%), BL BMPC % (≥50%, 50%; >0–<50%, 79%) and BL EMP (EMP+ 53%; EMP− 74%), and in pts with penta-refractory disease (68%).ORR was 72% (64/89) in pts with ≥4 prior LoTs and 70% (7/10) in pts with prior anti-BCMA antibody–drug conjugate (belantamab mafodotin) exposure. Time-to-event outcomes by subgroup will be presented.Treatment-emergent adverse events (TEAEs) occurred in all pts (Grade [Gr] ≥3 88%); 21% discontinued due to TEAEs. No new safety signals were observed. The most common TEAEs were CRS (any Gr 46%), neutropenia (44%), and diarrhea (42%). Infections occurred in 75% (Gr 3/4 37%) of pts, with the rate decreasing after 6 mos of treatment (0–<3 mos: any Gr 52%/Gr 3/4 21%; 3–<6 mos: 49%/22%; 6–<9 mos: 37%/6%; 9–<21 mos [in each 3-mo period]: 23–37%/0–8%).

Conclusions. Linvoseltamab 200 mg induced deep and durable responses and prolonged survival in pts with RRMM, including those with heavily pretreated and high-risk disease, with no new safety signals.

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EARLIER USE OF CILTACABTAGENE AUTOLEUCEL IS ASSOCIATED WITH BETTER IMMUNE FITNESS AND STRONGER IMMUNE EFFECTS AS SHOWN BY CORRELATIVE ANALYSIS OF PERIPHERAL BLOOD AND THE BONE MARROW TUMOR MICROENVIRONMENT FROM THE CARTITUDE-4 STUDY

F. Gay[1], S. Parekh[2], K. Li[3], N. W. C. J. Van De Donk[4], Y. Lin[5], T. G. Martin[6], S. Han[3], R. Montes De Oca[3], M. Suraneni[7], M. Gormley[3], B. Hodkinson[3], J. Yuan[3], F. Wang[8], A. Kumar[3], D. Yin[3], D. Smirnov[3], J. Patel[3], N. Lendvai[9], D. Madduri[9], J. Zhu[10], N. Patel[10], D. Geng[10], V. Plaks[3], S. Harrison[11|12|13]

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Introduction. Cilta-cel is approved in the US/EU for lenalidomide-refractory multiple myeloma (MM) after ≥1 prior line of therapy (pLOT) based on CARTITUDE-1 and CARTITUDE-4. We reported cilta-cel's mechanism of action by correlating peripheral blood and bone marrow TME biomarkers with progression-free survival (PFS) and pLOT in patients with relapsed/refractory MM (RRMM) from CARTITUDE-1 and CARTITUDE-4.

Methods. Biomarker analyses used peripheral blood and bone marrow aspirates (BMAs). Immunophenotyping was performed at baseline/time of apheresis. Mixed-effects models identified signatures/pathways modulated over time and in association with PFS and pLOT.

Results. Immunophenotyping data were obtained from 248 peripheral blood samples (1 pLOT, n=56; 2 pLOT, n=61; ≥3 pLOT, n=131). At apheresis, CD4+ naïve T cells were higher with 1 or 2 pLOT vs ≥3 pLOT (no difference with 3–4 vs 5–6 vs ≥7 pLOT). Higher baseline CD4+ naïve T cell levels were linked to longer PFS.TME gene expression data were obtained from 148 BMA samples (screening, n=50; Day 28, n=50; 6 months, n=48). Gene expression signatures suggest B-cell and antibody depletion at Day 28 post cilta-cel infusion (partial recovery at 6 months). Elevated expression was observed for myeloid- and cytotoxic-T cell–associated genes at Day 28, and for B-cell-receptor-, T-cell-differentiation-and-activation, and cytokine-signaling-pathway–associated genes at Day 28 and 6 months.Patients with >18 months PFS had higher levels of M1 tumor-associated macrophages (TAM) at Day 28; those with shorter PFS had higher regulatory T cells and more suppressed interferon pathway genes at 6 months. In patients with fewer pLOT, more profound B cell depletion occurred on Day 28, and better recovery at 6 months, plus elevated B-cell receptor signaling were inferred from gene expression. Patients with 1 pLOT showed higher M1 TAM expression on Day 28 vs 3 pLOT.

Conclusions. Correlative biomarkers indicate that longer PFS correlates with improved immune fitness and responses post cilta-cel. Peripheral immune fitness was more pronounced with 1 and 2 pLOT vs 3 pLOT and beyond, suggesting the impact of T cell immune fitness on PFS may be limited for >3 LOT. Other covariates may play a significant role in balancing this compromised intrinsic T cell immune fitness at apheresis, thereby contributing to PFS durability with >3 pLOT. © *American Society of Hematology (2025). Reused with permission.*

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Myeloma and other monoclonal gammopathies

MACHINE LEARNING MODEL FOR EARLY IDENTIFICATION OF FUNCTIONAL HIGH RISK MULTIPLE MYELOMA

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Background. Multiple Myeloma (MM) is a biologically and clinically heterogeneous disease. Functional high risk (FHR) identifies patients who relapse unexpectedly within 12-18 months. This study aimed to improve FHR prediction using machine learning (ML) methods.

Patients and Methods. We retrospectively analyzed 996 newly diagnosed MM patients. FHR definition included all patients relapsed within 12–18 months independently of risk factors except those with ≥ double hit cytogenetics, which were excluded. Models used routine baseline variables, including age, Hb, platelets, creatinine, LDH and albumin as continuous variable, in addition to performance status (PS) and FISH risk according to R2-ISS cytogenetics. Missing data were managed using k nearest neighbors and mode imputation, with sensitivity analyses for FISH missingness. Supervised ML models were trained using logistic regression selected as best-performing model. Model performance was evaluated using discrimination (ROC-AUC, PR-AUC), threshold-based classification metrics (Fβ-score), calibration (Brier score), and bootstrap confidence intervals.

Results. Overall, 225 patients (22.6%) met criteria for FHR and showed markedly inferior outcomes (PFS 6.6 vs 30.9 months; OS 11.1 vs 36.7 months) compared to non-FHR patients after a median follow-up of 38.5 months. Logistic regression with mode imputed FISH achieved the best performance (ROC AUC 0.647; PR AUC 0.364; recall 0.779), with high sensitivity and limited false negatives. Higher PS, high-risk cytogenetics, elevated LDH levels, and renal impairment at onset were associated with increased probability of FHR, while higher hemoglobin, platelet count, and albumin levels were associated with reduced risk.ML derived risk scores stratified patients into groups with significantly different PFS, with clear separation across tertiles (log rank p<0.001). The model outperformed ISS and R ISS in discrimination (C index 0.671 vs 0.623 and 0.631). Decision curve analysis (Fig.) showed modest but consistent net benefit at intermediate time horizons (18-24 months), supporting the model's utility for early identification of FHR patients.

Conclusion. We developed a simple, clinically applicable model to predict FHR MM using routine variables (available at: https://github.com/mannuccilucia/FHR-Predictor). By enabling earlier identification of patients unlikely to benefit from standard therapy, the model may support risk adapted strategies pending external validation.

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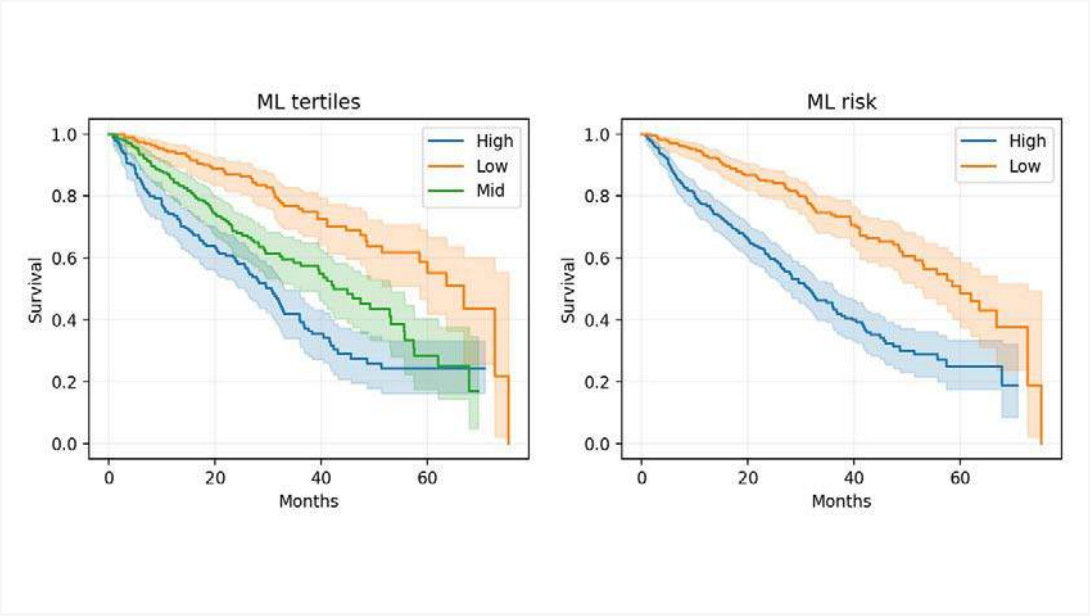

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Myeloma and other monoclonal gammopathies

EARLY RESOLUTION OF TALQUETAMAB ORAL SIDE EFFECTS IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED WATERLESS EMPIRICAL TASTE TEST AND PATIENT REPORTED OUTCOMES DATA FROM TALISMAN

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[1]Fondazione IRCCS Policlinico San Matteo; [2]Vrije Universiteit Amsterdam; [3]University College London Hospitals NHS Foundation Trust; [4]Cleveland Clinic; [5]National Cancer Center Hospital East; [6]Samsung Medical Center; [7]D'or Institute for Research and Education; [8]University of Amsterdam; [9]University of Pennsylvania; [10]The Central Nebraska Myeloma Support Group; [11]University of Rochester Medical Center; [12]Icahn School of Medicine at Mount Sinai; [13]University of California; [14]Brigham and Women's Hospital; [15]Johnson & Johnson; [16]Johnson & Johnson; [17]Johnson & Johnson; [18]Johnson & Johnson; [19]Johnson & Johnson; [20]Johnson & Johnson; [21]University Hospital of Würzburg

Introduction. In the phase 1/2 MonumenTAL-1 study, Tal elicited high response rates. Patients (pts) treated with Tal often experience taste changes oral side effects, but assessments for these events are limited. The WETT is an innovative tool to objectively detect discrete taste changes; measure onset, severity, and resolution of dysgeusia; and evaluate the effectiveness of prophylactic interventions. We report updated TALisman data with more pts and longer follow-up, and a 3-month futility analysis of Tal with dexamethasone oral rinse prophylaxis (prophy Dex) vs Tal only (control).

Methods. TALisman (NCT06500884) is an ongoing phase 2 study. Eligible pts have RRMM, prior exposure to a PI, IMiD, and anti-CD38 antibody. Primary endpoints are dysgeusia incidence and severity, time to first severe dysgeusia, and dysgeusia improvement/resolution at 3 and 6 months per WETT.

Results. As of December 2025, 30 pts were randomized (15 control; 15 prophy Dex); median age was 62.5 years. 25 pts completed ≥3 cycles and 11 completed ≥6 cycles. Overall, 86.7% had dysgeusia and 76.7% had severe dysgeusia at any time point. The highest proportion of pts with any grade dysgeusia occurred at C3D8 with the control (80.0%) and at C2D1 with prophy Dex (92.3%) (Figure). Median time to first dysgeusia was 15 days (control) and 8 days (prophy Dex); median time to first severe dysgeusia was 68 days and 9 days, respectively. Prophy Dex did not result in improved outcomes vs the control in a futility analysis at the end of month 3; improvement/resolution of dysgeusia was observed in 63.6% (control) vs 27.3% (prophy Dex) at the end of month 3, and in 60.0% vs 40.0%, respectively, at the end of month 5. Overall, the highest proportion of pts with severe dysgeusia (~60%) by WETT was detected earlier (C1D15) vs severe/complete loss by the Scale of Subjective Total Taste Acuity (STTA; C4D1).

Conclusions. Emerging data from TALisman may help to inform management strategies and clarify expectations for pts, caregivers, and healthcare providers to facilitate ongoing treatment and clinical benefit from Tal. *Accepted and presented at the European Hematology Association (EHA) Annual Congress 2026.*

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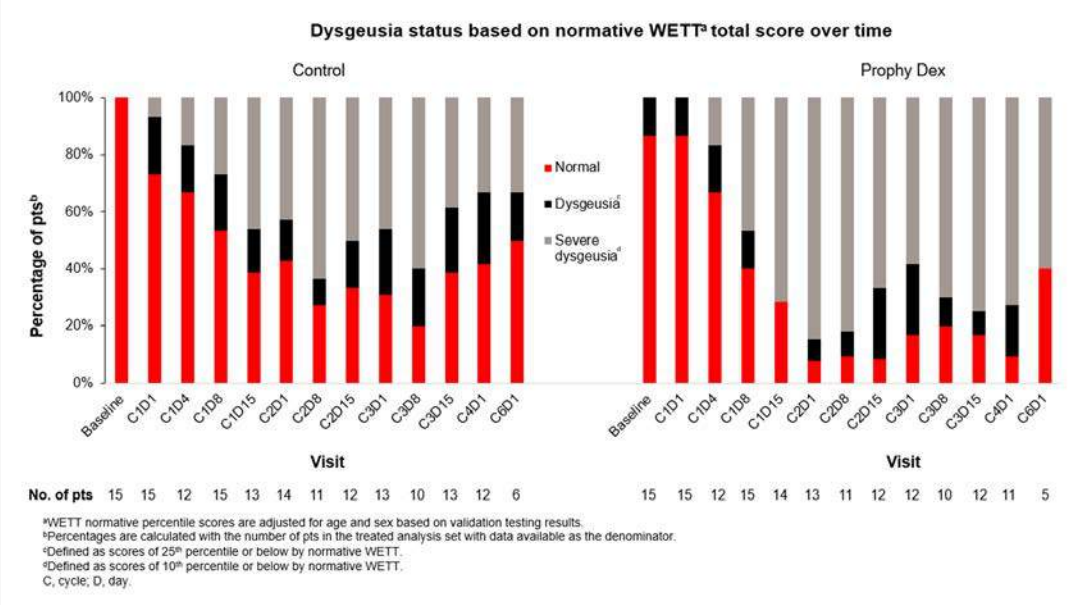
Dysgeusia status based on normative WETT[a] total score over time
Control
Prophy Dex
Percentage of pts[b]
100%
80%
60%
40%
20%
0%
Normal
Dysgeusia[c]
Severe dysgeusia[d]
Baseline
C1D1
C1D4
C1D8
C1D15
C2D1
C2D8
C2D15
C3D1
C3D8
C3D15
C4D1
C6D1
Visit
No. of pts
15 15 12 15 13 14 11 12 13 10 13 12 6
15 15 12 15 14 13 11 12 12 10 12 11 5
[a]WETT normative percentile scores are adjusted for age and sex based on validation testing results.
[b]Percentages are calculated with the number of pts in the treated analysis set with data available as the denominator.
[c]Defined as scores of 25th percentile or below by normative WETT.
[d]Defined as scores of 10th percentile or below by normative WETT.
C, cycle; D, day.

Myeloma and other monoclonal gammopathies

DYNAMIC CHANGES IN SOLUBLE BCMA *VERSUS* SOLUBLE FREE LIGHT CHAINS FOR THE EARLY PREDICTION OF THERAPEUTIC RESPONSE IN MULTIPLE MYELOMA

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This single-center, prospective study compares soluble B--cell maturation antigen (sBCMA) and soluble free light chains (FLC) assays for predicting short-term therapeutic response in newly diagnosed and relapsed Multiple Myeloma (MM) patients. While FLC is an established biomarker, its clinical utility can be limited by renal function. In contrast, sBCMA reflects clonal proliferation and may overcome FLC's analytical pitfalls. We evaluated 100 patients: 40 with newly diagnosed MM and 60 relapsed cases. Patients were stratified into 5 cohorts based on transplant eligibility and the number of prior relapses (R1, R2, R3). sBCMA and FLC levels were measured at baseline, 1 month, and 6 months. Response was assessed via IMWG criteria: at 6 months, 6 patients achieved CR, 34 VGPR, 42 PR, 18 PD. At baseline, only sBCMA differed significantly across cohorts ($p < 0.0001$), peaking in newly diagnosed non-transplant-eligible patients. Conversely, the FLC ratio (rFLC) showed no significant baseline differences. Absolute sBCMA, involved FLC, and rFLC values decreased significantly across the cohort at 1 and 6 months ($p < 0.0001$). However, only the 1-month percentage decrease of sBCMA varied significantly among subgroups ($p = 0.0001$). Greater reductions in all biomarkers correlated with superior clinical outcomes (CR/VGPR).While univariate analysis linked early reductions in all biomarkers to favorable 6-month responses, multivariate ordinal logistic regression revealed that only the 1-month sBCMA percentage decrease independently predicted an improved response. A <50% sBCMA decrease increased the likelihood of poorer 6-month outcomes 5.444-fold ($p = 0.007$). Dynamic changes in sBCMA significantly outperform FLC in differentiating baseline disease states and predicting early response. While existing literature primarily links absolute sBCMA to overall survival, this investigation validates the early dynamic percentage change of sBCMA as a rapid, independent indicator of treatment efficacy in a real world differently treated Multiple Myeloma population.

Myeloma and other monoclonal gammopathies

INFLAMMATION SCORE IN ELDERLY PATIENTS WITH MULTIPLE MYELOMA: A NEW EASY TOOL TO ASSESS PROGNOSIS

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Background. In patients (pts) with Multiple Myeloma (MM) chronic inflammation promotes malignant progression and proliferation, with development of drug resistance. Aging itself is associated with a chronic low-grade inflammation due to imbalance of the immune system. Interleukin-6 increases many inflammatory parameters, like Reactive C Protein (R-CP), Fibrinogen (Fb) and Ferritin (Fe). However, the relationship between these inflammatory biomarkers and the prognosis of MM is still unknown.

Objectives. We evaluated inflammation parameters in newly diagnosed elderly (>75 years) pts with MM and correlated their levels with age, haemoglobin (Hb), ISS and overall survival (OS), to provide an easy and cost-effective prognostic model.

Methods. A cohort of 109 elderly pts with MM newly diagnosed in 11 Hematologic Centres from 1/2019 to 4/2025 was collected and analysed. An Inflammation score (I-score) was built by assigning 1 point each to elevated RCP (>0.5 mg/L), Fb (>400 mg/dl) and Fe (>275 µg/L) and two different risk groups were defined: low-risk group (I-score 0) with 0-1 point and high-risk group (I-Score 1) with 2-3 points.

Results. Among the 109 pts, 73 (66.9%) had an I-score 0 and 36 (33.1%) an I-score 1. Median age was comparable in the two I-score groups (79.7 vs 80.9 years, p=0.28). Pts in the I-score 1 had a significant higher rate of anemia (Hb ≤10 g/dl), renal impairement (creatinine levels > 2 mg/L) and β2 microglobulin elevation (p<0.0001, p=0.0003 and p= 0.0025, respectively). In addition, pts in the I-score 1 group had a higher rate of ISS 3 compared to pts in the I-score 0 group (p=0.0086). As to treatment, 34 pts (31.19%) received dara-based triplets, 38 (34.8%) bortezomib-based doublets, 25 (22.9%) lena-based schemes and 12 (11%) MP and other low dose therapy. At the last follow-up, 67 patients (61,64%) are still alive, 5 (4,6%) were lost to follow-up and 36 (33%) died. Median OS of the whole cohort was 47.0 months (95%CI 32.0 – 65.0). Median OS of pts in the I-score 0 group was 51.9 months (95%CI 38.3 – 72.3) compared to 30.2 months (95%CI 12.6 – 68.8) of pts in the I-score 1 group (p=0.0083) (Figure).

Conclusions. I-score was very simple to assess and showed a good correlation with parameters of disease aggressiveness at diagnosis and with OS, providing a cost-effective risk stratification tool. It could be a good method to identify high-risk MM pts, in particular among elderly pts, in which karyotype is not routinarily performed.

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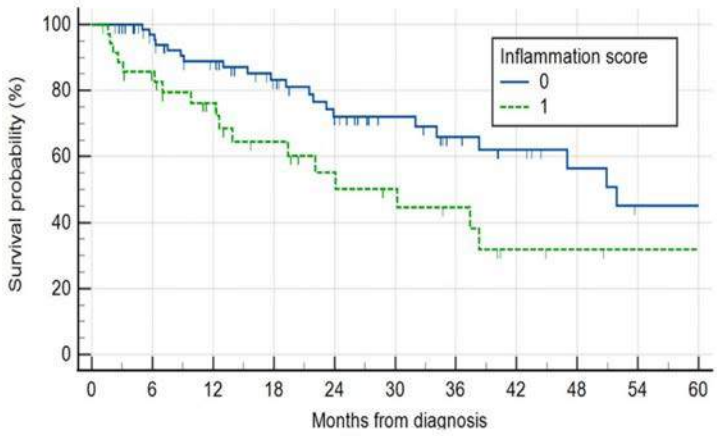
Figure – Overall survival according to I-score



Myeloma and other monoclonal gammopathies

ANTI-BCMA CAR-T CELLS KINETICS AND EARLY OUTCOMES AFTER IDE-CEL IN PATIENTS WITH RELAPSE/REFRACTORY MULTIPLE MYELOMA

G. Facchin[1], E. Favero[1], Ml. Battista[1], E. Toffoletti[1], L. Pavan[2], R. Zambello[2], A. Furlan[3], A. Pascarella[4], F. Marzuttini[1], R. Stocchi[1], A. Michelutti[1], M. Cavallin[1], R. Fanin[1], F. Patriarca[1]

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There are still limited data regarding dynamic of CAR-T cell subset expansion and its correlation with toxicities and response in relapsed/refractory multiple myeloma(MM) after ide-cel. We performed a retrospective analysis including all adult patients(pts) with MM treated with Ide-cel between October2024 and January2026. We evaluated CAR-T subsets expansion by flow cytometry monitoring on day 4,7,10,14,21,28 to observe CAR-T subsets dynamics following the infusion. A total of 21pts received Ide-cel. Median age was 62years(50-67), 67%of pts had R-ISS stage2-3, 40%had del(17p)/TP53 mutation. At the time of apheresis, median number of prior lines of therapy was 3(3-5) with 3 pts exposed to talquetamab as treatment before apheresis. Bridging therapy was required for 20pts mainly (40%) Selinexor based. Median time from apheresis to infusion was 49days(42-117). Only 29%of pts was in partial response at the time of infusion while the others were stable or in progression of disease. CRS was observed in 81%of pts(all grade 1-2), ICANS in 5%of pts(grade 3-4) and HLH in 5%of pts. One pt died due to septic shock after 23days from infusion while 1 pt developed TP53 mutated secondary dysplasia 3months after infusion. 15/20 pts(75%) were responders 3 months after reinfusion (at least partial response according IMWGcriteria). With a median follow up of 6 months(1-18), the 6month-PFS was 64% and 6month-OS was 95%. The overall median peak CAR-Tcell expansion was 265cells/µL(range,7–702), occurring at a median of 7days (range,4–14). Overall, CAR-TCD8+ cells predominated over CAR-TCD4+cells(Fig.1A). Responding pts showed a trend toward higher CAR-T peak expansion(315vs46 cells/µL, p=0.06; Fig.1B), while no significant difference in CAR-TCD8+ peak was observed. In contrast, higher CAR-TCD4+-peak was found in responders(p=0.007; Fig.1B). Pts who developed CRS exhibited higher peak of both CAR-TCD4+(49vs17cells/µL,p=0.05) and CAR-TCD8+cells(235vs42cells/µL,p=0.03). No significant differences in CAR-T composition at peak of expansion were observed in patients who developed grade 3–4 persistent cytopenia, early infections or according holding and bridging treatments. These results confirm the efficacy and safety of ide-cel in patients with relapsed/refractory MM(6-months-PFS 64%,NRM 5%). Greater CAR-T expansion, especially of CD4+cells, is associated with 3month-response, suggesting distinct roles of CAR-Tcell subsets and identifying a potential prognostic indicator of efficacy.

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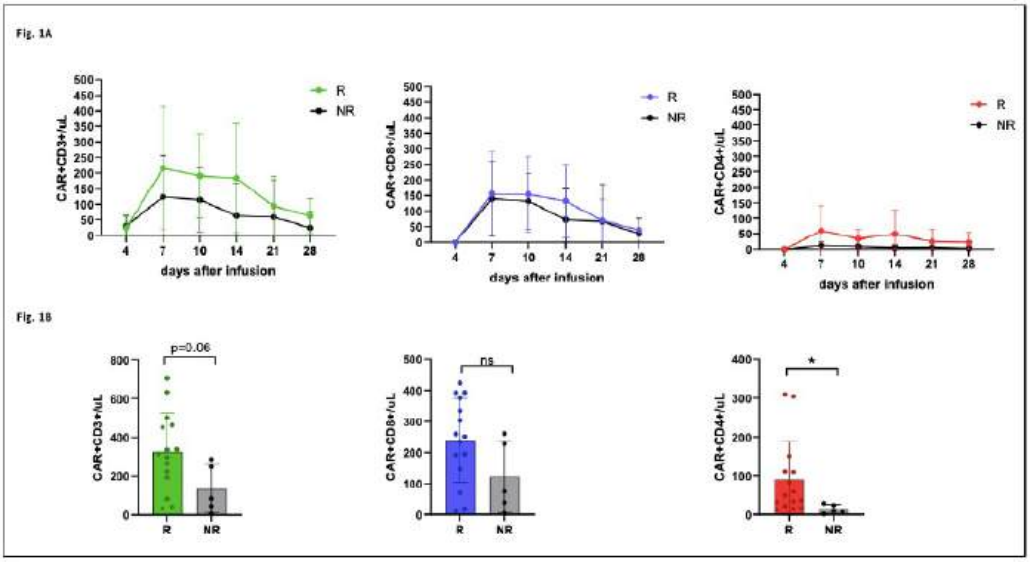
Figure 1 Longitudinal monitoring of circulating CAR-T cells by flow cytometry from infusion to day +28 **(A)** and association between CAR-T cells subtypes expansion and clinical outcomes **(B)**.



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Myeloma and other monoclonal gammopathies

BELANTAMAB MAFODOTIN-BASED COMBINATIONS FOR THE TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA: PATIENT CHARACTERISTICS AND TREATMENT SCHEMAS IN THE ITALIAN REAL-WORLD EXPERIENCE

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Background. Patients (pts) with multiple myeloma (MM) often relapse after initial treatment with triplet/quadruplet combination regimens. The DREAMM-7 and DREAMM-8 clinical trials demonstrated robust efficacy of the anti-BCMA antibody-drug conjugate belantamab mafodotin (belamaf) plus bortezomib and dexamethasone (BVd) or pomalidomide and dexamethasone (BPd) vs standard of care regimens in relapsed/refractory multiple myeloma (RRMM) pts after at least one prior line of therapy. A global managed access program was initiated to facilitate pts access to these treatments. In Italy, patient access was granted through a Named Patient Program (NPP).

Aims. The objective of this study was to examine pts characteristics and early dosing patterns in pts with RRMM treated with belamaf combination therapies in a real-world setting.

Methods. A retrospective chart review was initiated to examine pts treated with BVd or BPd. Data were captured on pt demographics, disease and clinical characteristics, and treatment history. The treatment period with belamaf was Jan 2025–Feb 2026.

Results. Overall, 43 pts were included in the study from Italy. 25 (58%) were treated with BVd and 18 (42%) with BPd. Median treatment period was 152 (IQR 79–251) days at data cutoff. The median age was 79 (IQR 72-81) years and 7 of 34 (21%) pts with data available had high cytogenetic risk. Before BVd/BPd, pts received a median of 2 (IQR 1–3) prior therapies with 35 (81%) pts being refractory to lenalidomide and 38 (88%) to anti-CD38 agents. At DCO, pts received a mean of 5 (standard deviation [SD] 3) doses of belamaf.-Most (39/43 [91%]) pts started belamaf on a 2.5 mg/kg dose at planned schedules of once every 3 weeks (Q3W) for BVd or once every 4 weeks (Q4W) for BPd, with planned reduction to 1.9 mg/kg Q4W from dose 2). Dose reductions (49% of pts) and delays (72% of pts) were frequently utilized, but 79% of patients (34/43) remained on treatment at data cutoff. For all pts, the median/mean time between doses increased from 4.0/4.4 weeks during the first three months of treatment to 5.0/7.3 weeks for months 6–9.

Conclusions. Similar to the DREAMM-7/DREAMM-8 clinical trials, Italian physicians utilize extended dosing to improve belamaf tolerability and keep pts on treatment. Real-world belamaf use in earlier lines of therapy signifies an unmet need for highly efficacious therapies at first relapse.This research was funded by GSK (Study 224207)

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

IMPACT OF VENETOCLAX-BASED THERAPY ON T- AND NK-CELL IMMUNITY IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) is characterized by profound immune dysregulation. Venetoclax (Ven) has shown strong clinical activity in both treatment-naïve and relapsed/refractory (R/R) settings; however, its immunological effects remain incompletely defined. We longitudinally characterized T- and NK-cell profiles in a multicenter observational study including 68 R/R CLL patients treated with Ven-based regimens, with peripheral blood collected at baseline and after 1, 6, and 12 months. Phenotype and functional activity of T and NK cells were assessed by flow cytometry. Along with leukemic cell reduction, Ven induced an early and sustained decrease in absolute CD3+, CD4+ and CD8+ T-cell counts. Within CD4+ T cells, naïve and central memory (CM) subsets remained stable, whereas effector memory (EM) declined and terminally differentiated (TEMRA) cells increased at 12 months; a similar shift toward TEMRA, with reduced CM and EM, was observed in CD8+ T cells. Immune checkpoint analysis showed early PD-1 downregulation on CD4+ T cells, followed by reduced BTLA, TIM-3 and LAG-3 expression at later timepoints, mainly within naïve and CM subsets; in $CD8^+$ T cells, BTLA was significantly reduced, particularly in less differentiated subsets, while other checkpoints remained unchanged. At 6 month, CD8+ T cells displayed increased proliferative capacity, whereas CD4+ T-cell expansion remained unchanged. Tregs and T follicular helper cells progressively declined in absolute count. Within the γδ T-cell compartment, both Vδ1 and Vγ9Vδ2 subsets significantly decreased, although Vγ9Vδ2 T cells exhibited enhanced degranulation capacity following IL2 and zoledronic acid stimulation. In parallel, Ven reduced total NK cell counts while progressively enriching the cytotoxic CD56dimCD16+ subset. Functionally, NK cells exhibited increased ADCC activity as early as 1 month after treatment initiation against a CD20+ cell line in the presence of rituximab or obinutuzumab. Overall, these findings support the notion of treatment-induced immune reprogramming that should be considered when defining optimal therapeutic sequencing, particularly in the context of immunotherapeutic strategies.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

FEASIBILITY AND SAFETY OF VENETOCLAX–OBINUTUZUMAB IN FIT AND UNFIT CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: ANALYSIS OF POOLED CLL13 AND CLL14 TRIALS AND AN ITALIAN CLINICAL PRACTICE COHORT

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Based on the CLL13/CLL14 clinical trials (CT), fixed-duration venetoclax–obinutuzumab (VO) became a standard first--line treatment for chronic lymphocytic leukemia (CLL) patients (pts), both fit and with comorbidities. However, in clinical practice (CP) longitudinal data on feasibility and outcomes remain limited.To investigate feasibility and safety of VO in CT and CP, we performed descriptive analyses on a prospective cohort of pooled CLL13/CLL14 pts and a multicenter retrospective Italian CP cohort (55 centers, treated from May 2022 to June 2023). Pts were analyzed by fitness status (unfit: CIRS>6 and/or creatinine clearance<70 ml/min; fit: CIRS≤6 and creatinine clearance≥70 ml/min). Analyses were conducted across early combination (cycle (C) 1–2), combination (C3–6) and maintenance (C7–end of treatment +28 days [C7+]).Overall, 711 pts received ≥1 dose: 440 in CT (257 unfit, 182 fit, 1 with missing fitness status) and 271 in CP (133 unfit, 138 fit). Median follow-up was 72.3 months (interquartile range 60.9–78.7) in CT and 29.3 months (28.3–30.3) in CP. Median age was 67 years in CT (71 unfit, 58 fit) and 66 years in CP (73 unfit, 60 fit). More CT pts had ECOG≥1 (42.5% vs 29.5% in CP), CIRS>6 (41.6% vs 20.7%) and an unmutated IGHV status (59% vs 51.2%).Treatment completion rate was 86.6% in CT (81.7% unfit, 93.4% fit) and 89.3% in CP (88% unfit, 90.6% fit). Toxicity-driven discontinuations occurred in 8% of CT (10.5% unfit, 4.4% fit) and 10% of CP pts (11.3% unfit, 8.7% fit). Venetoclax dose intensity <70% during C1-2, C3-6, and C7+ was observed in 22.7%, 18.9%, and 22.9% of CT, and in 7%, 10.4%, and 11.9% of CP pts. Obinutuzumab was not given at full dose during C1-2 and C3-6 in 11.8% and 9.5% of CT, and in 13.5% and 8.4% of CP pts.Grade ≥3 adverse events occurred in 59.3%, 40.9%, and 37.3% during C1-2, C3-6, and C7+ in CT, and in 38.4%, 21.2%, and 14.7% in CP pts. Grade ≥3 infections occurred in 4.5%, 3.8%, and 7% of CT, and in 6.3%, 4.6% and 5.2% of CP pts, respectively (Figure 1). During C1-2, tumor lysis syndrome was reported in 6.6% of CT and in 5.9% of CP pts, and infusion-related reactions in 48.6% and 36.9%, respectively.In CP, fixed-duration VO was feasible across fitness groups, achieving high treatment completion rates and dose intensities. Despite more systematic reporting in CT and shorter follow-up in CP, outcomes in CP were in line with those observed in CT and support the use VO as a frontline treatment in CP.

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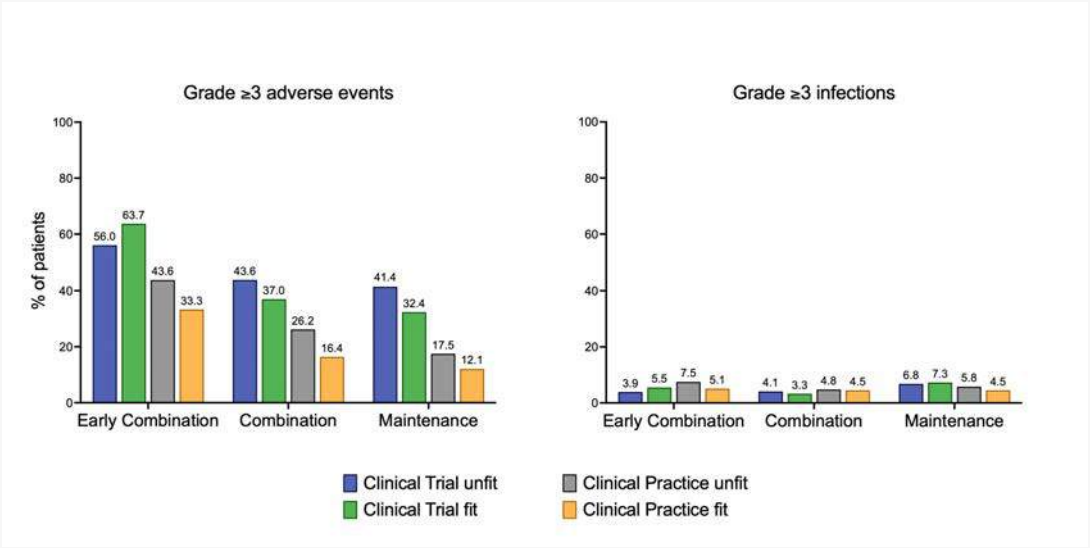
Grade ≥3 adverse events
% of patients
100
80
60
40
20
0
56.0
63.7
43.6
33.3
43.6
37.0
26.2
16.4
41.4
32.4
17.5
12.1
Early Combination
Combination
Maintenance
Grade ≥3 infections
3.9
5.5
7.5
5.1
4.1
3.3
4.8
4.5
6.8
7.3
5.8
4.5
Early Combination
Combination
Maintenance
Clinical Trial unfit
Clinical Trial fit
Clinical Practice unfit
Clinical Practice fit

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

PIRTOBRUTINIB IN POST-CBTKI CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: PHASE 1/2 BRUIN STUDY WITH MORE THAN 5 YEARS FOLLOW-UP (FINAL UPDATE)

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Pirtobrutinib (pirto), a highly selective, non-covalent BTKi is approved for treating CLL in adults in the EU and USA after prior BTKi treatment (tx). We report the final efficacy and safety results of pirto from the phase 1/2 BRUIN study with more than 5 years (yrs) follow-up (f/u).Pts with prior cBTKi-exposed CLL/SLL were eligible for pirto tx. Overall response rate (ORR) per 2018 iwCLL criteria, ORR including partial response with lymphocytosis (PR-L), duration of response (DOR), and progression-free survival (PFS), assessed by IRC, overall survival OS, and safety, were analyzed. Data cut was 27Jan2025, (median study f/u of 34.1 months [mos]; range:0.5-69.8).Among the 282 pts post-cBTKi with CLL/SLL, 84.4% (238/282) received pirto 200 mg as the starting dose. Median age was 69 yrs. Median number prior therapies; 4 (45.4% received prior BCL2i, and 77.0% discontinued due to progressive disease (PD), 19.5% due to toxicity). High-risk features: unmutated IGHV 85.8% (193/225), mutated TP53 40.4% (99/245), and del(17p) 29.2% (59/202). ORR was 72.3% (95%CI:66.7-77.5). ORR including PR-L: 81.6% (95%CI:76.5-85.9). Median DOR and PFS (mos, 95%CI): 18.4, 14.82-20.27 and 18.7, 16.6-21.8. 36-mos DOR and PFS rate: 28.0% (21.6-34.7) and 25.0% (19.4-31.0), respectively. Among all CLL/SLL: median f/u was 46.5 mos, median OS was not estimable (NE) (95%CI:47.8-NE), 36-mos OS rate: 62.0% (95%CI:55.8-67.7). Most frequent TEAEs, were fatigue (38.7%), neutropenia (35.8%), diarrhea (30.5%), cough (29.8%), COVID-19 (28.4%), and contusion (27.7%). Most frequent grade ≥3 TEAEs: infection (36.5%) and neutropenia (29.8%). Low rates of grade ≥3 TEAE of hypertension (5.3%), hemorrhage/hematoma (2.5%), and atrial fibrillation/flutter (2.1%) were observed. Grade 5 TEAEs, regardless of attribution, occurred in 35 (12.4%) pts.In heavily pretreated R/R post-cBTKi CLL/SLL, pirto continues to show favorable and durable efficacy and is well-tolerated, with low rates of grade ≥3 TEAE. Dose reductions/discontinuations were low. No new pirto safety signals were identified with more than 5 yrs of f/u.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

NON-BIOLOGICAL FACTORS DRIVE FRONTLINE FIXED - DURATION TREATMENT SELECTION IN CLL: REAL-WORLD EVIDENCE FROM THE GIMEMA CLL2121 STUDY

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Background. In chronic lymphocytic leukemia (CLL), frontline treatment choice should be guided by biological risk and patient fitness. However, the availability of fully oral fixed-duration regimens, such as ibrutinib–venetoclax (IV), and intravenous anti-CD20–based combinations, such as venetoclax–obinutuzumab (VO), may introduce additional determinants of choice. Real-world drivers of treatment allocation remain poorly defined.

Methods. We analyzed 539 patients with CLL treated frontline with IV or VO within the GIMEMA CLL2121 study. Baseline clinical and biological characteristics were compared between groups. A structured Physician's Treatment Decision Questionnaire, including ranking of prioritized factors, was completed for 437 patients (81%).

Results. Overall, 272 and 267 patients received IV and VO, respectively. Baseline biological risk features, including TP53 mutation, IGHV status, cytogenetics, as well as age, and key laboratory parameters, were balanced between the two groups.Biological factors were relevant in 40% of decisions of fixed duration therapy, without differences between groups, suggesting a limited role in discriminating between IV and VO. Similarly, age and expected efficacy influenced about one-third of decisions, without differences between groups.In contrast, non-biological factors significantly impacted allocation. IV was more frequently selected over VO due to oral administration (30% vs 4%, $p<0.001$), logistical considerations (12% vs 0%, $p<0.001$), and avoidance of anti-CD20 (4.9% vs 0%, $p=0.002$). Conversely, VO was more often chosen in patients with baseline comorbidities, mainly cardiovascular (25% vs 7.4%, $p<0.001$), and for perceived safety (19% vs 12%, $p=0.042$). The main drivers of treatment selection are summarized in Table 1.Ranking analysis confirmed that treatment-related and logistics factors were prioritized over biological features. After IV availability in Italy (March 2024), prescribing shifted markedly, with IV increasing (40 to 203 cases) and VO decreasing (130 to 64), with VO prescription rate plateauing at approximately 25% of cases.

Conclusions. Despite comparable biological profiles, treatment selection between IV and VO is largely driven by non-biological and logistics factors. The rapid shift to IV after its market availability supports a dynamic decision-making model in frontline CLL, where biological assessment defines eligibility for fixed-duration therapy, while access, logistics, and perceived safety drive real-world choice.

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Table 1. Drivers of treatment selection (IV vs VO)

Factor	Overall, n (%)	Ibrutinib + Venetoclax (IV), n (%)	Venetoclax + Obinutuzumab (VO), n (%)	p-value
Biological characteristics	174 (40%)	91 (37%)	83 (43%)	0.28
Age	171 (39%)	96 (40%)	75 (39%)	0.92
Efficacy expectations	151 (35%)	78 (32%)	73 (38%)	0.27
Clinical characteristics	118 (27%)	62 (26%)	56 (29%)	0.45
Co-morbidities	66 (15%)	18 (7.4%)	48 (25%)	**<0.001**
Safety profile	64 (15%)	28 (12%)	36 (19%)	**0.042**
Advantages in administration route	80 (18%)	72 (30%)	8 (4.1%)	**<0.001**
Logistical needs	30 (6.9%)	30 (12%)	0 (0%)	**<0.001**
Avoidance of anti-CD20 antibodies	12 (2.7%)	12 (4.9%)	0 (0%)	**0.002**

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

DOSE AND BTK OCCUPANCY RELATIONSHIP IN THE PROSPECTIVE PHASE 2 TAILOR STUDY: EXPLORATORY END POINT ANALYSIS OF THE IBRUTINIB MONOTHERAPY COHORTS IN PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction. Continuous BTK inhibitor therapy is standard for previously untreated CLL. Ibrutinib (Ibr), the first-in-class BTK inhibitor, has demonstrated durable clinical benefit with long-term follow-up, and dose modifications have been shown to improve tolerability without compromising activity. Previous research has shown that total BTK protein levels decrease during Ibr treatment, and a model-based approach demonstrated that reducing the dose of Ibr to 280 mg after an initial 28-day cycle at 420 mg can effectively sustain BTK inhibition (Ouerdani A et al, 2025). Supporting this, pilot clinical data have shown that the biological activity of Ibr is retained following a similar dose modification approach (Chen LS et al, 2018). Here we report exploratory pharmacokinetic (PK) and pharmacodynamic (PD) analyses from the randomized Ibr monotherapy cohorts of the phase 2 TAILOR study.

Methods. TAILOR (NCT05963074) enrolled untreated CLL patients who received Ibr + venetoclax or Ibr monotherapy. Monotherapy patients were randomized 1:1 to Ibr 420 mg once daily (QD) (Cohort 2a) or 420 mg QD for one cycle followed by 280 mg QD (Cohort 2b) until progression or intolerability. Samples at screening, Cycle 1 Day 14 (C1D14), and Cycle 4 Day 1 (C4D1) assessed predose BTK occupancy. Plasma Ibr concentrations were measured at C1D14 and C4D1 at predose, 2 h, and 4 h post-dose.

Results. Data were available for 21 patients (Cohort 2a n=10; Cohort 2b n=11). Median age was 76 years (59–84), and 85.7% were ≥65 years. Seven patients had TP53/del(17p), and 14/18 assessed had unmutated IGHV. In Cohort 2a, geometric-mean plasma Ibr concentrations were similar predose at C4D1 versus C1D14 (2.2 vs 2.1 ng/mL) but higher at 2h post-dose (58.8 vs 32.1 ng/mL). In Cohort 2b, concentrations were lower at C4D1 versus C1D14 (predose 1.7 vs 3.4 ng/mL; 2 h 19.2 vs 34.0 ng/mL). At C4D1, both predose and 2 h concentrations were lower in Cohort 2b than in Cohort 2a. Median predose BTK occupancy remained nearly complete and similar between cohorts at C1D14 (99.4% vs 98.9%) and C4D1 (both 99.5%), across measured concentration levels.

Conclusions. Both cohorts showed >99% median post-baseline BTK occupancy regardless of Ibr dose. Proactive reduction to 280 mg QD after one cycle at 420 mg maintained high BTK occupancy with lower circulating Ibr levels in Cohort 2b. Further analyses are needed to determine whether this translates into comparable efficacy with improved safety or tolerability.

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OUTCOMES OF PIRTOBRUTINIB IN SECOND-LINE (2L) CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA AFTER FIRST-LINE (1L) CBTKI THERAPY: BRUIN PHASE 1/2 AND BRUIN CLL-321 STUDIES POOLED ANALYSIS

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Pirtobrutinib (pirto), a highly selective, non-covalent BTKi, was safe and effective in the BRUIN Phase 1/2, which was confirmed in the phase 3 BRUIN CLL-321 study. Both studies were conducted in a broad population of pts withR/R CLL/SLL, including those who pre-treated with a cBTKi. We report the safety and efficacy of pirtofor patients (pts) with 2L CLL/SLL, using pooled data from the BRUIN Phase 1/2 and CLL-321 studies. This pooled analysis on BCL2i-naïve pts with CLL/SLL, treated with 2L pirto after 1L cBTKi therapy with/without an anti-CD20 antibody evaluated investigator assessed PFS/iwCLL 2018 criteria, OS, time to next tx (TTNT), and safety dataA total of 37 pts (BRUIN Phase 1/2, n=17; CLL-321, N=20) received pirto 200 mg daily and received prior cBTKi tx with ibrutinib (76%), acalabrutinib (14%), zanubrutinib (8%), or other cBTKi tx (3%), and CD20 antibody (11%). 22/26 (85%) had unmutated IGHV gene, 13/30 (43%) had mutated TP53, and 15/31 (48%) had del(17p). Pts discontinued prior cBTKi therapy due to disease progression (57%), toxicity (35%), or other (8%). Median follow-up was 30.3 months (mo), median PFS was 19.5 mo (95%CI:11.7-44.7). Median PFS for pts who discontinued their previous cBTKi due to disease progression: 13.9 mo (95%CI:7.4-19.5) and toxicity: 44.7 mo (95%CI:10.6-not estimable). Median TTNT for all pts: 32.5 mo (95%-CI:16.6-47.4). Median OS was not reached; the 24-mo OS rate was 81.1% (95%CI:61.9-91.3). Median time on tx was 17.6 mo (range:0.9-57.2), and 35% remained on pirto at data cutoff. 97% experienced ≥1 tx-emergent adverse event (TEAE), most commonly anemia (27%), neutropenia (24%), hemorrhage (22%), and pneumonia (22%). Grade ≥3 TEAEs occurred in 68%. TEAEs of atrial fibrillation/flutter occurred in 1 pt, hypertension in 5, and hemorrhage in 8 pts. Tx-related AEs led to pirto dose reductions in 3 pts.Pirto demonstrated clinical benefit and tolerability in pts with 2L CLL/SLL pre-treated with a cBTKi, including those with high-risk genetic features. Pirto is a 2L therapy option after 1L cBTKi use and may help inform future tx sequencing strategies.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

VENETOCLAX AND DELAYED RITUXIMAB WITH IBRUTINIB CONSOLIDATION AIMING AT UNDETECTABLE MINIMAL RESIDUAL DISEASE IN TREATMENT-NAÏVE PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: VALUABLE TRIAL

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In CLL, achieving undetectable measurable residual disease (uMRD4, <10^-4) with venetoclax (ven)-based therapy (tx) correlates with longer progression-free survival (PFS) and overall survival (OS), supporting MRD-guided tx duration. In randomized trials, ven plus obinutuzumab (obi) led to higher uMRD rates and longer PFS than ven plus rituximab (R), but with more frequent severe, including fatal, infections. A sequential approach using ven, delayed R, and subsequent ibrutinib (ibr) may improve efficacy while reducing toxicity.This phase 2 multicenter study aimed to increase uMRD4 rates by delaying R tx (cycles 7-12) during 12 months (mo) of ven tx and adding ibr in patients (pts) not achieving uMRD4 at the end of 12mo of Ven+delayed R tx. Given an expected uMRD4 rate of ~56% with ven+obi (CLL14 trial), an increase to 75% was considered clinically meaningful.TN pts ≤65 years received ven mono (up to 400 mg QD for 6 cycles), followed by R added in cycles 7–12. Patients achieving confirmed uMRD4 in peripheral blood (PB) in 3 consecutive tests the last one with concomitant uMRD4 in bone marrow (BM) at C13D1 discontinued therapy; the remaining continued ven up to 24 cycles with ibr (420 mg daily) until confirmed uMRD4, progression, or toxicity.At data cutoff, 36 pts were enrolled (Table.1). Median follow-up was 24 mo (range, 0-42). Overall response rate was 100% (58.4% complete, 41.6% partial response). Median time to first PB uMRD4 was 8 mo (range,3-24). At C13D1, 71.4% of evaluable pts (20/28) discontinued tx due to uMRD4; 28.6% (8/28) added ibr, among them 3/8 met uMRD4 criteria to stop tx subsequently, after a median time of 11 mo (range 6-12), 4 pts did not achieve confirmed uMRD4 after 12 cycles of Ibr-ven and 1 pt was still on Ibr-ven. Overall, 82.1% (23/28) achieved confirmed BM uMRD4, meeting the primary endpoint.The most common grade ≥3 adverse event (AE) was neutropenia (33.3%); others included diarrhea, hypertension, thrombocytopenia, and anemia with 2 cases of warm haemolytic autoimmune anemia (wAIHA) on ven mono. One laboratory tumor lysis syndrome (TLS), but no clinical TLS. Four serious AE occurred (11.1%): wAIHA, ankle fracture, lung cancer G5, lower limb paresthesia. No tx-related deaths were reported.These results suggest that delayed R after ven improves BM uMRD4 rates beyond historical ven-R and ven-obi data, and MRD-guided ibr intensification further enhances outcomes with good tolerability.

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Patient characteristic	Result
Median age (n=35)	59 y (range 48-65)
Sex (n=35)	F 10 (28.6 %), M 25 (71.4%)
Chromosome 17p deletion status (n=29)	NO 24 (82%), YES 5 (18%)
TP53 mutation status (n=28)	NO: 24 (85.7%), YES: 4 (14.3%)
IGHV mutational status (n=30)	Unm 26 (86.6%), Mut 4 (13.3%)
Disease clinical stage (RAI) (n=36)	0, 1 (2.7 %), I, 3 (8.3 %). II, 8 (22.2 %) III, 19 (52.7%) IV, 5 (13.8 %)
TLS baseline risk (N=28)	Low/medium, 15 (53.5%), High 13 (46 %)

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

TRACKING THE CELLULAR ORIGINS AND PREDICTIVITY OF CIRCULATING EXTRACELLULAR VESICLES IN CAR-T THERAPY

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Introduction. CAR T-cell therapy has revolutionized hematologic malignancy treatment but is frequently complicated by cytokine release syndrome (CRS), neurotoxicity (NT), and persistent cytopenia. Approved products include axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and brexucabtagene autoleucel (brexu-cel). Extracellular vesicles (EV) are emerging biomarkers of inflammation and cellular stress. We used a patented polychromatic flow cytometry (PFC) method to assess longitudinal changes in circulating EV after CAR T-cell infusion.

Methods. The study enrolled 30 patients with various lymphomas: diffuse large B-cell (n=20), follicular (n=6), mantle cell (n=3), and high-grade B-cell (n=1). Blood was collected before lymphodepletion (pre-Lym) and at days 0, 1, 3, 7, 10, 14, and 20–30 post-infusion. EV were quantified in fresh whole blood using BD Trucount™ tubes, phalloidin, lipophilic cationic dye, and antibodies to CD31, CD45, CD41a, and CD146. EV subsets from leukocytes (LK), endothelial cells (EC), platelets, and CD146+ activated EC/LK were analyzed by BD FACSLyric™. Mann-Whitney tests, logistic regression models (LRM), and ROC curves were applied; analyses used STATA 15 and SPSS 25.

Results. Twenty-one patients received axi-cel, 6 tisa-cel, and 3 brexu-cel. CRS occurred in 26 patients (grade 1: n=21; grade 2: n=5), while NT developed in 9 (grade 1: n=7; grade 2: n=2). Patients who developed CRS showed higher baseline CD146+ LK EV, with strong predictive value (AUROC 0.911). Eleven patients developed prolonged cytopenia and had increased pre-Lym total EV, CD146+ EV, and LK EV levels. Elevated pre-Lym CD146+ LK EV and their proportion over total LK EV were associated with CRS (p=0.010 and p=0.033), with a trend confirmed by LRM (OR 1.104; p=0.064). Pre-Lym EC EV and CD146+ LK EV were also higher in NT (p=0.049 and p=0.04), although not confirmed in LRM. Between infusion and NT onset (median 7 days), CD146+ EC EV significantly increased (p=0.003; OR 1.012; p=0.044).

Conclusions. Circulating EV show potential as CAR T-cell therapy biomarkers. While baseline CD146+ LK EVs are closely tied to CRS risk, elevated CD146+ EVs also correlate with lasting cytopenia. Additionally, dynamic increases in CD146+ EC EVs may signal endothelial roles in NT. Larger prospective trials are required to better characterize EV immunophenotypes and their connection to inflammatory and endothelial processes.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

SUBSEQUENT THERAPIES AND TIME TO SECOND PROGRESSION-FREE SURVIVAL EVENTS IN CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA PREVIOUSLY TREATED WITH ZANUBRUTINIB OR BENDAMUSTINE-RITUXIMAB

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Background. Cohort 1 of the phase 3 SEQUOIA trial compared zanubrutinib with bendamustine-rituximab (BR) in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) without del(17p). Zanubrutinib has demonstrated superior progression-free survival (PFS) and time to next treatment (TTNT). However, there are limited data on outcomes following subsequent therapies after progression on zanubrutinib.

Methods. Patients were randomized to continuous zanubrutinib or six cycles of BR. Those receiving BR could crossover to zanubrutinib after progressive disease (PD). Patients were followed post-PD for subsequent anti-CLL treatments. Endpoints included PFS, TTNT, TTNT or death (TTNT-D) and PFS2.

Results. A total of 479 patients were randomized (zanubrutinib, n=241; BR, n=238). With a median follow-up of 78.7 months, zanubrutinib sustained a PFS benefit compared to BR (HR, 0.28; 95% CI, 0.21-0.38; P<.0001), with 78-month PFS rates of 70.9% (95% CI, 64.2-76.6) vs 28.6% (21.7-35.8). After adjustment for COVID, PFS estimates were 73.7% (67.0, 79.3) for zanubrutinib and 29.0% (22.1, 36.3) for BR. TTNT and TTNT-D favored zanubrutinib (HR, 0.23 [95% CI, 0.15- 0.35; P<.0001; 0.37 [0.27-0.50; P<.0001]). Most zanubrutinib-treated patients (87.6%) had not received subsequent therapy. PD requiring next-line treatment occurred in 10.0% of zanubrutinib and 34.5% of BR patients. Among zanubrutinib patients receiving subsequent therapy, 54.2% received BCL2i-based regimens, 33.3% received chemoimmunotherapy, and 12.5% received BTKi. Of the BR patients receiving subsequent therapy, 93.9% received BTKi (including 71 crossover patients). Median time from PD to next therapy was 2.1 months with zanubrutinib and 7.4 months for BR. Zanubrutinib patients who had PD and received subsequent BCL2i-based therapy had a median follow-up of 33.5 months from initiation of nextline therapy. Among these patients, 10 remain alive and without PD, two had died, and one had PD. PFS2 favored zanubrutinib over BR (HR, 0.66; 95% CI, 0.45-0.98; P<.05) with 78-month PFS2 estimates of 81.3% (95% CI, 75.6-85.8) vs 73.8% (67.2-79.3), respectively (Figure).

Conclusions. Zanubrutinib demonstrated durable benefit with superior PFS2 despite extensive use of effective subsequent therapies in the BR arm. Importantly, BCL2i-based salvage after zanubrutinib achieved favorable outcomes, supporting zanubrutinib as an effective frontline option that preserves sensitivity to later therapy.

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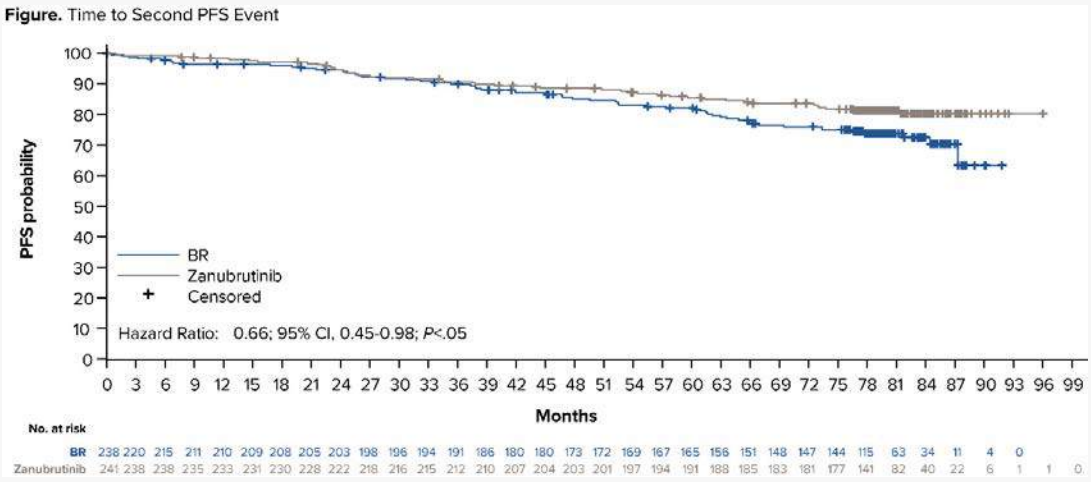
Figure. Time to Second PFS Event
PFS probability
100
90
80
70
60
50
40
30
20
10
0
BR
Zanubrutinib
Censored
Hazard Ratio: 0.66; 95% CI, 0.45-0.98; P<.05
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69 72 75 78 81 84 87 90 93 96 99
Months
No. at risk
BR 238 220 215 211 210 209 208 205 203 198 196 194 191 186 180 180 173 172 169 167 165 156 151 148 147 144 115 63 34 11 4 0
Zanubrutinib 241 238 238 235 233 231 230 228 222 218 216 215 212 210 207 204 203 201 197 194 191 188 185 183 181 177 141 82 40 22 6 1 1 0

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD FIRST-LINE FIXED-DURATION IBRUTINIB+VENETOCLAX TREATMENT IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: ANALYSIS FROM THE PROSPECTIVE REALITY-WW STUDY

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Background. Fixed duration (FD) ibrutinib plus venetoclax (Ibr+Ven) has demonstrated noninferiority to continuous Ibr with similar 3 year progression free survival and overall survival (OS) in previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), with a favorable safety profile. FD Ibr+Ven also achieves OS comparable to an age matched general European population. Prospective pooled analyses from the REALITY WW and REALITY 2 studies showed FD Ibr+Ven to be effective and manageable in routine clinical practice. We report an interim analysis of REALITY WW with full patient enrollment.

Methods. Patients aged ≥18 years with CLL/SLL per iwCLL 2018 criteria were enrolled across 63 sites in Europe, the Middle East, and Latin America. Patients received a 3 cycle Ibr lead in (420 mg once daily), followed by 12 cycles of FD Ibr+Ven, with venetoclax ramp up from 20 to 400 mg over 5 weeks. Data were collected approximately every 12 weeks during routine follow up. The primary endpoint was best overall response rate (ORR) by the end of 15 treatment cycles. Secondary endpoints included safety and patient reported outcomes.

Results. As of December 2025 data cutoff, 200 patients received FD Ibr+Ven, with a median time on study of 7.1 months. Median age was 65.5 years (range, 39–87); 53.5% and 16.0% were aged ≥65 and ≥75 years, respectively. Overall, 65.5% were male and 11.3% had a CIRS score >6. Unmutated IGHV was present in 42.7% of the population, while TP53 mutations and del(17p) were reported in 3.8% and 13.0%, respectively. Median treatment exposure was 6.8 months, with 185 patients remaining on therapy. Among 135 patients with ≥1 post baseline assessment, ORR by the end of 15 cycles was 91.1% (95% CI, 86.3–95.9), increasing from 80.0% after the 3 cycle Ibr lead in and stabilizing from cycle 9 onward. Complete responses were observed in 34.8% of patients. 12 patients discontinued therapy, 5 due to adverse events. Treatment emergent adverse events occurred in 60.0% of patients and grade 3/4 events in 11.5%. Any grade atrial fibrillation (AF) occurred in 3.5%. No cases of clinical or laboratory tumor lysis syndrome (TLS) were reported.

Conclusions. This interim REALITY WW analysis shows FD Ibr+Ven to be effective and well tolerated in real world clinical practice, with low AF incidence and no TLS, including in elderly and high-risk patients. Sub-analysis of Italian patients' cohort will be presented.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

A MULTIPARAMETRIC SCORE TO DISTINGUISH ACCELERATED CHRONIC LYMPHOCYTIC LEUKEMIA FROM RICHTER'S TRANSFORMATION AN ITALIAN MULTICENTRIC RETROSPECTIVE EXPERIENCE

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Background. Accelerated Chronic Lymphocytic Leukemia (aCLL) and Richter Syndrome (RS) represent distinct aggressive evolutions of CLL. The Giné criteria define aCLL as CLL with expanded proliferation centers, a mitosis count > 2.4, or Ki-67 expression > 40% per proliferation center but lacking the morphologic features of Diffuse Large B-Cell Lymphoma (DLBCL). Distinguishing these entities is crucial, as aCLL may respond to standard CLL therapies, to which RS is typically refractory.

Aims. The aim of our study was to develop a multiparameter score to facilitate the diagnosis of transformed CLL, enabling a more rapid distinction between aCLL and RS. Furthermore, this tool could aid centers lacking specialized pathology, as it is based on routine clinical and laboratory parameters.

Methods. We enrolled 158 patients with transformed CLL (72 aCLL, 86 DLBCL-RS) who underwent histopathological review, recruited from 9 different Italian centers between 2000 and 2025. We retrospectively collected clinical and laboratory data (stage, nodal and extranodal involvement, B symptoms, LDH levels, cytogenetic aberrations, molecular mutations, IGHV status), immunohistochemical parameters (Ki-67, CD5, CD23, PD-1, EBER, p53, cyclin D1, LEF1), and PET/CT metabolic data (SUVmax). Univariate analysis identified predictive factors; variables with $p < 0.05$ were included in a multivariate logistic regression model.

Results. In univariate analysis, the following parameters were significant: Ki-67 > 60%, CD5, and CD23 (all $p < 0.001$), p53 ($p=0.035$), LDH > 2 × the upper limit of normal ($p=0.001$), B symptoms ($p=0.015$), extranodal involvement ($p=0.006$), SUVmax > 9 ($p<0.001$), and at least one prior line of therapy ($p=0.016$). Based on multivariate analysis, we developed a composite scoring system including 3 covariates: Ki-67 (or SUVmax), CD23, and LDH; missing data were handled as a separate category. The model assigned 6 points for Ki-67 > 60% (or SUVmax > 9 if Ki-67 was NA), 3 for LDH > 2 × ULN, 2 for CD23 negativity, and −1 for CD23 positivity. Results in table 1.

Conclusions. Accelerated CLL is an underdiagnosed entity requiring expert histopathological evaluation. A multiparametric clinic-biological score may assist clinical differentiation from RS, integrating PET/CT metabolic and histopathological parameters. Although the model showed high diagnostic accuracy [AUC 0.92 (95% CI: 0.87–0.96)], prospective validation is warranted, and histopathological confirmation remains essential.

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SCORE	Potential diagnosis of RS	Potential diagnosis of aCLL
-1	4/41 (9.8%)	37/41 (90.2%)
0	2/11 (18.2%)	9/11 (81.8%)
1	0/0	0/0
2	4/17 (23.5%)	13/17 (76.5%)
3	3/7 (42.9%)	4/7 (57.1%)
4	0/0	0/0
5	14/19 (73.7%)	5/19 (26.3%)
6	19/21 (90.5%)	2/21 (9.5%)
7	0/0	0/0
8	22/23 (95.7%)	1/23 (4.3%)
>= 9	18/18 (100%)	0/18 (0%)

Table 1: Score results to support the differential diagnosis between aCLL and RS.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD TIME TO DISCONTINUATION AND SAFETY OF ACALABRUTINIB IN HIGH-RISK TREATMENT-NAÏVE CLL PATIENTS: INTERIM ANALYSIS FROM THE ARISE STUDY

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While controlled trials have established long-term efficacy and safety of acalabrutinib (acala), real-world evidence remains essential to better characterize its use in routine clinical practice, especially in those patients with an unfavorable risk profile (del17p/ TP53 mutation, unmutated IGHV).ARISE (NCT06205498) is an observational, longitudinal, secondary-data study based on a retrospective cohort of CLL patients who initiated first-line therapy with acala monotherapy between May 1, 2021, and April 30, 2022.The primary endpoint of this study was the Time to Treatment Discontinuation (TTD). Secondary endpoints include reasons leading to TD, type and rates of adverse events (AEs) and survival outcomes.By March 31, 2024, 151 treatment naive eligible patients, across 42 Italian sites were enrolled in this study. Among them, 55 patients (36.4%) with high-risk features received acala as first-line (1L) treatment. In this subpopulation enriched for high-risk feature, del17p was present in 10.9% (n=6) patients, TP53 in 9.1% (n=5), and unmutated IGHV in 90.9% (n=50). The median age of patients (± SD) was 72.0 (± 10.89) years; 65.5% of patients were ≥65 years and 58.2% (n = 32) were male.The median time from diagnosis to acala initiation was 30 months. ECOG PS at baseline was 0 or 1 in 74.5% of patients (n=41). The most relevant baseline cardiovascular comorbidities were hypertension (60.0%,n=33), cardiac rhythm disorders (7.3%,n=4), atrial fibrillation (5.5%, n=3) and congestive heart failure (1.8%,n=1).With a median follow-up of 28 months, only 3 (5.45%) patients discontinued acala with treatment discontinuation rate at 24 months of 94.5% (95% CI: 84.0%–98.2%). Median TTD was not reached.Of the 3 patients who permanently discontinued acala, 2 (3.6%) due to physician's decision and only 1 (1.8%) due to an adverse event, namely myocardial infarction. No discontinuations due to disease progression, patient's decision or death were reported.AE-related discontinuation with acalabrutinib was infrequent aligning with other real-world reports and confirming the optimal safety profile of continuous first-line treatment with acala also in CLL patients characterized by a high-risk genetic profile. Low discontinuation rate is crucial in this high-risk setting, potentially allowing for better adherence and represents a differentiating feature of acala compared with other BTK inhibitors, reinforcing its role as an effective real-world therapeutic option for high-risk CLL.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD EXPERIENCE OF FRONTLINE TREATMENT WITH IBRUTINIB AND VENETOCLAX FOR PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA IN THE CAMPANIA REGION

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Introduction. Fixed-duration frontline treatment with ibrutinib and venetoclax (I+V) has improved outcomes in patients (pts) with chronic lymphocytic leukemia (CLL) compared to chemoimmunotherapy, both in terms of efficacy and safety. Considering the encouraging trial results, our real-world study aimed to evaluate the real-world efficacy and safety of I+V in CLL pts treated in the Campania region.

Methods. This multicenter retrospective study was conducted by the "CLL Campania Group". We retrospectively analyzed data of 105 pts with CLL treated with the I+V regimen outside clinical trials between January 2024 and March 2026 in 12 hematological centers in the Campania region. Treatment was started for all pts according to current guidelines and therapy was administered following registered dose and schedule. For each patient, data were collected from the medical records of each center to assess clinical and laboratory characteristics. Dose reductions and treatment discontinuations due to adverse events were evaluated at any time.

Results. The median age at treatment initiation was 64 years (range, 36-83); the median follow-up was 10 months (range, 1-23). The pts' characteristics are shown in Figure 1. Of 105 pts enrolled, 77 were evaluable for response. Overall, the ORR was 100% (66.2% complete responses). We observed 4 early relapses, during treatment or within one year from the treatment completion (Figure 1). Concerning safety, 51.4% of pts experienced at least one adverse event (AE), the most frequent being neutropenia in 23.8% (7.6% G3-4), cardiovascular AEs in 13.3% (9.5% hypertension, 1.9% arrhythmias), infections in 7.6%, and bleedings in 6.7% of pts. Most pts (59%) received the standard IV regimen without a change in the dose of either ibrutinib or venetoclax. Ibrutinib was reduced in 18.1% (n=19) and suspended in 20% (n=21) of pts, in 7.6% (n=8) for more than 30 days. Venetoclax was reduced in 15.2% (n=16) and suspended in 13.3% (n=14) of pts, in 8.6% (n=9) for more than 30 days. Two deaths were observed, one due to disease progression and the other due to infection.

Conclusions. Despite its limitations, our real-world study of the Campania region experience with frontline I+V showed excellent ORR and low relapse rate. Overall, the treatment was well tolerated, and dose reductions or suspensions did not affect the efficacy of the therapy. A larger cohort and longer follow-up are needed to assess the long-term efficacy and safety.

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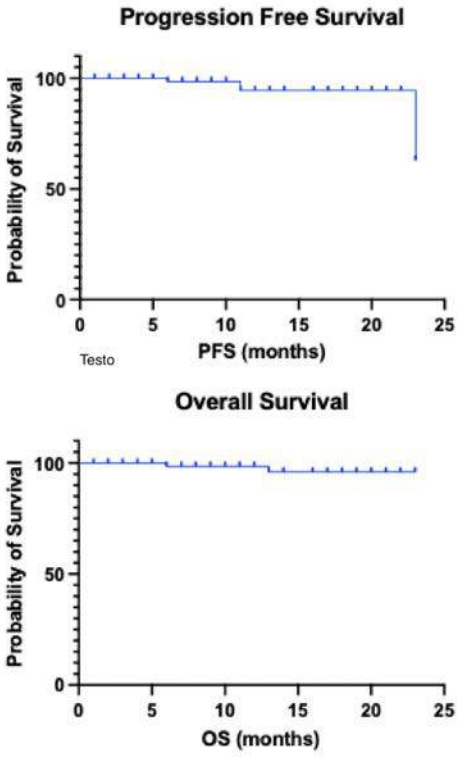
Figure 1. Patients' characteristics, progression free survival and overall survival.

Patient's characteristics	CLL patients (n=105)
Sex at birth	
Female	34.3% (36/105)
Male	65.7% (69/105)
Age at treatment start (median, range)	64 (36-83)
Comorbidities of interest	
Dyslipidemia	6.7% (7/105)
Diabetes	7.6% (5/105)
Arterial hypertension	41.9% (44/105)
Ischemic cardiac disease	1.9% (2/105)
Rai Stage at treatment	
I	0% (0/105)
II	21.9% (23/105)
III	42.9% (45/105)
IV	35.2% (37/105)
Binet stage at treatment	
A	15.2% (16/105)
B	51.5% (54/105)
C	33.3% (35/105)
IGHV mutational status	
Mutated	33.3% (35/105)
Unmutated	66.7% (70/105)
TP53/del17p alterations	7.0% (7/100)
Del13q	15.0% (15/100)
Del11q	4.0% (4/100)
Tris12	3.0% (3/100)
Treatment criteria	
Progressive lymphoadenopathies	47.6% (50/105)
Symptomatic splenomegaly	53.3% (56/105)
Cytopenias	45.7% (48/105)
B symptoms	5.7% (6/105)
Bulky lymphoadenopathy	13.3% (14/105)
Hypogammaglobulinemia	18.1% (19/105)



Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

SINGLE-CELL TRANSCRIPTOMIC ANALYSIS IDENTIFIES SUBSET-SPECIFIC T-CELL ALTERATIONS AND B-CELL REMODELING IN IMMUNE THROMBOCYTOPENIA

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Immune thrombocytopenia (ITP) is characterized by immune dysregulation, but the transcriptional alterations across immune cell subsets and their association with treatment response remain incompletely understood. To define disease mechanisms through single-cell multi-omics profiling of B- and T-cell compartments in ITP, integrating single-cell RNA sequencing with B-cell receptor (BCR) and T-cell receptor (TCR) analysis. T and B cells were isolated from peripheral blood of 10 ITP patients and 5 healthy donors (HD) by negative selection. Single-cell RNA sequencing was performed using the 10x Genomics platform, with sequencing on Illumina NovaSeq 6000. After quality control and integration, immune subsets were identified by unsupervised clustering, and differential gene expression (DGE) was analyzed within individual populations. A total of 135,971 cells were analyzed, identifying 16 T-cell and 11 B-cell clusters. Major T--cell subset distribution was broadly comparable between ITP and HD, but DGE analysis revealed heterogeneous, subset-specific transcriptional alterations without a universal disease signature. Treatment-sensitive patients showed transcriptional changes mainly in selected $CD8^+$ effector/memory and double-negative T-cell populations, involving PRF1 and TCR-related transcripts, with exhausted subsets co-expressing GNLY and TIGIT. In contrast, treatment-resistant patients demonstrated broader transcriptional perturbations across multiple T-cell populations, including $CD8^+$, γδ, double-negative, and innate-like subsets, with GZMK, PRF1, TRBV transcripts, and NF-kB pathway activation. B-cell analysis revealed significant reduction of memory B cells in ITP, with additional quantitative shifts across subsets. Transcriptionally, B cells displayed subset-specific activation signatures, including immunoglobulin variable region genes, CD69 in memory compartments, FCRL5 in activated naïve cells, and enrichment of cytokine signaling pathways. Notably, SYK was significantly upregulated in IgM^+ activated B cells, suggesting enhanced B-cell receptor signaling. ITP exhibits heterogeneous, subset-specific immune dysregulation involving both T- and B-cell compartments. Treatment resistance is associated with broader T-cell transcriptional remodeling, while B-cell alterations include memory depletion and enhanced BCR signaling. These findings support a distributed, multi-lineage immune pathology in ITP and identify potential mechanisms underlying therapeutic response variability.

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PREEMPTIVE RITUXIMAB IN ADAMTS13 RELAPSE DURING CLINICAL REMISSION OF IMMUNE THROMBOTIC THROMBOCYTOPENIC PURPURA: A MULTICENTER ITALIAN STUDY

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Background. Immune thrombotic thrombocytopenic purpura (iTTP) is a rare hematologic disorder caused by immune--mediated ADAMTS13 deficiency. ADAMTS13 activity monitoring during remission enables early detection of biochemical relapse (ADAMTS13 activity <20% without hemolysis, anemia or thrombocytopenia). In this setting, preemptive rituximab (RTX) is recommended, but real world data are limited.

Methods. We performed an observational study across 9 Italian hematology centers including iTTP patients (pts) treated with RTX for biochemical relapse. ADAMTS13 response was defined as activity ≥20% in 2 consecutive evaluations; ADAMTS13 complete response (CR) as ≥ lower limit of normal, corresponding to ≥60% in our lab (Cuker A et al.Blood 2021). Predictors of biochemical relapse included prior RTX or caplacizumab use, prior clinical relapse, RTX dose and 12-months ADAMTS13 kinetics.

Results. Forty-nine pts were included; 22 had prior RTX and 24 caplacizumab. At biochemical relapse, median age was 48.8 years; median ADAMTS13 activity and inhibitor were 3% (IQR 0.5–7.1) and 1.8 BU/mL (IQR 0.9–5.4). RTX was used standard dose (375 mg/m² weekly x4 or x6) in 46pts (93.9%); 3pts received a lower flat dose (200 mg x4).-Median follow up was 33.6 months (mos); 5 infections occurred.Forty-six pts (93.9%) achieved ADAMTS13 response, including 36 (73.5%) CR. Median ADAMTS13 activity increased over time, from 50% at RTX end to 78% at 12mos (Figure). Median time to best response was 5.0mos.Twenty responders (43.5%) experienced a second biochemical relapse (n.18, 90% after ≥1 yr from RTX, median 34.8mos). Prior RTX exposure (OR 3.67, p=0.047) and clinical relapses (OR 4.2, p=0.002) were associated with higher relapse risk. RTX retreatment was given in 19pts, with 18 responders. One clinical relapse occurred in a non responder.Overall, 21pts experienced a biochemical/clinical relapse or failed to achieve response ≥1 yr from RTX. Failure to achieve a complete ADAMTS13 response within 1 yr was associated with a significantly higher risk of non-response or subsequent clinical or biochemical relapse (p=0.001).

Conclusions. Preemptive RTX is effective in iTTP pts with biochemical relapse, with no clinical relapses observed in responders. Pts with a refractory/relapsing disease are at higher relapse risk after preemptive RTX. Early ADAMTS13 activity dynamics identify pts who may benefit from intensified preemptive therapy, reinforcing the value of systematic ADAMTS13 monitoring.

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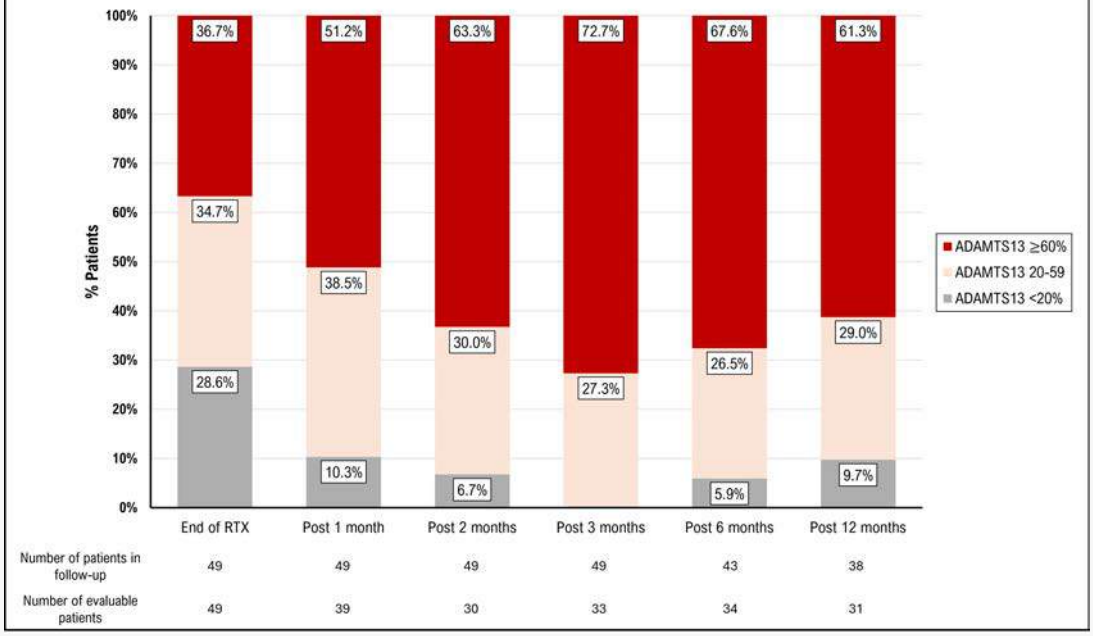
Figure: Longitudinal distribution of ADAMTS13 activity after preemptive rituximab



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PREVALENCE OF CODING-REGION VARIANTS IN THE PROC GENE IN A SINGLE-CENTER COHORT OF PC-DEFICIENT SUBJECTS

F. Ramundo, T. Malara, M. Rossi, T. Za, Am. Ciminello, S. Betti, F. Bartolomei, F. Di Landro, P. Arcuri, P. Chiusolo, V. De Stefano, E. Rossi

Catholic University, Fondazione Policlinico AGemelli IRCCS

Background. Protein C (PC) deficiency is a rare inherited thrombophilia that increases the risk of venous thromboembolism (VTE). This study investigated the prevalence of PROC germline variants in patients with PC deficiency.
Methods. Forty patients (M/F 18/22) with persistently low PC levels and no known acquired causes of deficiency were included. PROC gene analysis was performed on peripheral blood DNA using next-generation sequencing (NGS) to identify coding region germline variants.
Results. Thromboembolic events occurred in 15 patients (38%), including 13 venous and 2 arterial cases. Four patients (10%) experienced recurrent episodes. The median age at first event was 28 years (range 17-68). A family history of both PC deficiency and VTE was present in 27.5% of patients; 20% had a family history of VTE alone, and 20% had a family history of PC deficiency without VTE.The median PC activity in the cohort was 58% (range 38-68%) and did not differ significantly between patients with and without thrombosis (48.5% vs 60%, p = 0.0783).NGS analysis identified germline PROC variants in 18 patients (45%), including 8 (20%) with previous VTE and 10 (25%) with a family history of VTE. Missense variants were most common (n=14, 77.8%), including Arg32Cys (n=5, three unrelated families), Gly239Glu (n=3, two families), and Ser382Phe, Val317Phe, Cys160Phe, Leu55Pro, and Asn144Ser (each n=1). One patient had a stop-gained variant (Trp157Ter), and three siblings had a frameshift variant (Val248GlyfsTer2) (Figure).PC activity differed significantly by genotype (p = 0.0003), with higher median values in patients without variants (62.5%, range 49-68%) compared to those with missense variants (47%, range 38-65%), frameshift variants (47%, range 41-48%), or stop-gained variants (44%).Five of 22 patients without variants developed VTE. The VTE rate did not differ significantly between patients with and without variants (22.7% vs 20%, p = 0.14).
Conclusions. Approximately 45% of patients carried PROC variants, mainly missense. Patients with variants had lower median PC levels than those without, but mutation type did not affect deficiency severity. Notably, patients without detected variants had a VTE rate similar to those with variants, suggesting the presence of non-coding mutations or copy number variations affecting PROC expression.

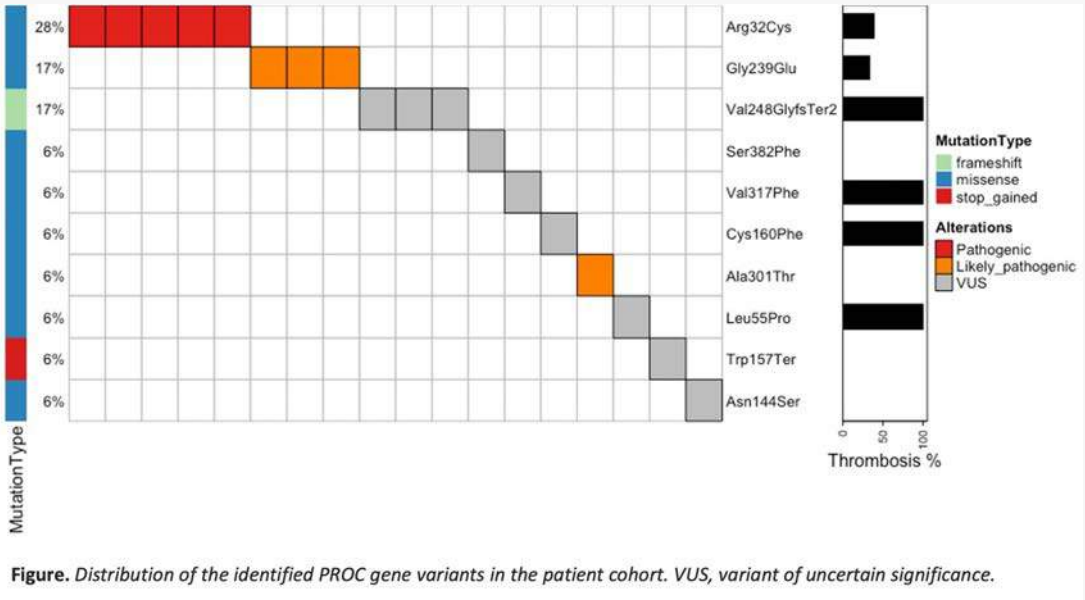

Figure. *Distribution of the identified PROC gene variants in the patient cohort. VUS, variant of uncertain significance.*

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

PROTEIN S HEERLEN AND OTHER PROS1 GENE VARIANTS IN PROTEIN S-DEFICIENT PATIENTS: A SINGLE-CENTER STUDY

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Catholic University, Fondazione Policlinico AGemelli IRCCS

Background. Diagnosing protein S (PS) deficiency is challenging due to varied functional defects and diagnostic assays, highlighting the importance of characterization of the PROS1 gene. The clinical significance of the Heerlen (Ser501Pro) variant remains unclear. This study aimed to determine the frequency of coding-region variants in individuals with PS deficiency.

Methods. We analyzed 55 subjects (M/F 21/34) with persistently reduced free PS levels (<65%) and no identifiable causes of acquired deficiency. Free PS was measured using immunological methods. Genetic analysis of peripheral blood DNA was conducted with next-generation sequencing to detect germline PROS1 variants.

Results. The mean free PS level was 41.6% (range 7–65%). Thrombotic events occurred in 38.2% of subjects (venous n=17; arterial n=4). The median age at first event was 49 years (range 17–88), with recurrence in 9.1%. Family history revealed both PS deficiency and venous thromboembolism (VTE) in 21.8% of patients, VTE alone in 18.1%, and asymptomatic PS deficiency in 21.8%. Free PS levels did not differ between patients with and without VTE (41.1% vs 42.4%, p = 0.7469).No mutations were found in 27 patients (49.1%, group A), of whom 40.7% had VTE and 29.6% had a family history of VTE. Thirteen patients (23.6%, group B) carried the Heerlen variant; 7.6% had VTE and 30.7% had a family history of VTE. Fifteen patients (27.3%, group C) carried other PROS1 variants; 33.3% had VTE and 60% had a family history of VTE. Those variants included Arg330Trp (n=3, two families), Gly357Arg (n=2, unrelated), and single cases (3.6% each) of Ala525Val, Pro667Leu, Glu360Lys, Ala557Val, Ile591Met, Arg316His, Glu437Lys, Tyr332Ter, Gln563Ter, and Ile546MetfsTer16.Median free PS levels were 48% in groups A (range 7-64%) and B (range 25-65%), and 35% (range in group C (10-53%) (group C vs A or B, p < 0.001) (Figure). Patients with truncating variants (frameshift and nonsense mutations) (n=3) had lower free PS levels (median 12%, range 10–16), indicating a severe loss-of-function effect.

Conclusions. PS-deficient subjects without coding-sequence variants or with the Heerlen variant had significantly higher free PS levels than carriers of other PROS1 variants. Additionally, carriers of Heerlen variant had a low rate of VTE. Amino acid substitutions were identified in about half of patients with free PS deficiency, suggesting that other defects may involve non-coding mutations or copy number variations affecting PROS1 expression.

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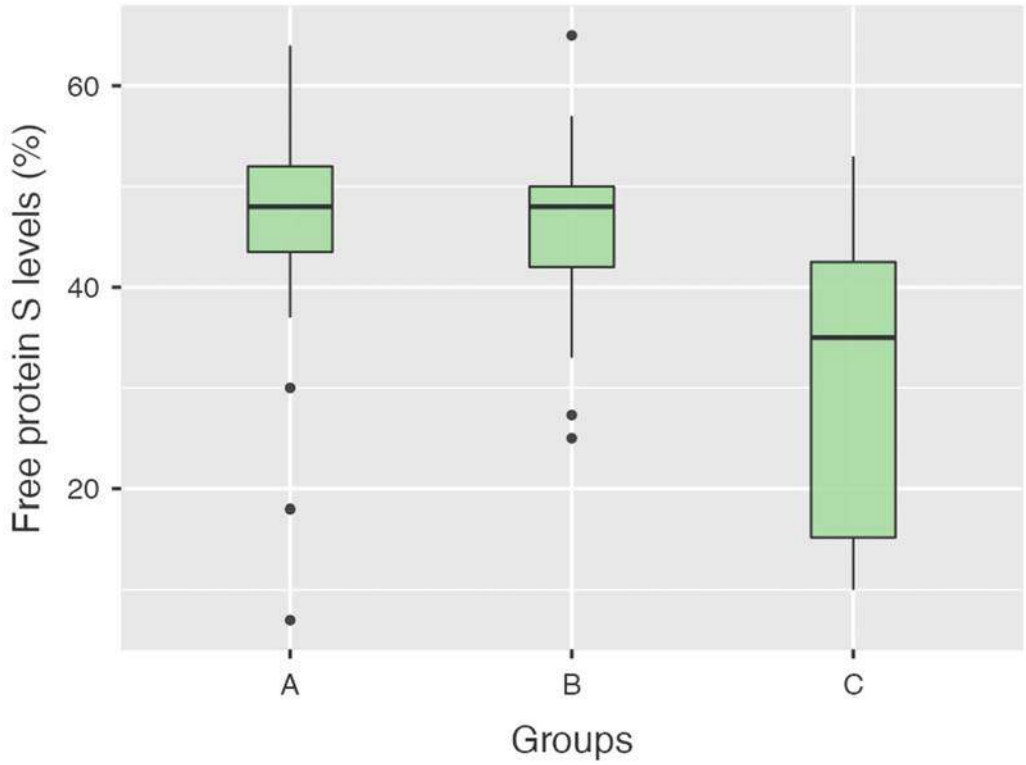

Figure. Free PS levels among patients without PROS gene variants (group A), with PS Heerlen (group B) and with other PS variants (group C).

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

PERIOPERATIVE MANAGEMENT OF MILD-TO-MODERATE HEMOPHILIA: A COMPARATIVE STUDY OF EXTENDED HALF-LIFE *VERSUS* STANDARD HALF-LIFE CONCENTRATES ON CLINICAL OUTCOMES AND FACTOR CONSUMPTION

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Background and Aims. In recent years, extended half-life concentrates (EHLs) have emerged as an effective alternative to standard half-life concentrates (SHLs) in hemophilia, offering improved pharmacokinetics and reduced infusion frequency. These features make EHLs ideal for perioperative management. While their surgical efficacy and safety are confirmed in severe hemophilia, evidence remains scarce for mild-to-moderate cases. This study aimed to confirm the perioperative safety and hemostatic efficacy of EHLs and to evaluate the reduction in factor consumption and infusion frequency compared to SHLs in patients with mild-to-moderate hemophilia A or B.

Methods. We retrospectively analyzed 191 patients, collecting data from 26 EHL-managed surgeries in 22 patients (20 mild, 2 moderate) between 2018 and 2026. These included 14 major (54%) and 12 minor (46%) procedures. Two patients underwent the same surgery with both SHLs and EHLs, allowing an intra-patient comparison. Data were compared with published literature, though direct comparison for major surgery was limited by data scarcity. Preoperative PK studies guided 15 procedures (58%), maintaining mean trough levels of 55% (24h) and 31% (72h). In two major surgeries, the urgent nature precluded PK analysis.

Results. In both comparisons we observed a reduction in the number of infusions (Table 1a) and total factor consumption (Table 1a, Table 1b).All 26 surgeries were managed with a single preoperative infusion. Postoperative infusions were administered once daily, whereas the literature reports twice-daily infusions when using SHLs. The sole exception in our cohort was a patient with mild HA undergoing cardiac surgery, who required more frequent infusions within the first 24 hours post-surgery before early transition to a single daily infusion.No patients developed inhibitors; a single bleeding event was due to poor hemostasis.

Conclusions. EHLs appear safe and effective for surgery in mild-to-moderate hemophilia, offering clinical advantages over SHLs across all analyzed populations, particularly in HB. While not statistically significant due to the limited cohort, these findings demonstrate a clinical advantage, despite the absence of baseline factor levels for literature-based cases. For HA, further improvements are expected with the advent of newer molecules.

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	Patient 1	Patient 2
Type of hemophilia	HB mild	HB moderate
% of basal factor	11%	2%
Type of surgery	Major	Major
N° of infusions with SHLs	5	15
Total factor consumption with SHLs	200 IU/Kg	925 IU/Kg
N° of infusions with EHLs	2	10
Total factor consumption with EHLs	67 IU/Kg	650 IU/Kg

1a

Type of surgery	Source	Patient	Peri-operative consumption	Bleeding treatment
Colonoscopies with biopsies	Literature with SHLs	Patient 1 - HA mild	142 IU/Kg	293 IU/Kg
		Patient 2 - HA mild	115 IU/Kg	
		Patient 3 - HB mild	283 IU/Kg	
		Patient 4 - HA mild	77 IU/Kg	
		Patient 5 - HA moderate	149 IU/Kg	32 IU/Kg
		Patient 6 - HA moderate	49 IU/Kg	393 IU/Kg
		Patient 7 - HB mild	270 IU/Kg	360 IU/Kg
	Local experience with EHLs	Patient 1 - HB mild	41 IU/Kg	
		Patient 2 - HA mild	45 IU/Kg	
		Patient 3 - HA mild	100 IU/Kg	
		Patient 4 - HA mild	66 IU/Kg	67 IU/Kg + 134 IU/Kg of SHLs + 2 blood transfusions
		Patient 5 - HA mild	34 IU/Kg	
Dental implant placement	Literature with SHLs	Patient 1 - HA moderate	100 IU/Kg + tranexamic acid	
	Local experience with EHLs	Patient 2 - HA mild	36 IU/Kg	

1b

Table 1: intra-patient comparison (1a) and literature comparison (1b).

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

THROMBOTIC RISK IS NOT UNIFORM ACROSS APHERESIS SETTINGS: INSIGHTS FROM CAR-T LYMPHOCYTAPHERESIS AND AUTOLOGOUS STEM CELL COLLECTION

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Background. Pericatheter thrombosis (PCT) is a recognised complication of large-bore venous catheters used for cell collection. An incidence of approximately 1.8% has been reported for Mahurkar catheters in peripheral blood stem cell collection. Data in patients undergoing lymphocytapheresis for CAR-T therapy are limited. This study evaluates PCT in this setting and compares thrombotic events with those observed in autologous stem cell collection.

Methods. A retrospective single-centre analysis included 62 patients undergoing CAR-T lymphocytapheresis with a Mahurkar catheter (September 2019–October 2025). During the same period, 127 patients underwent autologous stem cell collection; 62 required a Mahurkar catheter, and a subset of 21 with comparable diseases was analysed.Within the CAR-T cohort, analyses compared (1) PCT vs no PCT and (2) any thrombosis vs none. A third analysis compared CAR-T and autologous cohorts. Continuous variables were analysed with Student's t-test and categorical variables with chi-square or Fisher's exact test.

Results. In the CAR-T cohort, PCT occurred in 5/62 patients (8%) and 13/62 (21%) developed overall thrombosis. No variable was significantly associated with PCT, although platelet count showed a borderline trend (p=0.061). Procedural difficulty was more frequent in PCT cases (66% vs 18%), without statistical significance.In the autologous cohort, no PCT was observed (0/21), while 2 patients (9.5%) developed thrombosis at non-catheter sites.Compared to the autologous cohort, CAR-T patients showed lower platelet count (p<0.0001), haemoglobin (p=0.0276), and differences in white blood cell count (p=0.045). Disease status also differed significantly, with all autologous patients in partial or complete response (p<0.001). No differences were observed for LDH, Khorana score, or anticoagulation.

Conclusions. PCT was more frequent in CAR-T lymphocytapheresis than in autologous stem cell collection. This difference appears to reflect underlying patient characteristics rather than procedural factors. CAR-T patients represent a distinct population with more advanced disease and altered haematological profiles.Thrombotic risk should not be considered uniform across apheresis settings, supporting tailored risk assessment and preventive strategies.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

TPO-RECEPTOR AGONISTS AS INDEPENDENT RISK FACTOR FOR VTE IN ITP PATIENTS WITH PERSISTENT APL POSITIVITY

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Background and Aims. The presence of antiphospholipid antibodies (aPL) and TPO-RAs exposure may enhance the thrombotic risk in ITP patients. The aim of this study is to evaluate predictors of thrombotic events in patients with ITP and persistent aPL positivity.

Methods. We conducted a retrospective study including 56 consecutive ITP patients with persistent aPL positivity. A high risk aPL positivity profile was defined as positivity for LA, high titre single positivity or double/triple-positivity (ACR/EULAR, 2023). Thrombotic events (TEs) free survival (t-EFS) was defined as the time from diagnosis to the occurrence of thrombosis or last follow-up. Statistical analyses included univariate and multivariate logistic regression to identify predictors of thrombosis, and Kaplan-Meier method for time-to-event analysis with censure for patients without events at the last follow-up. A p-value<0.05 was considered statistically significant.

Results. Median age at diagnosis was 37 years (range 10–81); 44 patients (78.6%) were female and 12 (21.4%) male. They all were persistently positive for aPL: 32 (57.1%) had single positivity, 16 (28.6%) double, and 8 (14.3%) triple. Forty-seven patients (83.9%) presented a high-risk aPL profile (26 received a prophylactic antiplatelet agent). Twenty patients (35.7%) had a concomitant autoimmune disease other than ITP, 32 (57.1%) cardiovascular comorbidities. Twenty-four patients (42.9%) received antirheumatic therapy (22 hydroxychloroquine, 1 cyclosporine, 1 azathioprine). Fifteen patients (26.8%) experienced 20 TEs: 12 venous (VTE) and 4 arterial (AT). Median platelet count at thrombosis was $72x10^9$/L (range 30–298). Eleven patients (19.6%) received TPO-RAs; among them, 6 (54.5%) developed VTE during TPO-RA (21.5 events per 100 patient-years). Kaplan–Meier analysis showed a significantly reduced t-EFS in patients treated with TPO-RAs compared with those not exposed (log-rank p=0.032). (Figure 1). In univariate logistic regression analysis, TPO-RA therapy was associated with an increased risk of TEs (OR 6.94; 95% CI 1.58–30.43; p=0.01), antiplatelet prophylaxis (OR 0.20; 95% CI 0.048–0.799; p=0.02) and female sex (OR 0.26; 95% CI: 0.07–0.99; p=0.048) resulted protective. In multivariate analysis, TPO-RA exposure remained an independent risk factor (aOR 6.98; 95% CI 1.36–35.78; p=0.02), antiplatelet therapy retained a protective effect (aOR 0.20; 95% CI 0.04–0.97; p=0.046); whereas female sex lost its significance (p=0.42). Other variables, including age, aGAPSS score, and aPL profile, were not significantly associated with TEs in univariate logistic regression models.

Conclusions. TPO-RA therapy appears to significantly increase the risk of VTE in ITP patients with persistent aPL positivity, whilst antiplatelet prophylaxis appears to reduce this risk.

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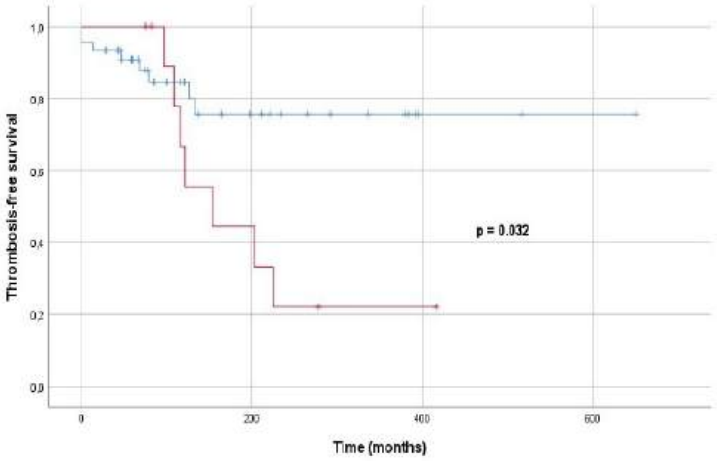

Time (months)	0	200	400	600
TPO-RAsexposed	11	3	1	0
TPO-RAsnaive	45	14	2	1

Figure 1. Kaplan–Meier curves showing time from diagnosis to first thrombotic event, stratified by TPO-RA exposure. Patients receiving TPO-RAs (red line) had a significantly higher risk of thrombosis compared with non-exposed patients (blue line) (p=0.032).

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

BALANCING BLEEDING AND THROMBOSIS: SAFETY OF LOW-MOLECULAR-WEIGHT HEPARIN THROMBOPROPHYLAXIS IN PATIENTS WITH HEMOPHILIA UNDERGOING MAJOR SURGERY

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[1]Regional Centre for Hemorrhagic and Thrombotic Diseases, AOU Città della Salute e della Scienza; [2]Division of Hematology, AOU Città della Salute e della Scienza, University of Turin; [3]Department of Molecular Biotechnology and Health Sciences, University of Turin; [4]Central Laboratory Baldi and Riberi, AOU Città della Salute e della Scienza, University of Turin

Background and Aims. In patients with hemophilia, the risk of venous thromboembolism (VTE) is traditionally considered low, but may become clinically relevant in the setting of major surgery, particularly orthopedic and oncologic procedures. Current evidence is limited and heterogeneous. International guidelines recommend an individualized assessment of thrombotic and bleeding risk, favoring mechanical over pharmacological thromboprophylaxis, which should be reserved for selected patients under adequate factor replacement and without inhibitors. In this context, we aimed to retrospectively evaluate the safety of pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) in patients with hemophilia undergoing major surgery.

Methods. Medical records of 105 patients with moderate/severe hemophilia A or B followed at our center were retrospectively reviewed. Among these, 12 patients undergoing 18 major surgical procedures received postoperative LMWH thromboprophylaxis. Data were verified through comparison with the rare diseases registry.

Results. All included patients had severe hemophilia A and received perioperative factor replacement therapy. Trough factor levels during the first three postoperative days were ≥14%, and ≥11% thereafter. Patient characteristics, type of surgery, and trough levels are reported in *Table 1*. A single bleeding event occurred in a patient undergoing intestinal reanastomosis for previous rectal adenocarcinoma, who presented on postoperative day 4 with hematemesis and rectal bleeding, requiring LMWH discontinuation and transfusion support. No other major or minor bleeding events were observed. One patient developed a clinically evident VTE on postoperative day 8 despite LMWH thromboprophylaxis, in the presence of multiple risk factors (high-risk inherited thrombophilia and smoking). No additional clinically evident thromboembolic events were observed.

Conclusions. In a setting of limited and conflicting evidence, all patients underwent individualized assessment of thrombotic and bleeding risk. They received adequate factor replacement therapy and were monitored through factor levels. In this context, LMWH thromboprophylaxis appeared safe in the vast majority of cases. These findings support the feasibility of a personalized approach to pharmacological thromboprophylaxis in patients with hemophilia undergoing major surgery, although prospective studies are warranted to confirm its safety.

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Pt	Age at surgery	Preoperative prophylaxis	Additional VTE risk factors	Surgery	VTE	Bleeding	Trough fVIII POD 1-3 (%)	Trough fVIII >POD3 (%)
1.1	60	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	Laparoscopic cholecystectomy + endoscopic bile duct clearance	NO	NO	44	80
1.2	63	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	TKA	YES	NO	59	88
2	65	Replacement	Obesity	THA	NO	NO	100	50
3	50	Replacement	History of PICC-related VTE	Infected TKA removal + debridement + knee arthrodesis with external fixation	NO	NO	55	16
4.1	66	Non replacement (Emicizumab)	Rectal adenocarcinoma + smoking	Thoracoscopic lung biopsy	NO	NO	45	NA
4.2	60	Replacement	Rectal adenocarcinoma + smoking	Rectal resection for adenocarcinoma with ileostomy	NO	NO	47	20
4.3	61	Replacement	Rectal adenocarcinoma + smoking	Surgical revision for anastomotic leak after rectal resection	NO	NO	24	17
4.4	61	Replacement	Rectal adenocarcinoma + smoking	Intestinal reanastomosis	NO	YES	35	21
5.1	54	Replacement	Klinefelter syndrome	TKA	NO	NO	49	95
5.2	50	Replacement	Klinefelter syndrome	TKA	NO	NO	106	50
6	36	Replacement	NO	TKA	NO	NO	152	160
7	62	Replacement	NO	TKA revision for periprosthetic fracture	NO	NO	58	40
8	41	Replacement	NO	TKA	NO	NO	63	11
9	67	Non replacement (Emicizumab)	NO	TKA	NO	NO	39	49
10.1	54	Replacement	NO	Patellar tendon repair	NO	NO	14	14
10.2	51	Replacement	NO	THA	NO	NO	84	104
11	28	Replacement	NO	Ischial tuberosity exostosis resection (osteoma)	NO	NO	60	45
12	67	Replacement	NO	THA	NO	NO	63	40

Abbreviations: Pt, patient; VTE, venous thromboembolism; POD: postoperative day; TKA, Total knee arthroplasty; THA, Total hip arthroplasty; NA, not available.

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

FOSTAMATINIB IN IMMUNE THROMBOCYTOPENIA SECONDARY TO LYMPHOPROLIFERATIVE DISORDERS: A MULTICENTER REAL-WORLD EXPERIENCE

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Secondary immune thrombocytopenia (sITP) is a rare autoimmune disease, representing up to 10% of ITP. sITP complicates the clinical course of chronic lymphoproliferative disorders (LPDs) in up to 5% of patients and is poorly responsive to conventional treatments. Fostamatinib, an orally bioavailable SYK inhibitor, is a consolidated treatment for refractory ITP, but to the best of our knowledge it has not been investigated in sITP related to LPDs. We collected real-world data from four Italian referral centers to evaluate the efficacy and safety of fostamatinib in this specific subset. Seven cases were retrospectively identified and included, with median age was 77 years (range 52–80), and six were male (86%). Underlying LPDs included lymphoplasmacytic lymphoma (n=3), marginal zone lymphoma (n=2), mantle cell lymphoma (n=1) and low-grade B-cell non-Hodgkin lymphoma (n=1). All cases had refractory sITP, they were not in need of active treatment for the underlying LPDs, and they all underwent bone marrow evaluation, showing a median bone marrow infiltration index of 24% (range 10–35%). Cases were heavily pretreated, with a median of 3 prior lines for sITP and 1 prior line for the LPDs. All included patients had received rituximab (100%), 71% had failed TPO receptor agonists, and two (29%) had splenectomy. Fostamatinib was administered as monotherapy (n=4) or in combination (n=3; romiplostim n=1, intravenous immunoglobulins IGEV n=2). Median platelet count at fostamatinib initiation was 25 $\times 10^9$/L, higher in combination (26 $\times 10^9$/L) than monotherapy (11 $\times 10^9$/L). Overall response rate (IWG criteria) was 86% (6/7), including 2 complete responses—one achieved with fostamatinib in combination with romiplostim and one with fostamatinib monotherapy; responses were durable (≥4 months) in 57% of cases (4/7). After a median follow-up of 33 months (range 8-49), median duration of response was 10 months (range 2–49) with 71% and 43% of patients remaining on treatment at 6 and 12 months, respectively. One non-responder patient unfortunately died of intracranial hemorrhage. Two cases discontinued fostamatinib because of lymphoma progression. Treatment was generally well tolerated, with one grade 3 diarrhea and one septic shock in the splenectomized patient; one case required rescue with IGEV. In our small real-world series, fostamatinib showed promising activity in patients with sITP to LPDs, with a manageable safety profile. Our preliminary findings will need to be confirmed in a prospective setting.

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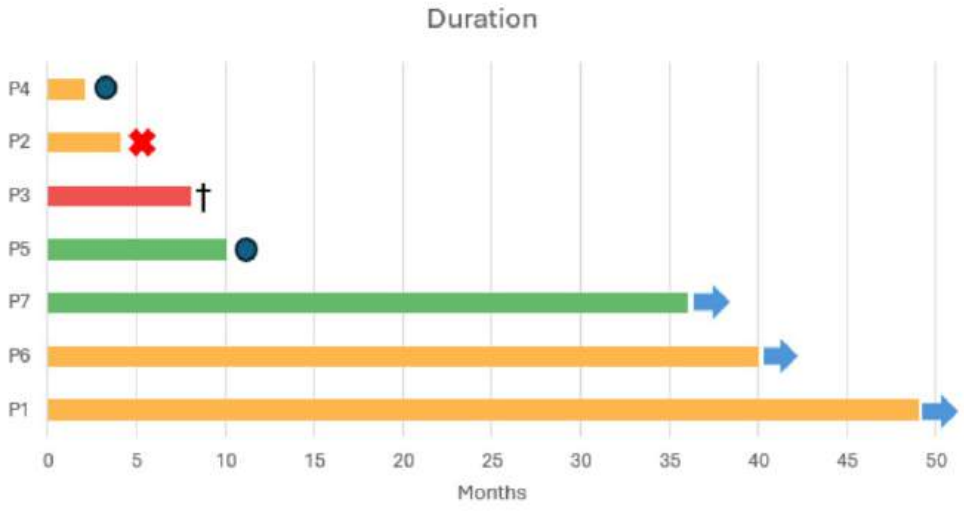
Figure 1

Swimmer plot of treatment duration and response to fostamatinib. Each bar represents an individual case, labeled by patient ID and underlying lymphoproliferative disorder: lymphoplasmacytic lymphoma (P1 and P5), mantle cell lymphoma (P4), marginal zone lymphoma (P2 and P7), and low-grade B-cell non-Hodgkin lymphoma (P6). Bar length indicates treatment duration (months), and colors denote best response according to International Working Group criteria (green: complete response, P5; orange: partial response, P1, P2, P4, and P6; red: no response, P3). Symbols indicate treatment events: ● initiation of BTK inhibitors due to lymphoma progression; ✕ fostamatinib discontinuation with initiation of romiplostim; † death due to intracranial hemorrhage. Arrows indicate ongoing treatment.



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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

SUSTAINED RESPONSE OFF-TREATMENT WITH THROMOBOPOIETIN RECEPTOR AGONISTS AND FOSTAMATINIB: A 15-YEAR SINGLE-CENTER REAL-WORLD EXPERIENCE IN IMMUNE THROMOBOCYTOPENIA WITH IDENTIFICATION OF BIOLOGICAL PREDICTORS

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UOC Ematologia ARNAS Garibaldi

Introduction. Thrombopoietin receptor agonists (TPO-RAs) and fostamatinib have significantly improved outcomes in immune thrombocytopenia (ITP). Beyond platelet response, sustained response off-treatment (SROT) is increasingly recognized as a relevant therapeutic goal, although its feasibility and predictors remain poorly defined in real-world settings.Patients and aim: We retrospectively analyzed all consecutive adult ITP patients treated at Hematology Unit of Garibaldi Hospital in Catania from 2011 to 2025. Treatments included eltrombopag, romiplostim, avatrombopag, fostamatinib, or sequential combinations. SROT was defined as maintenance of a stable platelet count (≥50×10⁹/L) for at least 6 months after treatment discontinuation without need for rescue therapy. The primary aim was to assess SROT rate; secondary aims included treatment distribution, survival status, and identification of clinical or biological predictors of SROT.

Results. A total of 197 patients were included. Treatments consisted of eltrombopag (n=84), romiplostim (n=66), avatrombopag (n=33), fostamatinib (n=20), and sequential TPO-RA combinations (n=19). At last follow-up, 176 patients (89.3%) were alive and 21 (10.7%) deceased, mainly due to non–treatment-related causes. Overall, 26 patients achieved SROT (13.2%). Among SROT cases, romiplostim accounted for 53.8% (n=14), eltrombopag for 42.3% (n=11), and avatrombopag for 3.8% (n=1). No SROT events were observed with fostamatinib, possibly reflecting both limited exposure and differences in mechanism of action. Institutional tapering was attempted in 44 patients, with only 26 (59.1%) achieving a sustained SROT of ≥6 months. Notably, patients who failed tapering or experienced early SROT loss exhibited significantly higher LDH levels compared to those achieving durable SROT (approximately 1.5-fold increase; p<0.01). Fig. 1.

Conclusions. Over 15 years, SROT was attainable for a significant number of ITP patients receiving TPO-RAs, especially with romiplostim and eltrombopag. Careful patient selection and structured tapering are key to optimize treatment discontinuation. Elevated LDH levels may identify patients less likely to sustain SROT, suggesting a potential role as a biomarker of disease activity and treatment-free remission. Prospective validation is warranted.

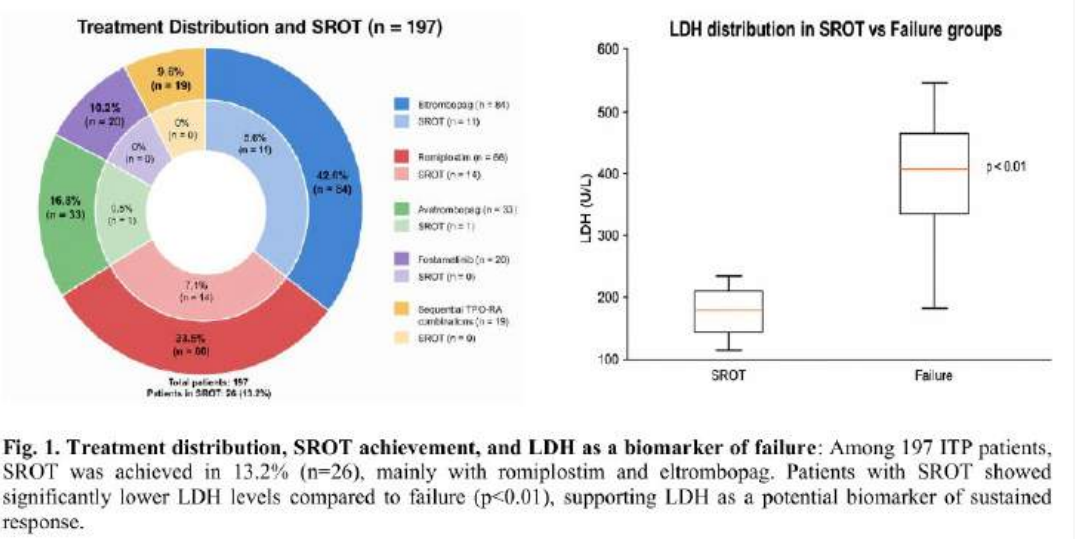

Fig. 1. Treatment distribution, SROT achievement, and LDH as a biomarker of failure: Among 197 ITP patients, SROT was achieved in 13.2% (n=26), mainly with romiplostim and eltrombopag. Patients with SROT showed significantly lower LDH levels compared to failure (p<0.01), supporting LDH as a potential biomarker of sustained response.

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STRATIFYING RELAPSE RISK AFTER PRE-EMPTIVE RITUXIMAB IN IMMUNE-MEDIATED TTP: THE ROLE OF ADAMTS13 INHIBITOR TITER

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In immune-mediated thrombotic thrombocytopenic purpura (iTTP), relapse is often preceded by recurrent severe ADAMTS13 deficiency. Pre-emptive rituximab restores ADAMTS13 activity during clinical remission, but predictors of durable protection are poorly defined. We retrospectively analyzed 18 pre-emptive rituximab courses in 17 patients with iTTP in clinical remission and ADAMTS13 activity <10%. Outcomes were ADAMTS13 response, incidence of biochemical and clinical relapse, duration of response (DoR) and overall survival (OS). ADAMTS13 inhibitor level was tested using ROC analysis, while Fisher's exact test and Kaplan-Meier analysis were used to identify potential predictive factors of DoR. Patients' median age was 46 years (range 18-74) with female/male ratio of 1.43/1 and one patient received two courses of therapy. Median time to next treatment before rituximab was 15.7 months and median baseline inhibitor titer was 40.5 U/L (range 2-137). Eight patients previously received caplacizumab (44%). Rituximab was given at 375 mg/m2 weekly for 4 doses, except in one patient who stopped after 2 doses due to urticaria. ADAMTS13 activity recovery (>20%) was achieved in 16/18 courses (89%) after a median of 4 weeks (range 1-7): 11/16 responses (69%) were complete (CR, >40%) and 5/16 (31%) partial (PR, 20-40%). Two low-grade infections occurred. After a median follow-up of 38.4 months (range 8.5-112), biochemical relapse occurred in 8/16 responding courses (50%), while 5/18 cases had clinical relapse (28%) with an OS of 100%. ROC analysis identified baseline inhibitor titer pre-rituximab ≤28 U/L as predictive for biochemical relapse within 24 months (p=0.03). Kaplan-Meier analysis showed longer biochemical DoR in patients with inhibitor titers >28 U/L than in those with titers ≤28 U/L (median 71 vs 31 months; HR 7.3, 95% CI 1.22-43.8; p=0.03), with similar results for clinical DoR (HR 9.3, 95% CI 1.06-81.7; p=0.04). Sex and caplacizumab exposure were not associated with DoR. Furthermore, complete biochemical response was associated with a trend toward fewer clinical relapses by Fisher's exact test (p=0.06). Pre-emptive rituximab restored ADAMTS13 activity in most iTTP courses with limited toxicity, but relapses remained frequent. Lower baseline ADAMTS13 inhibitor titer was associated with shorter biochemical and clinical DoR, possibly due to stronger association between disease pathogenesis and higher inhibitor levels and improved outcomes using rituximab.

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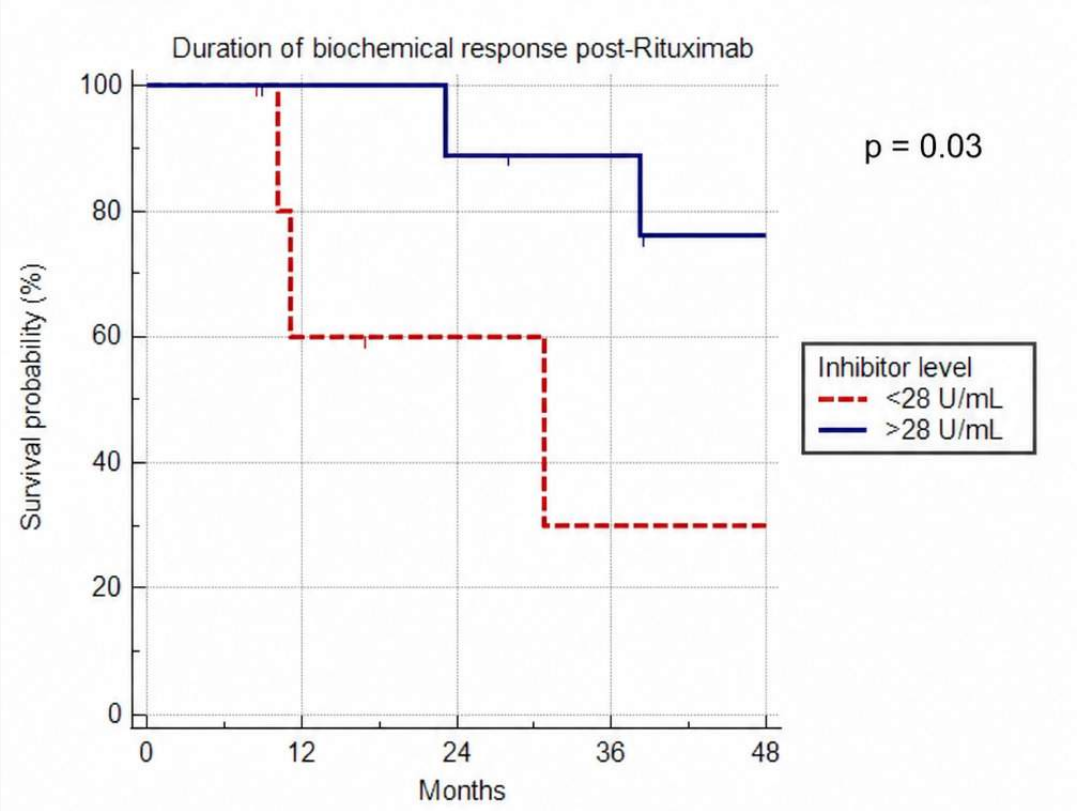
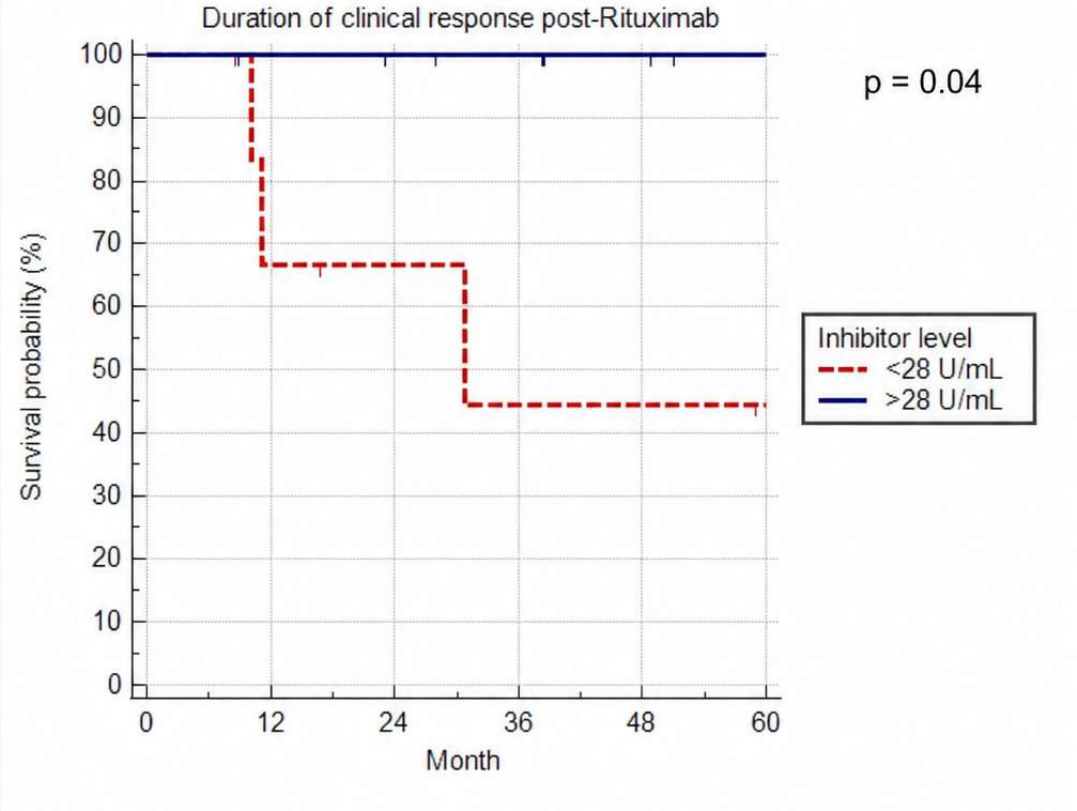

Duration of biochemical response post-Rituximab
Survival probability (%)
100
80
60
40
20
0
0
12
24
36
48
Months
p = 0.03
Inhibitor level
<28 U/mL
>28 U/mL


Duration of clinical response post-Rituximab
Survival probability (%)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
Month
p = 0.04
Inhibitor level
<28 U/mL
>28 U/mL

Non-Hodgkin's Lymphoma

PRE-EMPTIVE CORTICOSTEROIDS FOR TOXICITY MITIGATION IN CD28-COSTIMULATED CD19 CAR-T CELL THERAPY: AN ITALIAN SINGLE-CENTER EXPERIENCE

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CD19.CAR T-cell therapy improved the outcome of relapsed/refractory B-cell non-Hodgkin lymphoma (r/r B-NHL). However, severe toxicities, such as Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), may affect CAR T-cell outcome. Among strategies to mitigate these adverse events, prophylactic or pre-emptive corticosteroid therapy has been proposed, as also suggested by the Italian Society of Hematology guidelines. However, clear evidences about the efficacy of this approach and its impact on CAR T-cell therapy outcomes remain to be fully elucidated. This retrospective, single-center study evaluates the impact of pre-emptive corticosteroid therapy in a cohort of patients receiving CD28-costimulated CAR T-cells (axi-cel and brexu-cel). According to Institutional Procedures from 2022, methylprednisolone (2 mg/kg/day or dexamethasone equivalent) has been administered to all patients with persistent (>24h) grade 1 CRS, refractory to 1–3 doses of tocilizumab; tapering was started on the first day following CRS resolution. The study cohort included 127 consecutive patients with LBCL (80%) and MCL (20%); 102 patients received axi-cel and 25 brexu-cel. After infusion, 87 patients (69%) received pre-emptive steroid therapy as above described (Figure 1). Globally, 124 (98%) patients developed CRS, with 5 (4%) grade ≥3. Twenty-four (19%) patients developed ICANS, with 7 (6%) grade ≥3 ICANS. The median follow-up of the entire cohort was 18 months (95% CI, 16-23). The 2-year overall survival (OS) was 67% (95% CI, 55-77) and 82% (95% CI, 59-93) for LBCL and MCL respectively; 2-years PFS was 50% (95% CI, 39-60) and 52% (95% CI, 29-72). 2-years non-relapse mortality was 4% (95% CI, 2-8). These findings show that the incidence of grade ≥3 CRS, ICANS, and grade ≥3 ICANS in a cohort of patients treated with pre-emptive steroid therapy in case of persistent grade 1 CRS is markedly lowercompared to the rates reported in pivotal studies such as ZUMA-1 and ZUMA-4 trials (grade ≥3 CRS: 13-15%; ICANS: 64-63%; grade ≥3 ICANS: 28-31%) as well as in multiple real-world studies. Notably, the OS and PFS observed in this cohort were consistent with current literature, finally suggesting that early corticosteroid intervention could effectively mitigates CD28-costimulated CAR T-cell-associated toxicities without compromising therapeutic efficacy.

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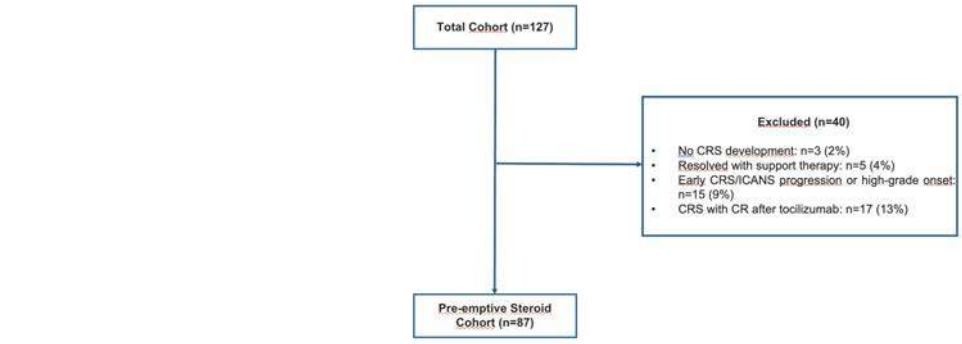
Figure 1) Study cohort composition and derivation of the pre-emptive steroid group



CRS: Cytokine Release Syndrome); ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome

Non-Hodgkin's Lymphoma

PRO-MIND: HEALTH-RELATED QUALITY OF LIFE AND OUTCOMES WITH TAFASITAMAB-LENALIDOMIDE IN PATIENTS WITH AUTOLOGOUS STEM CELL TRANSPLANTATION-INELIGIBLE RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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R/R DLBCL prognosis is mainly driven by disease- and treatment-related factors. HRQoL is a pt-reported outcome that may have prognostic value (Von Tresckow. Blood suppl 2023; Huang. Cancer Med 2022; Jung. Ann Hematol 2012). The global HRQoL measures Global Health Status (GHS) and EORTC QLQ-C30 Summary Score integrate multiple functional and symptom dimensions reflecting clinically relevant aspects of disease burden and pt function (Johnson. Front Oncol 2024). We evaluated associations between baseline global and domain-specific HRQoL and progression-free survival (PFS) in pts enrolled in PRO-MIND.PRO-MIND is a prospective, multicenter, observational study evaluating Tafa-Len in ASCT-ineligible adults with R/R DLBCL (NCT06299553). Baseline HRQoL was assessed using EORTC QLQ-C30. PFS was defined from treatment start to disease progression (PD)/death, with censoring at last contact. Associations between baseline GHS/Summary Score and PFS were evaluated using univariable Cox models (HR per 10--point increase). Domain-level analyses were exploratory (nominal p-values, no multiplicity adjustment). Median-split high vs low HRQoL analyses were illustrative. Analyses were on complete cases (no imputation); multivariable adjustment was not available at submission.As of 25 July 2025 (N=90; median follow-up 4.5 mos), 78 pts had evaluable baseline QLQ-C30 scores. Among 89 evaluable pts, there were 34 PFS events; 55 pts were censored. Median PFS was 10.4 mos. Each 10-point increase in baseline GHS was significantly associated with a 21% reduction in the risk of PD/death (HR 0.79, 95% CI 0.66, 0.93; p=0.006), and each 10-point increase in Summary Score was significantly associated with a 28% reduction in risk of PD/death (HR 0.72, 95% CI 0.59, 0.88; p=0.001). Pts with high vs low baseline Summary Score showed a lower risk of PD/death (HR 0.34, 95% CI 0.15, 0.77), with similar observations for GHS (HR 0.44, 95% CI 0.21, 0.95). In secondary domain-level analyses, higher baseline physical functioning (HR 0.83, 95% CI 0.73, 0.95 per 10-point increase, p=0.005) and baseline fatigue (HR 1.27, 95% CI 1.12, 1.45 per 10-point increase, p<0.001) were strongly associated with PFS; other functional/symptom domains were directionally consistent but had less pronounced associations.Validation in larger cohorts with multivariable adjustment and longer follow-up is needed. However, this preliminary analysis suggests that baseline global HRQoL may have prognostic associations with PFS.

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Non-Hodgkin's Lymphoma

A REAL-WORLD STUDY EVALUATING EFFECTIVENESS AND SAFETY OF CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY AFTER TAFASITAMAB IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: AN ITALIAN SUBGROUP ANALYSIS

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Optimal sequencing of CD19-directed therapies such as tafa and CAR-T for the treatment (tx) of R/R DLBCL remains unclear, given the theoretical potential for CD19 antigen loss or masking. However, there is growing evidence demonstrating maintenance of CD19 expression and epitope availability following tafa tx. A retrospective US and EU panel–based chart review study evaluating CAR-T effectiveness and safety following tx with tafa in patients (pts) with R/R DLBCL was conducted (EHA 2026, PS2089). Here we report data from the Italian subgroup.Adult R/R DLBCL pts treated with tafa (± lenalidomide) followed by CAR-T in second line (2L), 3L, or 4L were included; pts had ≥6 mo of follow-up post CAR-T except in the event of death, and were followed until the start of new anticancer tx after CAR-T, end of data availability, or death, whichever occurred first. Key outcomes assessed were overall response rate (ORR) to CAR-T, and proportion of pts and grade of cytokine release syndrome (CRS) <6 weeks and immune effector cell–associated neurotoxicity syndrome (ICANS) <3 months after CAR-T.Of 338 pts included in the overall study, 59 (17.5%) were from Italy, whose data were abstracted by 27 physicians. Among these 59 pts, 38 (64.4%) were male and 35 (59.3%) had primary refractory disease. At the time of CAR-T administration, median (IQR) age was 60.7 (51.1, 65.5) y, 33 (55.9%) had revised IPI score of ≥3 and 14 (23.7%) had ECOG PS ≥2. Similar to the overall study population, majority of pts (32 [54.2%]) in the Italian cohort used tafa for 2L (± as subsequent bridging tx) and 20 (33.9%) as bridging tx only immediately preceding CAR-T. Median (IQR) time between last tafa dose and CAR-T administration was 1.0 (0.5, 2.1) mo; median (IQR) follow-up time post CAR-T was 7.5 (3.2, 9.0) mo; 41 (69.5%) pts were alive at last known contact. Consistent with overall study results, CAR-T was administered predominantly in 3L (36 [61.0%]) and 4L (15 [25.4%]); axi-cel was the most frequent CAR-T tx used (39 [66.1%]). ORR and complete response rate are shown (Table). Severe (grade ≥3) CRS and ICANS occurred in 25 (7.4%) and 13 (3.8%) pts, respectively, in the overall study population, and in 1 (1.7%) pt each in the Italian cohort.Results from this Italian subgroup analysis are similar to those of the overall population. Findings add to increasing evidence demonstrating that tafa exposure does not appear to compromise the effectiveness and safety of subsequent CAR-T among R/R DLBCL pts.

Table. Overall response rate to CAR-T therapy following tafasitamab

Variable	Italian subgroup (n=59)	Overall population (N=338)
ORR to CAR-T, n (%)	51 (86.4)	274 (81.1)
CR, n (%)	36 (61.0)	198 (58.6)
CAR-T in 2L, n	8	37
ORR, n (%)	7 (87.5)	34 (91.9)
CR, n (%)	4 (50.0)	22 (59.5)
CAR-T in 3L, n	36	243
ORR, n (%)	30 (83.3)	195 (80.2)
CR, n (%)	23 (63.9)	146 (60.1)
CAR-T in 4L, n	15	58
ORR, n (%)	14 (93.3)	45 (77.6)
CR, n (%)	9 (60.0)	30 (51.7)

2L/3L/4L, second/third/fourth line; CAR-T, chimeric antigen receptor T-cell; CR, complete response; ORR, overall response rate.

Non-Hodgkin's Lymphoma

SECOND PRIMARY MALIGNANCIES AFTER BENDAMUSTINE-RITUXIMAB IN INDOLENT LYMPHOMAS: INCREASED RISK IN WALDENSTRÖM MACROGLOBULINEMIA? A COMPARATIVE ANALYSIS WITH FOLLICULAR LYMPHOMA FROM FIL FOLL12 TRIAL

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The prolonged survival of patients (pts) with Waldenström Macroglobulinemia (WM) has raised concerns about long-term complications, including second primary malignancies (SPMs), and real-world data remain limited. We aimed to evaluate, in a multicenter real-life cohort, the incidence, type, and risk factors of SPMs in WM pts treated with bendamustine-rituximab (BR), and to compare them with follicular lymphoma (FL), treated with BR in the FIL FOLL12 trial.We retrospectively analyzed 168 WM pts (median follow-up 6.8 years) and 341 FL pts (median follow-up 8.4 years). Median age was 65 years (IQR 57–74) in WM and 64 (IQR 55–71) in FL; M/F ratio was 2.2 vs 0.7.In WM, median overall survival (OS) was not reached, while median progression-free survival (PFS) was 8.9 years and event-free survival (EFS, time to relapse, death from any cause, or SPM) was 6.8 years. Fifty pts (29.8%) relapsed, and 44 received second-line therapy. SPMs occurred in 20 WM pts (11.9%): 16 solid (6 prostate and 2 colorectal carcinomas, 2 melanomas, 1 hepatocarcinoma, 1 esophagus carcinoma, 1 urothelial and 1 neuroendocrine neoplasms, 1 seminoma and 1 leiomyosarcoma) and 4 hematologic (2 myelodysplastic syndromes, 1 acute myeloid leukemia and 1 chronic myelomonocytic leukemia).In FL, OS, PFS, and EFS were not reached; 105 pts (30.8%) relapsed and 75 received second-line therapy. SPMs occurred in 30 pts (8.8%): 27 solid (7 breast, 5 colorectal, 3 lung, 2 gastric, 1 prostate, 1 bladder, 1 parotid, 1 renal, 1 thyroid carcinomas, 1 melanoma, 1 myosarcoma, 1 neuroendocrine neoplasm, and 2 unknown) and 3 hematologic (2 myelodysplastic syndromes, 1 chronic lymphocytic leukemia).Cumulative SPM incidence in WM was 10.4% and 14.9% at 48 and 96 months vs 5.6% and 9.0% in FL (Figure 1). The incidence observed in WM is consistent with previous reports (Leblond et al., Leukemia 2026 in which SPM cumulative incidence was 17.6% at 96 months, p= 0.27). WM pts showed a significantly higher incidence of SPMs compared to FL (p=0.045). Deaths related to SPMs were proportionally more frequent in WM (8/31, 25.8%) than in FL (10/64, 15.6%).In conclusion, WM pts treated with BR appear to have a higher risk of developing SPMs compared to FL, with a relevant impact on mortality. These findings support structured long-term surveillance in WM and prospective studies to clarify the drivers of increased oncologic risk, including treatment, disease biology, and patient susceptibility.

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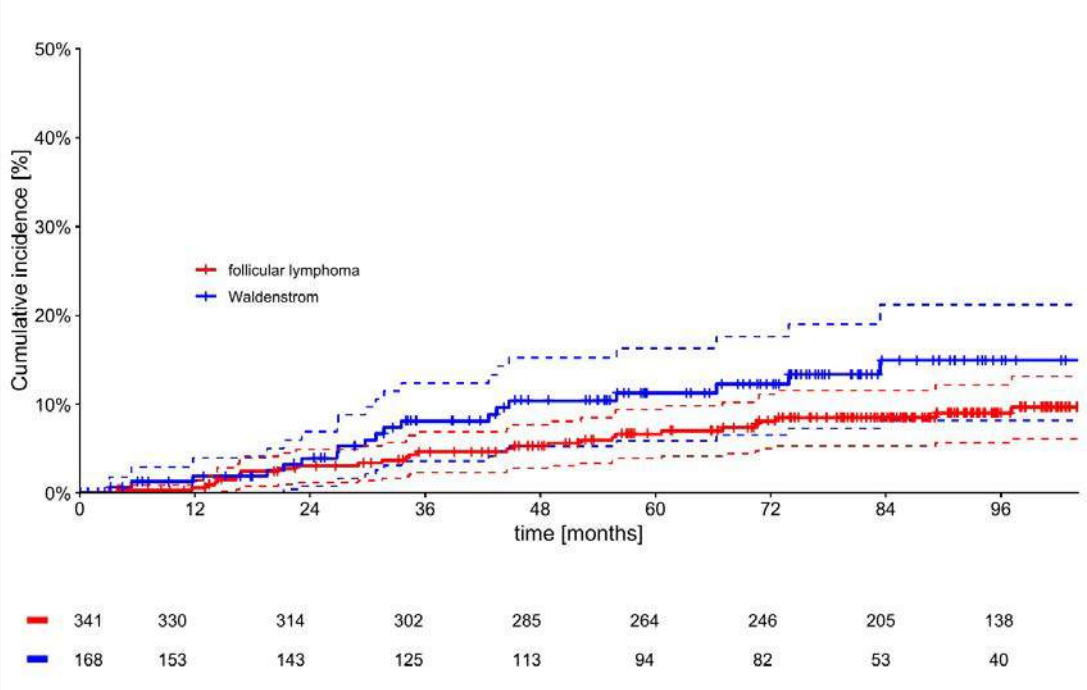
Non-Hodgkin's Lymphoma



Non-Hodgkin's Lymphoma

RELAPSED OR REFRACTORY POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS: REAL-LIFE MULTICENTER ITALIAN EXPERIENCE WITH TABELECLEUCEL

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Background. Epstein Barr virus related (EBV+) PTLD is a rare complication occurring after stem cell (HSCT) or solid organ transplant (SOT), with a poor outcome if first line therapy fails. Tabelecleucel is an allogeneic T-cell immunotherapy that targets EBV-positive cells selectively based on human leukocyte antigen (HLA) restriction. It is available in Italy as monotherapy in adult and pediatric patients with R/R EBV+PTLD, since February 2023 as compassionate use and since March 2025 as commercial use.The phase 3 ALLELE study demonstrated an overall response rate (ORR) of 51%, with a complete remission (CR) rate of 28% and a 1 year-overall survival (OS) of 84% for responding patients.

Methods and results. This retrospective observational analysis describes the preliminary Italian real-life experience with tabelecleucel use.From January 2024 to February 2026, 27 patients were enrolled across 13 centers. The median age was 62 years (range 12–81), including also pediatric setting. Prior transplants include 12 (44%) HSCT and 15 (56%) SOT (8 thoracic and 7 abdominal ones). Nineteen patients had monomorphic PTLD (diffuse large B cell lymphoma in half of cases). PTLD-adapted prognostic index was high in 10 patients (56%), 22 (82%) had extranodal localization, 3 (11%) with central nervous system (CNS) involvement and one with CNS progression, 19 (70%) with IV stage disease. In 12 cases the origin of PTLD was determined on the basis of high-resolution HLA typing. The median time from transplant to PTLD onset was 12 months (range 1-227) and 16 cases (70%) had early-onset. The median time from PTLD diagnosis and relapse to tabelecleucel administration was respectively 3 months (range 0.9–155) and 33 days (range 7-78). The median number of cycles was 2 (range 0–8), without significant toxicity: 3 patients didn't receive tabelecleucel (1 death, 2 lot unavailability). ORR was 38% (CR rate of 29%). In the subcohort of SOT recipients, ORR was 46% (CR rate of 39%); among refractory patients, 3 died of disease, 4 were alive with disease. Among HSCT recipients, ORR was 27% (CR rate of 18%); among refractory patients, 6 died of disease, 2 achieved CR with a rescue treatment. After a median follow-up of 5 months, 12 patients were alive.

Conclusions. This Italian experience supports the efficacy and safety of tabelecleucel, consistent with the results of the ALLELE trial, especially in SOT. It is essential to identify early potential candidates for this promising therapy.

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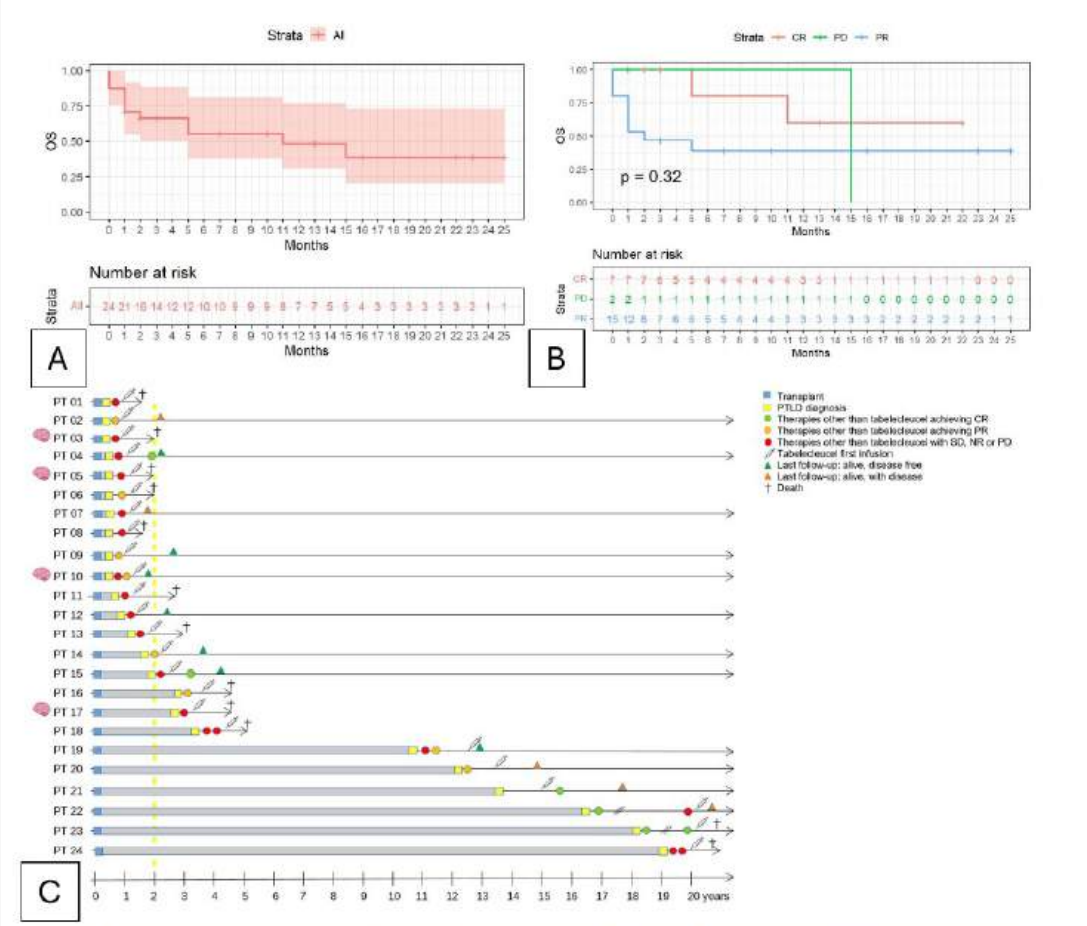

Figure 1 A: Kaplan–Meier survival curve of the overall study population. Figure 1B: Kaplan–Meier survival curves stratified according to response to cellular therapy. Figure C: Swimming plot illustrating diagnosis, treatment, response, and follow-up for patients who received cellular therapy.

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Non-Hodgkin's Lymphoma

CLINICALLY RELEVANT SUBGROUP ANALYSIS FROM THE RANDOMIZED PHASE 3 EPCORE FL-1 TRIAL: TREATMENT EFFECT OF EPCORITAMAB WITH LENALIDOMIDE AND RITUXIMAB (R²) IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA

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Background. Epcoritamab (E) is FDA approved as fixed-duration therapy with R² for second-line or later (2L+) treatment of FL based on the Phase 3 EPCORE FL-1 trial (NCT05409066), which showed superiority vs R² in overall response rate (ORR; *P*<.0001) and progression-free survival (PFS; *P*<.0001) (Falchi *Lancet* 2026). Here we explore if E+R² benefit and tolerability extended across clinically relevant subgroups.

Methods. Patients (pts) ≥18 y old with CD20+ R/R FL, ECOG 0–2, and ≥1 prior therapy were randomized to E+R² or R² for ≤12 cycles (C). E was given QW in C1–3 (C1 step-up dosing) and Q4W in C4–12. Oral lenalidomide (Len) was given QD in C1–12 (Days 1–21) and IV rituximab QW in C1 and Q4W in C2–5. Clinically relevant subgroups were assessed, including baseline FLIPI score, POD24 status, and the validated NHL-5 comorbidity score. Outcomes were also assessed by Len relative dose intensity (RDI).

Results. As of 24May2025, 488 pts were enrolled; 243 in E+R² and 238 in R² who received ≥1 study drug dose. Median duration of E was 10.4 mo overall and was similar across FLIPI and NHL-5 subgroups. Between FLIPI subgroups, ORR was higher with E+R² vs R² (FLIPI 0–2, 96.5% vs 84.8%; FLIPI 3–5, 93.0% vs 72.6%); high complete response rates (CRR) indicated deeper responses with E+R² vs R² (FLIPI 0–2, 86.6% vs 62.1%; FLIPI 3–5, 77.0% vs 35.4%). PFS HRs (95% CIs) favored E+R² vs R² for FLIPI 0–2 (0.18 [0.10–0.33]) and FLIPI 3–5 (0.25 [0.15–0.42]) subgroups. In non-POD24, ORR and CRR were higher with E+R² vs R² and PFS favored E+R², with a similar trend in POD24. In NHL-5 subgroups, ORR, CRR, and PFS favored E+R² vs R² for low and high+intermediate subgroups. Additional subgroup analyses showed clinically meaningful and consistent ORR, CRR, and PFS improvement with E+R² vs R² (Table).In pts with lower Len RDI, AE rates (ie, neutropenia, infections) were higher but ORR/PFS remained higher with E+R² vs R².The E+R² safety profile across subgroups was manageable and consistent with the overall trial population, with no new safety signals.

Conclusions. E+R² led to sustained, improved efficacy with manageable safety, regardless of baseline risk. Clinically meaningful improvements were observed across lower-risk disease features and lower Len RDI, supporting E+R² as an option for a diverse R²-eligible population. The EPCORE FL-1 findings position fixed-duration E+R² as a new benchmark standard of care for a broad population of pts with R/R FL in 2L+ treatment.

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Table: EPCORE-FL-1 Efficacy Subgroup Analysis

		ORR (95% CI)	CRR (95% CI)	PFS HR (95% CI) for E+R²:R²
Age ≥65	E+R² (n=88)	94.3 (87.2–98.1)	80.7 (70.9–88.3)	0.24 (0.13–0.44)
	R² (n=106)	80.2 (71.3–87.3)	44.3 (34.7–54.3)	
Age <65	E+R² (n=155)	95.5 (90.9–98.2)	83.9 (77.1–89.3)	0.20 (0.12–0.33)
	R² (n=139)	78.4 (70.6–84.9)	54.0 (45.3–62.4)	
FLIPI 0–2	E+R² (n=142)	96.5 (92.0–98.8)	86.6 (79.9–91.7)	0.18 (0.10–0.33)
	R² (n=132)	84.8 (77.6–90.5)	62.1 (53.3–70.4)	
FLIPI 3–5	E+R² (n=100)	93.0 (86.1–97.1)	77.0 (67.5–84.8)	0.25 (0.15–0.42)
	R² (n=113)	72.6 (63.4–80.5)	35.4 (26.6–45.0)	
NHL-5 low	E+R² (n=166)	94.0 (89.2–97.1)	81.3 (74.6–86.9)	0.27 (0.17–0.42)
	R² (n=149)	75.8 (68.2–82.5)	50.3 (42.0–58.6)	
NHL-5 H+I	E+R² (n=77)	97.4 (90.9–99.7)	85.7 (75.9–92.6)	0.14 (0.06–0.29)
	R² (n=96)	84.4 (75.5–91.0)	49.0 (38.6–59.4)	
Non-POD24	E+R² (n=131)	96.2 (91.3–98.7)	85.5 (78.3–91.0)	0.17 (0.09–0.32)
	R² (n=144)	85.4 (78.6–90.7)	57.6 (49.1–65.8)	
POD24	E+R² (n=106)	95.3 (89.3–98.5)	80.2 (71.3–87.3)	0.22 (0.13–0.37)
	R² (n=93)	69.9 (59.5–79.0)	38.7 (28.8–49.4)	
1 prior LOT	E+R² (n=145)	95.9 (91.2–98.5)	86.9 (80.3–91.9)	0.20 (0.12–0.34)
	R² (n=141)	80.1 (72.6–86.4)	53.2 (44.6–61.6)	
≥2 prior LOT	E+R² (n=98)	93.9 (87.1–97.7)	76.5 (66.9–84.5)	0.24 (0.13–0.42)
	R² (n=104)	77.9 (68.7–85.4)	45.2 (35.4–55.3)	
Not double refractory	E+R² (n=152)	95.4 (90.7–98.1)	84.9 (78.2–90.2)	0.19 (0.11–0.34)
	R² (n=154)	85.1 (78.4–90.3)	58.4 (50.2–66.3)	
Double refractory	E+R² (n=91)	94.5 (87.6–98.2)	79.1 (69.3–86.9)	0.23 (0.13–0.39)
	R² (n=91)	69.2 (58.7–78.5)	35.2 (25.4–45.9)	

Subgroups were dichotomized.
CRR, complete response rate; H+I, high and intermediate; HR, hazard ratio; LOT, line of therapy; ORR, overall response rate; PFS, progression-free survival; POD24, progression of disease ≤2 years from the date of initiation of frontline therapy.

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Non-Hodgkin's Lymphoma

CLONAL HAEMATOPOIESIS IN CAR-T PATIENTS: IMPACT ON LATE CYTOPENIAS AND OUTCOME

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Background. Chimeric Antigen Receptor T-cells (CAR-T) therapy is associated with prolonged cytopenias and potential risk of secondary Myeloid Neoplasia (t-MN). Cytopenia risk factors include clonal haematopoiesis of indeterminate potential (CHIP).

Aim. The primary objective was to identify CHIP in myeloid and in CD3+ compartment in patients with R/R Lymphoid Malignancies receiving CAR-T cells for the approved indications. Secondary aims were to search correlations between myeloid and lymphoid CHIP and prolonged cytopenias and t-MNs after CAR-T.We included 20 consecutive patients (minimum 6 months follow up). A myeloid NGS panel on 51 genes was performed (Myeloid Solution, Sophia Genetics). We analyzed bone marrow (BM), peripheral blood (PB) and immunomagnetically enriched T lymphocytes (CD3+) before T-lymphodepletion chemotherapy and at 6 months after CAR-T infusion or in case of prolonged cytopenia. All CD3+ fractions had a purity greater than 90%. CHIP was defined as a variant allelic frequency (VAF) of 1% or greater.

Results. We observed prolonged cytopenias (at least WHO grade 1 neutropenia and/or thrombocytopenia or anemia after day 30) in 14/20 patients (70%), prolonged grade 3-4 neutropenia in 13/20 cases (65%) and 2 cases of myelodysplastic syndromes at 3 and 9 months after CAR-T infusion. 3 patients relapsed at 1, 4 and 6 months after CAR-T.We identified CHIP in 15 patients (75%), *fig.1*. The same mutations were found in both BM and CD3+ in 8 cases. In 7 cases, different mutations were present in CD3+ cells compared with BM. The CD3+ CHIP affected only DTA genes: *DNMT3A*, *TET2* and *ASXL1*. CHIPs were not significantly correlated with prolonged cytopenia, regardless of the compartment examined (BM, PB and CD3+ cells). However, a trend of a more frequent lymphoid CHIP was observed in patients without grade 3-4 neutropenia (86% vs 54%) and all relapsed patients had previous CD3+ CHIP. Both patients who developed t-MN had shown previous severe cytopenia: they had pre-CAR-T myeloid CHIP and after CAR-T showed an increase in number and VAF of preexisting CHIP.We conclude that CHIP is frequent in CAR-T candidates and mutations can be different in myeloid and lymphoid compartment. Although lymphoid CHIP has been less studied yet, our results may suggest its role in relapse after CAR-T. Moreover, we confirm that t-MNs after CAR-T are associated with the accumulation of multiple mutations, some of which were present before lymphodepletion. *(PRIN20227RLEL8)*

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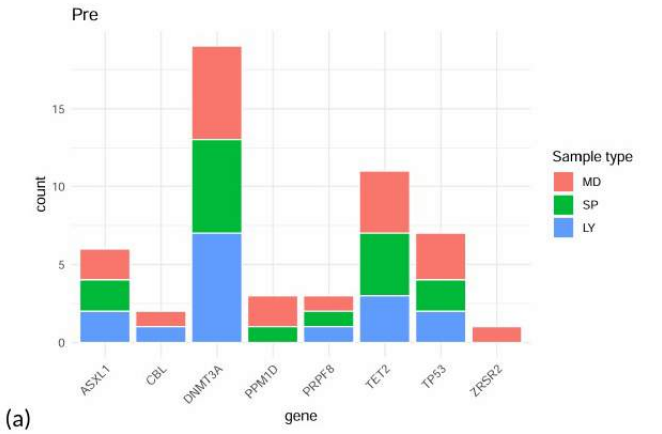

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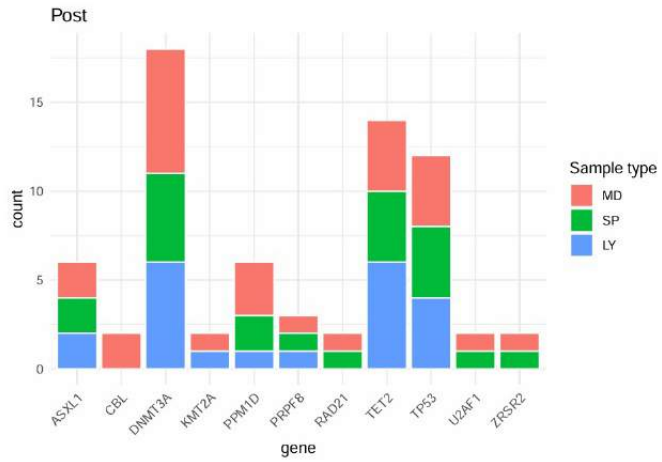

(b)

Fig.1 – Frequency of mutated genes in CHIP positive patients, in relation to the three matrices (bone marrow, peripheral blood and CD3+ lymphocytes), detected (a) pre-lymphodepletion and (b) post CAR-T infusion (at 6 months or in case of cytopenia). *MD= bone marrow; SP= Peripheral Blood; Ly= CD3+ lymphocytes.*

Non-Hodgkin's Lymphoma

LARGE B-CELL LYMPHOMA DE NOVO AND TRANSFORMED FROM FOLLICULAR LYMPHOMA WITH MYC ALTERATIONS: AN ITALIAN SINGLE CENTER EXPERIENCE

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Introduction. In Large B-cell lymphomas (LBCL) MYC gene translocation has shown a negative prognostic impact as well as transformation from follicular lymphoma (FL) following the diagnosis (Rusconi C. et al., Br J Haematol. 2019;185(4):713-717), but there are few data about MYC alterations in LBCL transformed from FL (tLBCL).Aim: To evaluate the impact of MYC alterations on clinical features and outcome of tLBCL and de novo LBCL (dLBCL).

Methods. In this retrospective observational study we evaluated all consecutive patients (pts) of a single Hematology unit, diagnosed with dLBCL and tLBCL [diffuse large B cell or high grade B cell lymphoma (Ly) according to the 2022 WHO Classification] and alterations of MYC detected by FISH.Pts were classified according to genetic alterations [single hit Ly (SHL), double/triple hit Ly DHL/THL and Ly with MYC gain copy number: atypical SHL (aSH) and DHL-THL (aDHL/THL)] and if tLBCL according to the onset time of FL [trasformed at diagnosis (group1) or later (group 2)].

Results. From January 2011 to October 2025 we identified 226 pts: 167 dLBCL and 59 tLBCL (22 in group 1, 37 in group 2).Table 1 shows clinical and histological characteristics and type of treatment: tLBCL had more frequently advanced stage, DHL/THL and germinal center B phenotype (GCB) according to Hans algorithm and more frequently received upfront autologous stem-cell transplantation as consolidation; in dLBCL, SHL were significantly more frequent and Ki67proliferative index was significantly higher.With a median follow up of 77 months (range 2-174), 3-year overall (OS) and progression free survival (PFS) were significantly better in dLBCL [OS 69% and 52% and PFS 64% and 41% in dLBCL and tLBCL respectively (both p 0,03)]. According to the onset of LBCL, no significant difference in OS and PFS was found between dLBCL and group1 of tLBCL.In DHL/THL, we confirmed a survival advantage in dLBCL [3-years OS 69% vs 53% (p 0,067), 3-year PFS 66% and 37% (p 0,01) in dLBCL and tLBCL respectively]; conversely, in SHL and aDHL/THL no significant difference in OS and PFS was found between the two groups.In multivariate analysis tLBCL, ECOG≥2 and age>60 years showed a negative prognostic impact on OS and PFS, non intensive chemotherapy (i.e RCHOP or RCHOP like) only on PFS, SHL had a positive prognostic impact only on OS.

Conclusions. In this retrospective analysis, tLBCL with MYC alterations showed a worse PFS and OS compared to dLBCL, except in pts with transformation concomitant with the FL diagnosis.

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	dLBCL (167 pts)	tLBCL (59 pts)	*p*
CLINICAL CHARACTERISTICS			
Median age (Range) years	68 (31-88)	63 (34-86)	ns
Sex Male	102 (61%)	39 (66%)	ns
Stage III-IV	122 (73%)	51 (86%)	0,037
CNS involvement	8 (5%)	2 (3%)	ns
kidney/adrenal gland involvement	23 (14%)	7 (12%)	ns
ECOG≥2	77 (46%)	23 (39%)	ns
IPI int high-high	112 (67%)	41 (69%)	ns
Bone marrow involvement	30 (18%)	15 (25%)	ns
HYSTOLOGY			
DLBCL HGBCL DH HGBCL NOS	106 (63%) 43 (26%) 18 (11%)	22 (37%) 36 (61%) 1 (2%)	0,0001 0,0001 0,031
SHL aSHL DHL/THL aDHL/THL	37 (22%) 9 (5%) 54 (32%) 66 (39%)	6 (10%) 0 37 (63%) 16(27%)	0,044 ns 0,0001 ns
Median Ki67% (range)	90 (10-100)	80 (20-100)	0,0001
DEL	82/132 (62%)	39/52 (75%)	0,024
BCL2 translocation	59 (35%)	46 (78%)	0,001
BCL6 translocation	42 (25%)	16 (27)%	ns
COO GCB COO ABC	85/110 (77%) 25/110 (23%)	38/40 (95%) 2/40 (5%)	0,012
THERAPY			
R-CHOP/R-CHOP like R-DA-EPOCH Intensified therapy* Palliative	58 (35%) 58 (35%) 44 (26%) 7 (4%)	15 (25%) 23 (39%) 15 (25%) 6 (10%)	ns
Rituximab maintenance	0	11 (19%)	0,0001
AutoSCT in first CR/PR	40 (24%)	18 (30%)	0,04

ns: not significant; CNS: central nervous system; DEL: double expressor ly; COO: Cell of origin according to Hans algorithm; GCB: germinal center B cell like; ABC: activated B cell like; autoSCT: autologous stem cell transplant

*GMALL or or other regimens containing HD MTXand ARA-C or autologous stem cell transplant

Non-Hodgkin's Lymphoma

ODRONEXTAMAB PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: FIRST RESULTS FROM PART 1 (SAFETY LEAD-IN) OF THE PHASE 3 OLYMPIA-5 STUDY

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Background. The Phase 3 OLYMPIA-5 study (NCT06149286) evaluates the efficacy and safety of Odro (CD20×CD3 bispecific antibody) + Len in pts with R/R FL or marginal zone lymphoma after ≥1 prior line of therapy (LOT). We report results from the Part 1 (safety lead-in) FL cohort.

Methods. Pts aged ≥18 years (yrs) with R/R Grade (Gr) 1–3a FL after ≥1 prior LOT received Odro + Len in 12 × 28-day cycles: intravenous Odro with 0.7/4/20 mg step-up dosing on Cycle (C)1 (Day [D]1/8/15), followed by a full dose (40 mg, dose level [DL]40; 80 mg, DL80) on C1D22 and C2–3 (D1/8/15/22), 2 full doses on C4–6 (D1/15), and 4 full doses on C7–12 (D1). Oral Len 20 mg was given once daily per cycle on D1–21. Primary endpoints included dose-limiting toxicities (DLT) and treatment-emergent adverse events (TEAEs). Secondary endpoints included investigator-assessed objective response rate (ORR), complete response (CR) rate, and duration of response (DOR) per Lugano criteria. Exploratory endpoints included biomarkers.

Results. At data cut-off (Sep 17, 2025), 32 enrolled pts (DL40 n=6; DL80 n=26) were evaluable for efficacy/safety. Median age, 59 yrs (range 35–80); male, n=14; Lugano stage III/IV disease, n=23; median prior LOT, 1 (range 1–7); progression of disease within 2 yrs, DL40 0%, DL80 3.8%. Median duration of Odro + Len exposure: DL40 47.9 weeks (range 5.7–49.3); DL80 43.1 weeks (4.0–58.3).No DLT-evaluable pts (DL40 n=6; DL80 n=24) had DLTs. All pts experienced TEAEs (Gr ≥3: DL40 66.7%; DL80 96.2%), most commonly neutropenia (66.7%; 80.8%) and cytokine release syndrome (CRS, 33.3%; 53.8%). All CRS events were Gr 1 (DL40 33.3%; DL80 34.6%) or Gr 2 (0%; 19.2%). One Gr 3 immune effector cell-associated neurotoxicity syndrome event occurred (DL80). Due to TEAEs, 4 pts (DL80) discontinued treatment and 2 died (1 in DL40 [influenza] and 1 in DL80 [hemorrhagic stroke]). Infections occurred in 83.3% (Gr ≥3 33.3%) of pts in DL40 and 76.9% (Gr ≥3 19.2%) in DL80.In DL40 and DL80, ORR was 83.3% and 84.6%, and CR rate was 66.7% and 69.2%, respectively. Median DOR was not reached in both DLs.CD4/8 T-cell counts were higher from C7 to treatment end versus baseline. Step-up dosing depleted B-cell counts with no recovery for ≤90 days post-last dose. Interleukin (IL)-6, IL-8, and interferon-γ levels were similar in both DLs post-first full dose (C1D22).

Conclusions. Odro + Len had a generally manageable safety profile and promising preliminary efficacy in pts with R/R FL after ≥1 prior LOT.

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Non-Hodgkin's Lymphoma

PATTERNS OF INFECTION AND THEIR IMPACT ON THE OUTCOMES OF NEXT-GENERATION B-CELL DEPLETING IMMUNOTHERAPIES IN NON-HODGKIN'S LYMPHOMAS: FINDINGS FROM A MULTICENTER RETROSPECTIVE REAL-LIFE COHORT

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Background. Novel immunotherapies have changed the outcome of relapsed/refractory (R/R) non-Hodgkin's lymphomas (NHL) patients (pts), but with increased susceptibility to infections.

Aims. This observational retrospective multicenter study evaluated the incidence, type, timing and outcome of infections in NHL pts treated with novel immunotherapies.

Methods. NHL pts from three Italian centers who started treatment between December 1, 2019, and October 31, 2025, were included.

Results. 158 NHL pts received 195 immunotherapy lines: 108 CAR-T cells (58 Axi-cel, 33 Tisa-cel, 16 Brexu-cel, 1 Liso-cel), 40 bispecific MoAbs (13 glofitamab, 18 epcoritamab, 9 mosunetuzumab), 26 ADCs (11 anti-CD19 ADC: loncastuximab, 15 anti-CD79b ADC Polatuzumab with rituximab-bendamustine), and 21 naked MoAbs (tafasitamab-lenalidomide). Multiple consecutive lines were given to 30 pts. Median age was 67 years (IQ, 58–74). Clinical features included: advanced stage 84%, elevated LDH 62%, bulky disease 33%, extranodal involvement 75%, IPI 3-5 69%, and ECOG PS≥2 20%. Median previous treatments was 2 (range 1–7); 42 pts received ASCT and 3 allo-SCT. Total infective events were 162: 93 bacterial, 48 viral, 4 mixed, 15 FUO, and 2 fungal, with higher viral events in ADC-treated pts (p=0.017). Infection grade was 1-2 in 70 cases, 3-4 in 35, and 5 in 6. Hospitalization was needed in 46% of pts, and treatment modification in 21%. Median time to first infection was 21 days, with 76% occurring in the first 100 days. Onset time was shorter for CAR-T and bispecifics (15 and 17 days) than for naked MoAbs or ADCs (30 and 70 days, p=0.069). Bispecifics correlated with higher infection rates (p=0.035). G-CSF and IGIV were used in 63% and 43% of cases, respectively, with higher use in CAR-T or bispecifics (p<0.001). Anti-PJ and antiviral prophylaxis were given to 99% and 97% of pts. In univariate analysis, bispecifics (HR 3.38, p=0.023) and IGIV (HR 2.32, p=0.005) correlated with higher infection risk, while progressive disease showed lower risk. In multivariate analysis, only IGIV remained significant (HR 2.14, p=0.023), indicating pts with more infections likely received more IGIV support. Of 74 deaths, 56 were from lymphoma progression and 6 from infections.

Conclusions. Infections are common in novel immunotherapy for NHL; however, most cases occurred early (<100 days) and were mild-to-moderate and manageable. In R/R NHL pts, the main cause of death remains lymphoma progression.

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Non-Hodgkin's Lymphoma

FIRST STEP OF A PHASE 2 TRIAL ADDRESSING DARATUMUMAB-BORTEZOMIB-DEXAMETHASONE COMBINATION IN RELAPSED OR REFRACTORY PLASMABLASTIC LYMPHOMA: THE DALYA TRIAL ON BEHALF OF THE FONDAZIONE ITALIANA LINFOMI

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Introduction. Plasmablastic lymphoma (PBL) is a rare, aggressive B-cell malignancy, often associated with HIV infection, which carries a poor prognosis. Relapses are frequent after first line chemotherapy, and median post-relapse survival is ~3 months. The overlapping biology between PBL and multiple myeloma, with high expression of plasma cell markers (i.e., CD38), suggests that anti-myeloma agents may be effective in PBL. Accordingly, we conducted a single-arm phase 2 trial (DALYA) addressing activity and tolerability of daratumumab, bortezomib, and dexamethasone as salvage therapy for relapsed/refractory (R/R) PBL. Here, we report the first-step analysis.

Methods. DALYA recruits adults (≥18 ys) with histologically confirmed PBL per WHO 2017 criteria (CD38 expression in ≥5% tumor cells), R/R to ≥1 prior line of therapy, and relapsed after ASCT or not eligible for it. HIV-negative and positive patients (pts) with controlled HIV infection on cART were eligible. Treatment is detailed in the Table. The primary endpoint was best overall response rate (ORR; CR + PR), assessed per Lugano 2014 criteria after the first course and every three courses thereafter. The null hypothesis ORR of 15% was tested vs a one-sided alternative of 35% using Simon's two-stage design (α=0.05, power=0.80). 28 pts were planned: 15 in stage 1 (expand if >2 responses), followed by 13 additional pts; the regimen was deemed active if ≥8 responses were observed overall.

Results. Fifteen pts (median age 62, range 33-80; 14 males) were included in this analysis; 3 had HIV infection. Most pts had advanced stage (n=13), increased LDH (n=11), extranodal disease (n=12), and IPI ≥2 (n=15). Median number of prior lines was 1 (range 1-3); one pt had prior ASCT. Two CR and 4 PRs were registered, yielding an ORR of 40% (95%CI=15-65). Notably, 4 responses were achieved after the first course, which consisted of daratumumab single agent. Eighty-one adverse events (AEs) were reported: 68 (83%) were grade 1-2 and 13 (16%) were grade ≥3. Among grade ≥3 AEs, 9 were hematologic and 4 non-hematologic (infections). All but one pt recovered; one died of septic shock. No treatment interruptions or clinically relevant delays occurred.

Conclusion. Daratumumab-bortezomib-dexamethasone met predefined efficacy criteria in the first step of the DALYA trial, showed acceptable toxicity, and supports further investigation of these agents in PBL, including their incorporation into frontline therapy. Accrual is ongoing.

Table. Regimen assessed in the DALYA trial

Phase	Cycle #	Interval (days)	Daratumumab (subcutaneous)	Bortezomib (subcutaneous)	Dexamethasone (oral route)
Induction	1	21	1800 mg days 1,8, & 15	-	-
	2-3	21	1800 mg days 1,8, & 15	1,3 mg/m^2 days 1,4,8, &11	20 mg ds 1,2,4,5,8,9,11,12
	4-9	28	1800 mg on day 1	1,3 mg/m^2 days 1,4,8, &11	20 mg days 1,2,4,8,11
Maintenance	10-15	28	1800 mg on day 1	-	-

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Non-Hodgkin's Lymphoma

IBRUTINIB IN SECOND-LINE RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA: EFFICACY AND SAFETY RESULTS FROM THE SECOND INTERIM ANALYSIS OF THE OLIMPUS STUDY

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Background. Mantle cell lymphoma (MCL) is an aggressive, incurable hematologic malignancy; ibrutinib is approved for relapsed/refractory (R/R) disease, sustained by broad trial literature. However, prospective second line and real-world data remain limited.

Aims. OLIMPUS is a multicenter, prospective collection of patients with first R/R MCL, designed to describe Italian real-world efficacy and safety outcomes of second-line ibrutinib. This interim analysis (IA) updates and expands prior results.

Methods. 106 R/R MCL patients were prospectively enrolled from 34 Italian centers. Data were extrapolated up to the last available visit at the data cut-off with median follow-up of 18.04 months by Kaplan–Meier (95%CI, 16.56–21.95). The first interim analysis cohort (IA1 n=51) was updated to a median follow-up of 24.57 months (95%CI, 22.44–NR). Primary endpoint was overall response rate (ORR) per Lugano criteria.

Results. Median age was 71 years (35–90); 73.6% were male. High sMIPI was observed in 33%, TP53 mutation in 51% (16/31 tested), blastoid/pleomorphic histology in 17% (12/71). POD24 occurred in 55% (58/106). Median starting ibrutinib dose was 560 mg; 21% had significant cardiovascular disease. ORR was 73% (95%CI, 58.1–85.4) with complete response rate (CRR) 50% (CRR 53% in IA1); 10% had stable disease and 17% progressive disease. Progression free survival (PFS) rate at month 24 was 57.3% (95%CI 45.5–67.4) in IA and 61.5% (95%CI 45.5–74.0) in IA1; among POD24 patients, month-24 PFS was 46.2% (95%CI 31.1–60.0) and 48.5% (95%CI 29.0–65.5), respectively. Overall survival was 72.6% (95%CI 59.8–81.9) in IA and 80.1% (95%CI 63.9–89.6) in IA1. Median duration of response was 28.45 months (95%CI, 23.39–NR) and not reached in IA1. Adverse events (AE) occurred in 68% (grade 3: 19.8%; grade 4: 7.5%); infections were most frequent (23.6%), followed by general disorders (20%; pyrexia 8.5%, asthenia 4.7%) and blood disorders (20%; neutropenia 9.4%, anemia 7.5%). Cardiac disorders occurred in 15% (atrial fibrillation 6.6%, cardiac failure 1.9%). Treatment interruption due to AEs occurred in 37% (39/106), with permanent discontinuation in 4.7% (5/106).

Conclusions. The second interim analysis of OLIMPUS confirms that second-line ibrutinib is effective and has a manageable safety profile in real-world MCL. Results are consistent with clinical trials and strengthen the role of ibrutinib in second-line R/R MCL.

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Hodgkin's Lymphoma

MINIABVD AS FIRST-LINE TREATMENT FOR OLDER PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA: EFFICACY AND SAFETY IN A MULTICENTER RETROSPECTIVE COHORT

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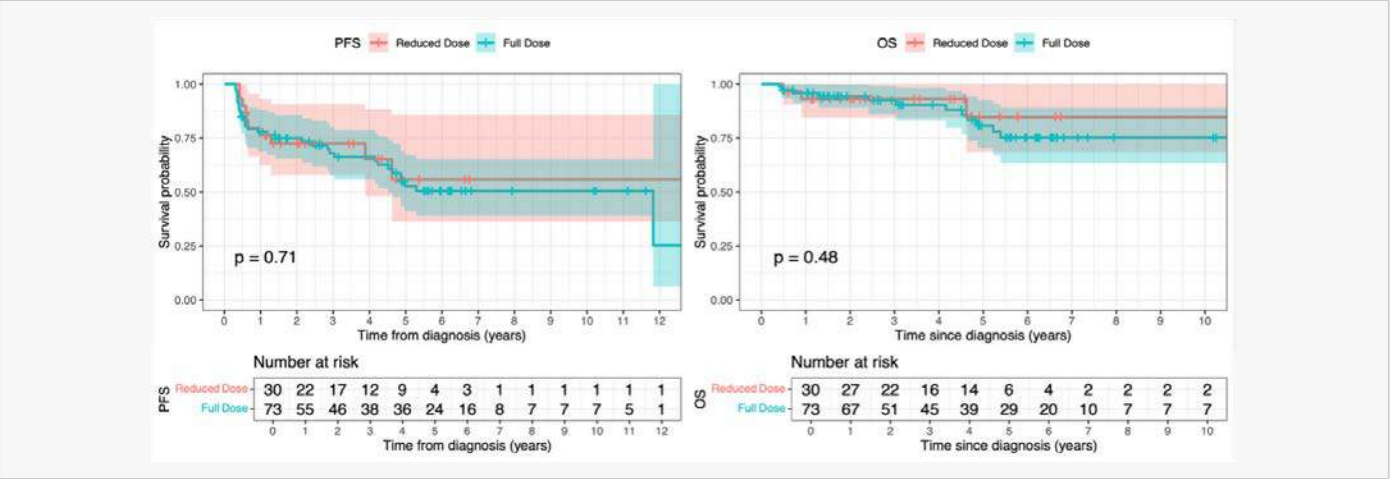
Background. Older cHL patients (pts) have a poor prognosis both because of disease recurrence and treatment (Tx) toxicity. ABVD is the standard Tx, but anthracycline (AC) dose reduction and bleomycin omission are frequent.
Aims To evaluate: the frequency of use and outcomes of reduced-dose (RD) ABVD in older cHL pts; the median AC dose administered in cycle 1 (C1) in RD regimens (defining a "miniABVD" regimen); the prognostic role of geriatric parameters.
Methods. This retrospective multicenter study enrolled ≥60 yo cHL pts treated with ABVD between 2010 and 2023. An AC ≤ 80% from the standard dose (SD) in C1 defined the RD regimen. The primary endpoint was the frequency of use of RD regimens. Secondary endpoints included the median AC dose in cycle 1, CRR, PFS, OS, acute and late toxicities (CTCAE v5.0), and the prognostic impact of the simplified Geriatric Assessment (sGA), which incorporates Activities of Daily Living (ADL), instrumental ADL (IADL), and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Survival was estimated using Kaplan-Meier and Cox models.
Results. 103 pts (median age 70y; 45% stage IV) were included; 31 (significantly older, with higher CIRS-G and greater functional impairment) received RD ABVD. In the RD group, the median AC dose administered in C1 was 18.6 mg/m² (25% reduction from FD). CRR was 79.6% (80.9%/76.7% FD/RD, p=0.5). 3y and 5y PFS/OS were 69.0%/92.6% and 53.2%/81.7%, respectively, with no significant differences between FD and RD groups. Hematologic, pulmonary and cardiac toxicity rates were comparable across groups. Tx-related mortality was 2.9%. In univariate analyses, a higher CIRS-G burden and sGA-frail status were associated with shorter PFS; functional impairment (ADL/IADL) and sGA-frail status strongly predicted worse OS.
Summary/Conclusions. The miniABVD regimen (defined as a RD regimen with 75% of the planned intention-to-treat AC dose in C1) achieved efficacy results comparable to those of the FD ABVD regimen in a subgroup of older cHL pts, characterized by a significantly higher median age, comorbidity burden, and functional impairment. The miniABVD regimen also showed an acceptable safety profile, thus representing an effective and feasible option for pts considered unsuitable for FD Tx. Frailty and comorbidities, rather than chemotherapy dose intensity, emerged as the main determinants of outcome in older pts. Therefore, a comprehensive GA and comorbidity profiling are essential to guide Tx decisions.



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Infections

LAMIVUDINE PROPHYLAXIS FOR PREVENTION OF HEPATITIS B VIRUS REACTIVATION IN HEMATOLOGIC PATIENTS UNDERGOING IMMUNOSUPPRESSIVE THERAPIES: A SINGLE-CENTER EXPERIENCE

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Background. Hepatitis B virus (HBV) reactivation represents a life-threatening complication in hematologic patients receiving immunosuppressive therapy. Current international guidelines (AASLD, EASL, NCCN) recommend entecavir or tenofovir as preferred agents for HBV prophylaxis.

Aim. This single-center retrospective study aimed to evaluate the real-world efficacy of lamivudine prophylaxis in preventing HBV reactivation (HBVr) in anti-HBc-positive hematologic patients undergoing chemotherapy and/or immunotherapy.

Methods. We analyzed data from a prospectively maintained database including 380 hematologic patients diagnosed and followed at SC Ematologia 1 IRCCS Policlinico San Matteo. Eligible patients were those who received immunosuppressive therapy between 2002 and 2025 and who started anti-HBV prophylaxis according to the guidelines available at the time, with lamivudine administered 2 weeks before the initiation of hematologic treatment and continued for 18 months after its completion. Only patients with available HBV serological markers (HBsAg and anti-HBc) were included in the final analysis.

Results. The baseline characteristics of the 380 patients included in the analysis are reported in Table 1. According to the latest EASL guidelines, patients were stratified into three HBVr risk groups: high risk (301/380, 79.2%), intermediate risk (77/380, 20.3%), and low risk (2/380, 0.5%). Overall, 10 out of 380 patients (2.6%) experienced HBVr during follow-up. The 5-years cumulative incidence of HBVr was 3.5% (95% CI: 1.7–6.4%), with an incidence rate of 67.4 per 10000 person-years (95% CI: 32.3–124.0). No statistically significant differences in reactivation rate were observed according to serological pattern, hematologic disease or type of immunosuppressive therapy. At the time of reactivation, median HBV-DNA was 976 IU/mL (range 165-5.831.642 IU/mL). Following reactivation, 7 patients (70%) were treated with entecavir, 2 patients (20%) with tenofovir, and 1 patient (10%) continued lamivudine. All patients achieved complete virological response, defined as undetectable HBVDNA.

Conclusions. This study shows that lamivudine prophylaxis resulted in a low rate of HBVr and was safe in anti-HBc-positive hematologic patients undergoing immunosuppressive therapy. Despite current guideline preferences for newer antivirals, our findings suggest that lamivudine remains a reasonable and well-tolerated option.

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Table 1. Baseline patients' characteristics

Characteristic	Overall population (N = 380)
Sex, n (%)	
Male	234 (61.6%)
Female	146 (38.4%)
Age, years, median (IQR)	67 (59-76)
Risk of HBV reactivation, n (%)	
Low	2 (0.5%)
Intermediate	77 (20.3%)
High	301 (79.2%)
Hematologic diagnosis, n (%)	
Lymphoproliferative disease	230 (60.5%)
Acute Leukemia	52 (13.7%)
Myelodisplasia	12 (3.1%)
Multiple Myeloma	69 (18.2%)
Other	17 (4.5%)
Hematologic therapy, n (%)	
Immunochemotherapy	177 (46.6%)
High dose chemotherapy	43 (11.3%)
Immunotherapy	40 (10.5%)
Chemotherapy	38 (10.0%)
Anthracycline based Chemotherapy	15 (4.0%)
Allogenic Hemopoietic Stem Cell Transplantation	13 (3.4%)
Tyrosine Kinase Inhibitor	8 (2.1%)
T-cell Depleting Therapy	2 (0.5%)
Other	44 (11.6%)
HBV serological status, n (%)	
HBsAg positive	8/380 (2.1%)
Anti-HBc positive	357/380 (93.9%)
Anti-HBs positive	278/380 (73.1%)
Detectable HBV-DNA	21 (5.5%)
Steroid therapy, n (%)	
PDN >2 mg/kg/day ≥14 days	97 (25.5%)
PDN >1 mg/kg/day ≥28 days	124 (32.6%)
Stem cell transplantation, n (%)	
Autologous SCT	57 (15.3%)
Allogeneic SCT	55 (14.6%)

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Infections

CARBAPENEM-SPARING STRATEGIES IN TREATING SECOND FEBRILE EPISODE IN ONCOHEMATOLOGIC PATIENTS UNDERGOING CHEMOTHERAPY OR CELLULAR THERAPIES: A MONOCENTRIC RETROSPECTIVE OBSERVATIONAL STUDY

L. Celona[1], E. Audisio[1], S. Corcione[2], M. Cerrano[1], S. D'Ardia[1], C. Frairia[1], V. Giai[1], E. Santambrogio[1], I. Urbino[1], E. Boscaro[1], F. Catania[1], G. Berutto[1], B. Patarnello[1], C. Dellacasa[1], C. Secreto[1], D. Stella[1], C. Gariazzo[1], A. Busca[1], R. Freilone[1].

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Background. In oncohematologic patients carbapenems are traditionally considered the reference antibiotic treatment for severe Gram-negative infections, particularly in neutropenic patients. However, their use is associated with an increased risk of hospital multiresistant infections. Carba-sparing strategies aim to optimize antimicrobial therapy by reducing selective pressure without compromising outcomes. ECIL-10 guidelines for febrile neutropenia in leukemia highlight the need for a risk-stratified approach, reserving carbapenems for hemodynamically unstable patients or those colonized by resistant pathogens.Aim To analyze the feasibility of carba-sparing strategies for anti-infective therapy in hospitalized oncohematologic patients.

Methods. Retrospective observational study including all hospitalizations of oncohematologic patients in the "Ematologia Ospedaliera" department of "Città della Scienza e della Salute" Hospital (Torino) in 2024. Data on hematological disease, treatment, rectal swab colonization, infection incidence, and antibiotic therapy (duration/type) were collected.

Results. The cohort included 364 patients (229 males, 135 females; mean age 58 years). Hematological therapy received was chemotherapy in 64.6% of cases, cellular therapy in 20.0%, while no specific hematologic therapy in 15.4% of patients, hospitalized for complications. No patients received antibiotic prophylaxis. Infectious complications requiring antibiotic therapy occurred in 229 hospitalizations (63%). Rectal swab screening for multiresistant bacteria was performed in all patients with a low rate of positivity (14% for ESBL-positive bacteria and 3.3% for KPC-producing bacteria). The cumulative incidence was 20.9% for bacteremia, 15% for clinically documented infection and 23.6% for fever of unknown origin (FUO). A second febrile episode occurred in 86 cases and a carbapenem was administered in 61 (70%). A total of 498 carbapenem days of carbapenem therapy (DOT) were administered for second febrile episodes. Notably, 87 DOT (17.5% of total second-line carbapenem use) were prescribed in patients with a final diagnosis of FUO, without hemodynamic instability or documented resistant colonization.

Conclusions. This study highlights and quantifies the inappropriate overuse of carbapenems in the analyzed setting in the treatment of second febrile episodes. Specifically, 17.5% of second-line carbapenem consumption could potentially have been avoided according to ECIL-10 guidelines.

Infections

INFECTION MANAGEMENT IN AN ACCREDITED PRIVATE HOSPITAL IN ONCO-HEMATOLOGY OUTPATIENTS FROM THE EMERGENCY ROOM

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Considering population aging, new therapies and prolonged treatments for many haematological diseases, the care of hematologic patients in an outpatient setting has become the standard of care and the management of complications in this population, frequently infections, represent a challenging issue. As a result, clinically relevant events occurring in this outpatient population may be managed by the family doctor, the hematology clinic or the emergency room according to the severity and the patient risk. A further crucial aspect in the management of haematological patients who access the emergency room is the subsequent transfer to the inpatient wards. We report the experience of an internal medicine ward of a private accreditated hospital as a reference for the admission of haematological patients from various emergency rooms in Rome.

Patient and Methods. Since February 2022 to December 2025, we admitted in our Internal Medicine ward 365 pts (183 M, 182 F), median age of 77 yrs (range 29-98), sent by Emergency Departments. Of the entire cohort, 155 (42%) (89M/66F) were hospitalized for infective complications. In this report we present data of 98 infective episodes occurring in pts affected by MM, MDS, AML and CLL, admitted in our ward. Characteristics of these patients are described in table 1.

Results. Pts with MDS are the oldest of the cohort: 82 yrs vs 76-77 yrs of MM, AML and CLL, considered together. Median hospital stay was 7 day (range 2-30) with longer hospitalization only for the AML (9 vs 7 days). All patients were treated with a combination of broad-spectrum antibiotics. The choice of antibiotics was made on the basis of type of infection, patient's comorbidities, degree of immunosuppression and number of white blood cells or, in the case of sepsis, according to their antibiogram. 52% of pts (51/98) were on active treatment for hematological disease and 47/98 (48%) were in follow-up or at diagnosis. Most pts (68.4%) were sent back to the referral center for further follow-up or to restart specific therapy. Only 14 (14%) were sent to rehabilitation or hospice; 8 pts died from their or additional complications or disease progression during hospitalization. There was good satisfaction from patients with the overall management of the complication.

Discussion and Conclusions. This model of collaboration between the public emergency room and an accredited private hospital has demonstrated positive aspects in terms of quality of care and satisfaction on the part of patients. This shared health protocol appears to improve the care of hematological out-patients by speeding-up diagnostic-therapeutic process and reducing the overload of Hematology Departments. Treatments of MM, CLL, MDS/LMA in old and young pts are increasingly outpatient based. The increased exposure to pathogens due to new medications, careful assessment and prevention of infectious complications is strictly necessary. The increasing number of outpatients attending the hematologic institutions makes the management of complications complex from a logistical point. Our collaborative model between a public facility and an accredited private hospital represents a virtuous example of quality care, cost containment, and emergency room overcrowding management.

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	Entire case history (98 pts)	MM (29 pts)	AML (27 pts)	MDS (22 pts)	CLL (20 pts)
Males/Female	50/29	19/10	19/8	12/10	8/12
Median age (range)	77 (43-93)	77 yrs (56-89)	76 yrs (43-88)	82 yrs (60-93)	77 (59-89)
No treatment/support	47	10	11	19	7
On treatment	51	19	16	3	13
Median Days of hospitalization (Range)	7 (2-30)	7 (2 – 20)	9 (4-30)	6.5 (2-22)	7 (3-18)
Fever of unknown origin	7	5	1	1	0
Pneumonia	55	15	18	10	12
Sepsis	17	4	5	6	2
Others infections	19	5	3	5	6
Death (%)	8 (8%)	2 (6.9%)	3 (11.1%)	1 (4.5%)	2 (10%)
Type of discharge					
At home (%)	67 (68.4%)	19 (65.5%)	17 62.9%)	18 (81.8%)	14 (70%)
Rehabilitation/Hospice))	14 (14.3%)	5 (17.2%)	3 (11.1%)	2 (0.9%)	4 (20%)
Others departments	9	3	4	1	0

MM= Multiple Myeloma; AML= Acute Myeloid Leukaemia, MDS= Myelodysplastic Syndrome; CLL= Chronic Lymphocytic Leukaemia

Infections

IMPACT OF MULTIDRUG-RESISTANT BACTERIA COLONIZATION IN HEMATOLOGICAL PATIENTS: NOT JUST A MATTER OF NEUTROPHILS

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Background. Colonization by multidrug-resistant (MDR) bacteria in hematological patients receiving antineoplastic treatment represents a major clinical challenge, particularly during aplasia, due to the risk of sepsis following bacterial translocation. This risk is traditionally associated with severe (<500/µL) and prolonged (>7 days) neutropenia. However, additional factors may contribute, including underlying disease, type of treatment, specific colonizing pathogens, patient frailty, and the use of invasive medical devices. Moreover, the timing of translocation is critical for optimizing therapeutic strategies, particularly the early initiation of de-escalation approaches (i.e., targeted antibiotic therapy based on known colonization) at the onset of fever.

Aim. The aim of our analysis was to identify clinical and microbiological variables associated with post-colonization outcomes, specifically the risk of bacterial translocation and sepsis-related mortality.

Patients and methods. Patients admitted to our hospital from January 2023 to December 2025 and testing positive for MDR bacteria by molecular swab and/or rectal/pharyngeal culture were observed for 100 days following the date of colonization.

Results. The study population consisted of 60 patients colonized by Klebsiella pneumoniae (68%), Pseudomonas aeruginosa (18%), Acinetobacter baumanii (3%), and other pathogens (11%); affected by acute leukemias (63%); with a central venous (52%) and/or urinary catheter (25%); undergoing antineoplastic chemotherapy (53%) and with severe neutropenia at the date of colonization (55%). All patients (100%) were managed with a de-escalation strategy at the onset of fever. The cumulative incidence of translocation was 29% (Figure 1a), with a median time to translocation of 7.5 days (range: 1-49). Colonization with Pseudomonas aeruginosa emerged as an independent predictor of translocation (HR=0.08; 95%CI:0.023-0.279, p<0.001, Figure 1b), whereas no association was demonstrated with neutropenia, underlying disease, and devices. The risk of death after translocation due to a septic event was double compared to non-translocated patients (34% vs. 17%, p=0.10 (Figure 1c).

Conclusions. In this cohort, neutropenia was not associated with an increased risk of translocation or sepsis-related mortality, likely reflecting the systematic use of early targeted (de-escalation) antibiotic therapy in all colonized patients at fever onset.

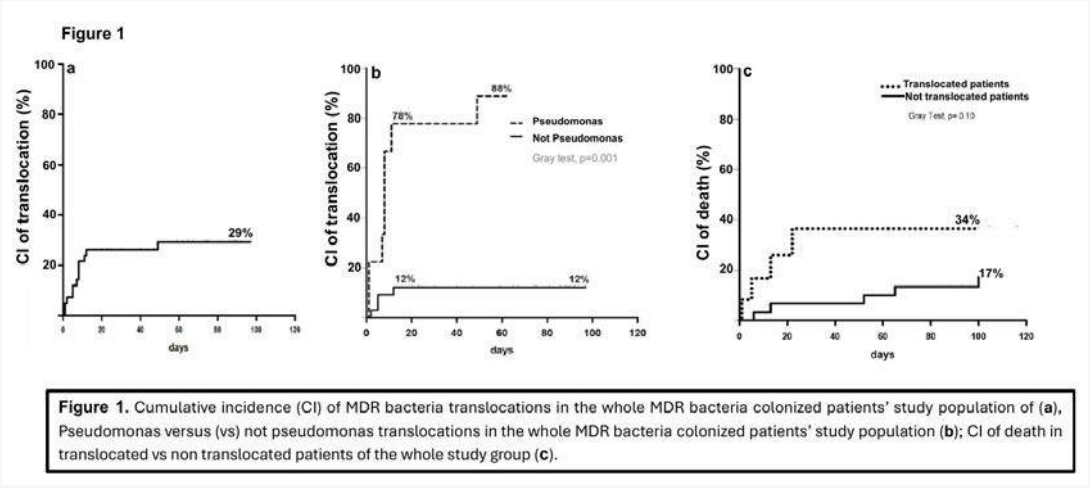

Figure 1. Cumulative incidence (CI) of MDR bacteria translocations in the whole MDR bacteria colonized patients' study population of (**a**), Pseudomonas versus (vs) not pseudomonas translocations in the whole MDR bacteria colonized patients' study population (**b**); CI of death in translocated vs non translocated patients of the whole study group (**c**).

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Red blood cell pathologies

LUSPATERCEPT IMPROVES BONE METABOLISM IN THALASSEMIC PATIENTS: A MULTICENTER BIOLOGICAL AND DENSITOMETRIC STUDY

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Backgroud. Due to osteoporosis, fractures occur in 16 to 49% of patients with transfusion-dependent beta-thalassemia (TDT). The causes of this complication depend upon various factors, mainly iron-chelating therapy, growth hormone reduction and ineffective erythropoiesis. Luspatercept (Lus) is a TGF-beta ligand that stimulates erythropoiesis and is currently used to improve Hb levels in TDT patients. Administration of Lus in animal models induces an increase in bone mass. The aim of our study was to evaluate parameters of bone metabolism in patients affected by TDT treated with Lus.

Materials and Methods. 105 patients (60 F/45 M), aged 19-70 yrs, were enrolled, 57 were treated with Lus (group 1) and 48 did not (group 2). Lus was administered every 21 days, at a dose from 1 to 1.25 mg/kg/day, based on the clinical response. In each group we evaluated serum levels of ionized calcium, C3-C4, IL-6; IL-1β, S100 calcium-binding B, calcitonin, FGF23, osteoprotegerin (OPG), osteocalcin, vitamin D, pentraxin 3 (PTX3), PINP, C-terminal telopeptide of type I collagen (CTX). DEXA scans of the lumbar spine and femoral neck were also performed at baseline, 12, and 24 months.

Results. Among all biomarkers analyzed, the only significant differences we observed were a reduction of CTX (0.32 ± 0.25 vs 0.72 ± 0.45, p=0.004), OPG (1.68 ± 2.94 vs 3.03 ± 2.4, p=0.02) and vitamin D (33.64 ± 13, vs 45.82 ± 19.29, p=0,001), as well as an increase of PTX3 (5798 ± 5089 vs 3513 ± 1749, p=0.005) in group 1 respect to group 2 (Fig.1). After 24 months, Lus treatment led to a measurable densitometric improvement, with femoral T-scores increasing from –1.39 to –0.96 (p=0.0052) and lumbar T-scores from –2.13 to –1.83 (p=0.026). Conversely, the control group showed no significant variation (Fig. 2).

Discussion. The reduction of CTX (a primary marker of bone resorption) indicates that Lus effectively slows down the pathological bone degradation typical of this population. This is further supported by the rise in PTX3 (a marker associated with matrix deposition and bone repair), suggesting an anabolic rebalancing of the bone microenvironment. The known inhibition of OPG by Lus and a possible consumption of Vitamin D, along with DEXA scan results, are consistent with other findings. Our study suggests that Lus may improve bone density and modulates key regulators of bone turnover in TDT patients.

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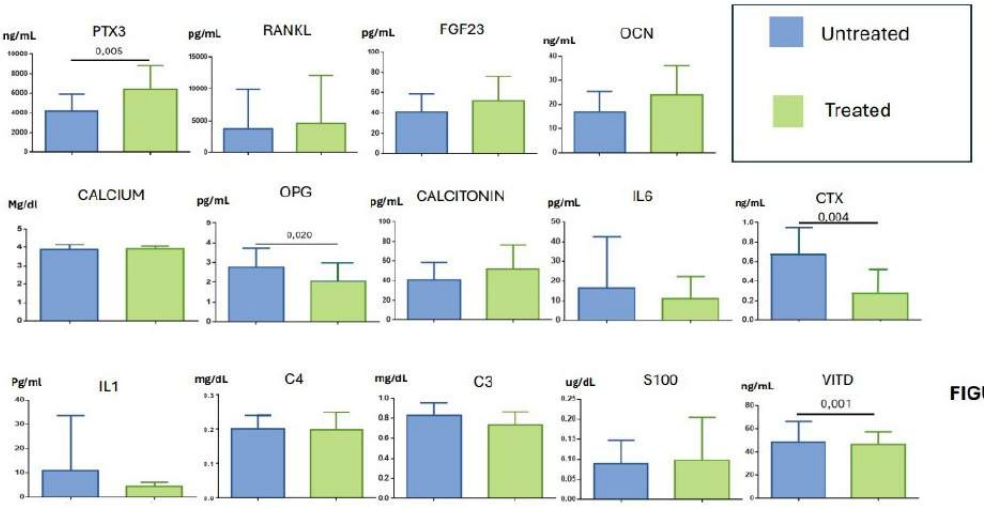

FIGURE 1

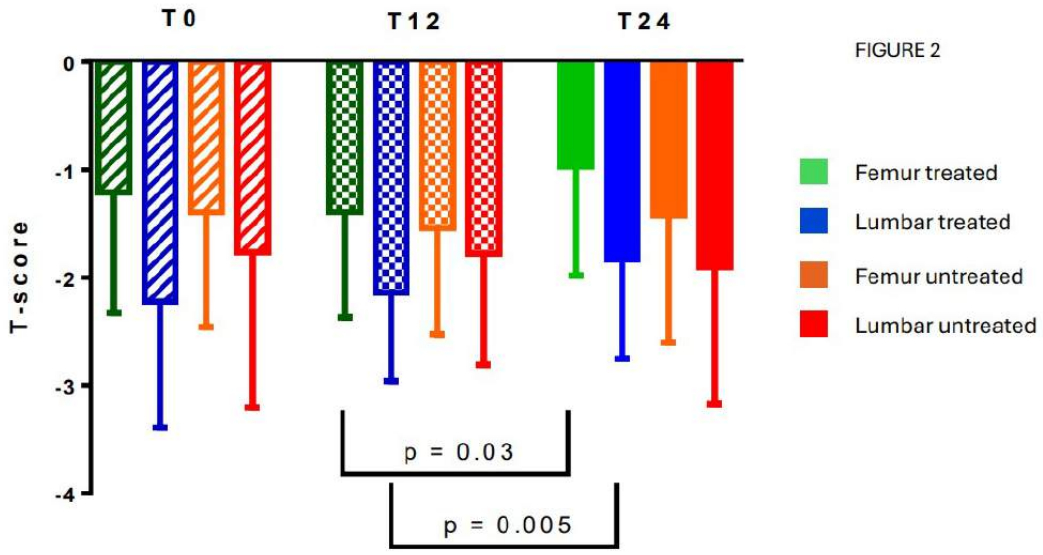

FIGURE 2

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Red blood cell pathologies

REPRODUCTIVE HEALTH AND PREGNANCY OUTCOMES IN WOMEN WITH HEREDITARY HEMOLYTIC ANEMIAS

M. Bortolotti[1], E. Sambruna[2], G. L. Pedone[2|3], P. Bianchi[1], E. Fermo[1], A. Marcello[1], A. Zaninoni[1], C. Vercellati[1], F. Filippi[4], E. Somigliana[4|5], W. Barcellini[1], F. Passamonti[1|2], B. Fattizzo[1|2]

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Hereditary hemolytic anemias (HHAs), are a group of disorders characterized by variable degree of anemia, chronic hemolysis, splenomegaly, gallstones and iron overload. Differently from other more common hereditary anemias, few data about reproductive health are available for HHAs. The aims of this study were to evaluate this aspect in a cohort of women with HHAs followed at our center, through a specifically designed questionnaire submitted to each woman through a face-to-face or telephone interview. Descriptive statistical methods were adopted to analyze data.In the last 15 years we collected a cohort of 241 women with HHAs (163 hereditary spherocytosis, HS; 18 hereditary elliptocytosis, HE; 19 hereditary stomatocytosis, HSt; 16 congenital dyserythropoietic anemias, CDA; 25 pyruvate kinase deficiency, PKD). In this abstract we present preliminary data from the first 60 women (36 HS, 9 CDA, 8 PKD, 4 HSt, 3 HE), for a total of 88 pregnancies (Table1). The mean age at interview was 53±18 yrs. Fifteen patients were splenectomized, one was transfusion dependent and 14 presented an iron overload. Mean age at menarche was 12.5±1.5 yrs, menstrual cycle was regular in 68% of patients [median time between cycles: 28 (14-60) days]. Estrogen-progestin therapy was used in 48% of women with no related thrombotic events. Mean age at menopause was 48.5±4.5 yrs.Fourteen women never tried to conceive. The psychological burden of the heritability of the disease was reported as a major obstacle to seek a pregnancy. Among the others, 89% got spontaneously pregnant, 4% conceived through medically assisted reproduction, whilst 7% were unable to conceive. Mean age at 1° child was 27±5 yrs. Infertility (>12 months of unsuccessful research) was diagnosed in 9 patients (12% in HS and 44% in CDA).Maternal complications occurred in 13% of pregnancies and transfusions were necessary in 18%, reaching 50% in PKD; no thrombosis occurred with thrombotic prophylaxis performed only in 13% of pregnancy. Fetal complications occurred in 23% of pregnancies, with prolonged neonatal jaundice the most frequent one. Miscarriage rate was 15%.Preliminary results of this study suggest that fertility is generally preserved in HHAs but appears more impacted in CDAs. Maternal and fetal outcomes were overall favorable except for the increased transfusion need, in particular in PKD women. Broadening the study, we hope to give more insights about reproductive health in women with these rare disorders.

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	All	Hereditary membrane disorders (HS, HSt, HE)	CDAs	PKD
n° of women	60	43	9	8
n° of pregnancy	88	63	13	12
Infertility, n (%)	9 (15)	5 (12)	4 (44)	0
Outcome of pregnancies, n (%)				
- Childbirth	71 (81)	51 (81)	10 (77)	10 (84)
- Miscarriage	13 (15)	10 (15)	2 (15)	1 (8)
- Voluntary termination of pregnancy	3 (3)	2 (3)	0	1 (8)
- Ectopic pregnancy	1 (1)	0	1 (8)	0
Maternal complications, n (%)				
- Worsening of anemia with transfusion need	13 (18)	6 (12)	2 (20)	5 (50)
- Preeclampsia	3	2	0	1
- Biliary colic	2	1	0	1
- Hypothyroidism	2	1	0	1
- Renal colic	1	1	0	0
- Gestational diabetes	1	1	0	0
- Phlebitis	1	1	0	0
- Hyperbilirubinemia and/or liver enzymes elevation	2	1	0	1
Fetal complications, n (%)				
- Premature birth or small for gestational age	6	4	1	1
- prolonged neonatal jaundice	6	5	0	1
- Fetal ascites	2	2	0	0
- Congenital malformations	2	2	0	0

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Red blood cell pathologies

SAFETY AND EXPECTED BENEFIT DRIVE GENE THERAPY ACCEPTANCE IN B-THALASSEMIA AND SICKLE CELL DISEASE: A MULTICENTER MEDIATION ANALYSIS

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Background. Gene therapy is an emerging potentially curative option for β-thalassemia and sickle cell disease, but patient acceptance may depend on perceived safety, expected benefit and treatment-related risks.

Aims. To evaluate the determinants of willingness to undergo gene therapy among young adults with hereditary hemoglobinopathies.

Methods. A cross-sectional survey was conducted in 14 centers of the Sicilian Regional Network for Thalassemia and Hemoglobinopathies (RRTE) between June 2025 and January 2026. Adult patients aged 18-35 years completed a structured questionnaire using 6-point Likert scales. Composite indices assessed perceived information, safety, expected benefit, oncological and infertility risk, health status, emotional concern and willingness to undergo gene therapy. Internal consistency was assessed by Cronbach's alpha. Predictors of acceptance were explored by multivariable linear regression and bootstrap mediation analysis (5,000 resamples).

Results. Overall, 105 patients were included: 88 with β-thalassemia (83.8%) and 17 with sickle cell disease (16.2%). Mean age was 27.6 +/- 5.0 years; 50.5% were female. Perceived safety and expected benefit showed high internal consistency (Cronbach's alpha 0.87 and 0.90). No significant differences emerged by diagnosis or sex. In multivariable analysis, perceived safety (β=0.45, p<0.001) and expected benefit (β=0.43, p<0.001) were independent predictors of willingness to undergo gene therapy, explaining 66% of its variance. Perceived risks, emotional concern, sex and diagnosis were not independently associated with treatment willingness. Mediation analysis showed that expected benefit partially mediated the association between perceived safety and acceptance (indirect effect 0.39, 95% CI 0.25-0.53; p<0.001), accounting for 43% of the total effect (Figure 1). The small number of patients with sickle cell disease limits subgroup interpretation.

Conclusions. In young adults with β-thalassemia or sickle cell disease, gene therapy acceptance appears to be driven mainly by cognitive appraisal of safety and individual expected benefit. Counselling should therefore go beyond eligibility and procedural information, supporting a clear, balanced and personalized discussion of safety and realistic treatment benefit to promote shared decision-making.

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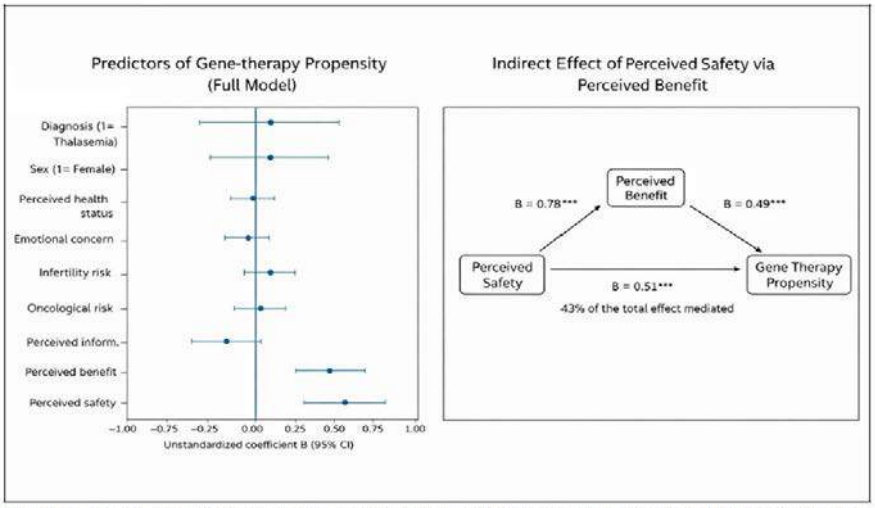

Predictors of gene therapy propensity and mediation model showing the indirect effect of perceived safety via perceived benefit

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Red blood cell pathologies

EARLY COMPLETE RESPONSE WITHIN 60 DAYS AND RETICULOCYTE DYNAMICS PREDICTS THE DURATION OF STEROID'S RESPONSE IN WAIHA

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Introduction. Steroids is the standard first-line therapy for warm Autoimmune Hemolytic Anemia (wAIHA), yet relapse is frequent. Guidelines differ on optimal full-dose duration and tapering, and whether treatment duration or early response kinetics better predict long-term outcome remains unclear.We evaluated the impact of full-dose steroid duration on relapse-free survival (RFS) and whether early hemolytic response kinetics identify patients at differential relapse risk.

Methods. We retrospectively analyzed consecutive wAIHA patients treated with first-line steroids alone between 2017 and February 2026. Out of 124 patients, 13 and 14 were excluded because steroids and immunosuppressive drugs or rituximab, 10 had incomplete data, 26 cold agglutinin disease. Complete response (CR) was defined as hemoglobin > 120 g/L with normalization of bilirubin, LDH, haptoglobin andreticulocytes. CR60 was defined as CR within 60 days from onset, selected as a landmark to reflect early post-induction assessment. The primary endpoint was RFS. Time-to-event outcomes were analyzed using Kaplan-Meier and Cox regression; predictors of CR60 were assessed by logistic regression.

Results. Among 47 included patients, the median age was 75 years (56-80), 60% were females, 62% had secondary wAIHA, 47% were DAT IgG without C3d. Median full-dose prednisone duration was 21.5 days (Range 5-58). After a median follow-up of 25 months (95%CI 20-40), median RFS was 8 months (95%CI 2.5-20). Overall, 65% (30/46) achieved CR (median time to CR: 61 days, 95%CI 40-114). Full-dose duration (>21 days), DAT profile and secondary disease were not associated with RFS. CR achievement significantly reduced relapse risk (HR 0.29, 95%CI 0.13-0.63, p=0.002). CR60 identified distinct prognostic groups: 24--month RFS was 56% vs 35% in non-CR60 patients (Figure 1, HR 0.32, 95%CI 0.10-0.96, p=0.042). Early reticulocyte normalization (<60 days), but not haptoglobin kinetics, strongly correlated with CR60 (OR 39.0, 95%CI 6.3-769, p=0.001) and CR at any time (OR 5.67, 95%CI 1.33-24.11, p=0.019).

Conclusions. Full-dose steroid duration does not impact RFS in first-line wAIHA. Early reticulocyte normalization predicts CR within 60 days which identifies patients with lower relapse risk. These findings shift the focus from treatment duration to early response quality, suggesting a 60-day clinically actionable landmark for earlier therapeutic escalation in poor responders. Prospective validation is warranted

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Infections

INCIDENCE OF MULTIDRUG-RESISTANT ORGANISMS INFECTIONS AND ROLE OF MICROBIOLOGICAL SURVEIL-LANCE IN PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Introduction. Bacterial infections represent a major complication in patients undergoing hemato-poietic stem cell transplantation (HSCT), especially during the pre-engraftment phase. The emer-gence of multidrug-resistant organisms (MDRO) has increased morbidity and mortality. This study aimed to evaluate the incidence of febrile neutropenia and microbiologically documented infections (MDIs) and to investigate the role of MDRO colonizations comparing culture and molecular-based methods.

Methods. This retrospective study included 77 adult patients undergoing autologous or allogeneic HSCT between 2023 and 2024. All patients underwent rectal swab screening for MDRO coloniza-tions with culture methods and weekly monitoring. 52 patients were also evaluated with molecular techniques. Clinical, microbiological, and therapeutic data were analyzed using descriptive and sta-tisticalmethods.

Results. 30 patients (39%) were colonised by MDRO (14 E. Coli ESBL, 6 K. Pneumoniae KPC, 5 K. Pneumoniae ESBL, 3 Enterococco VRE, 2 Ps. Aeruginosa carbapeneme-resistant). Among 52 patients tested with molecular and cultural methods,18 (35%) were identified as MDRO carriers. The both methods were concordant in 46 cases (88%) and discordant in 6 (12%). Colonization pre-dicted subsequent MDRO infections in 44.4% of cases with cultural methods and 50% with molec-ular techniques(p NS). Febrile neutropenia (FN) occurred in 64 patients (83%), 38% were MDIs. MDRO were identified in 15 cases (63%): 7 K. Pneumoniae KPC, 3 E. Coli ESBL, 4 Ps Aeruginosa VIM, 1 methcillin-resistant Staph. Aureus (MRSA).First-line empirical antibiotic therapy (EAT) was piperacillin/tazobactam–based in 37 cases (58%). Ceftazidime-Avibactam (CAZAVI) or Cefidero-col were administered in 13% and 3% of cases, respectively. In multivariate analysis , MDIs were more frequent in allogeneic HSCT (67% vs 31%) and in heavily pre treated patients (33% vs 2%) p 0.03.Transplant-related mortality (TRM) +30 was 8% (6 patients who underwent alloHSCT). TRM +1 year was 30% in patients who had MDI (30% vs 1% in patients without MDI, p0.001),Figure.1.

Conclusions. In HSCT, MDIs and MDRO colonisation is associated to a higher mortality. In our study MDIs were more frequent in allo-HSCT and heavily pre patients and was associated to a higher TRM. MRDO colonisation was predictive of MDIs in at least half of these. Culture and mo-lecular-based methods were concordant in 80% of patients.

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INFECTIONS

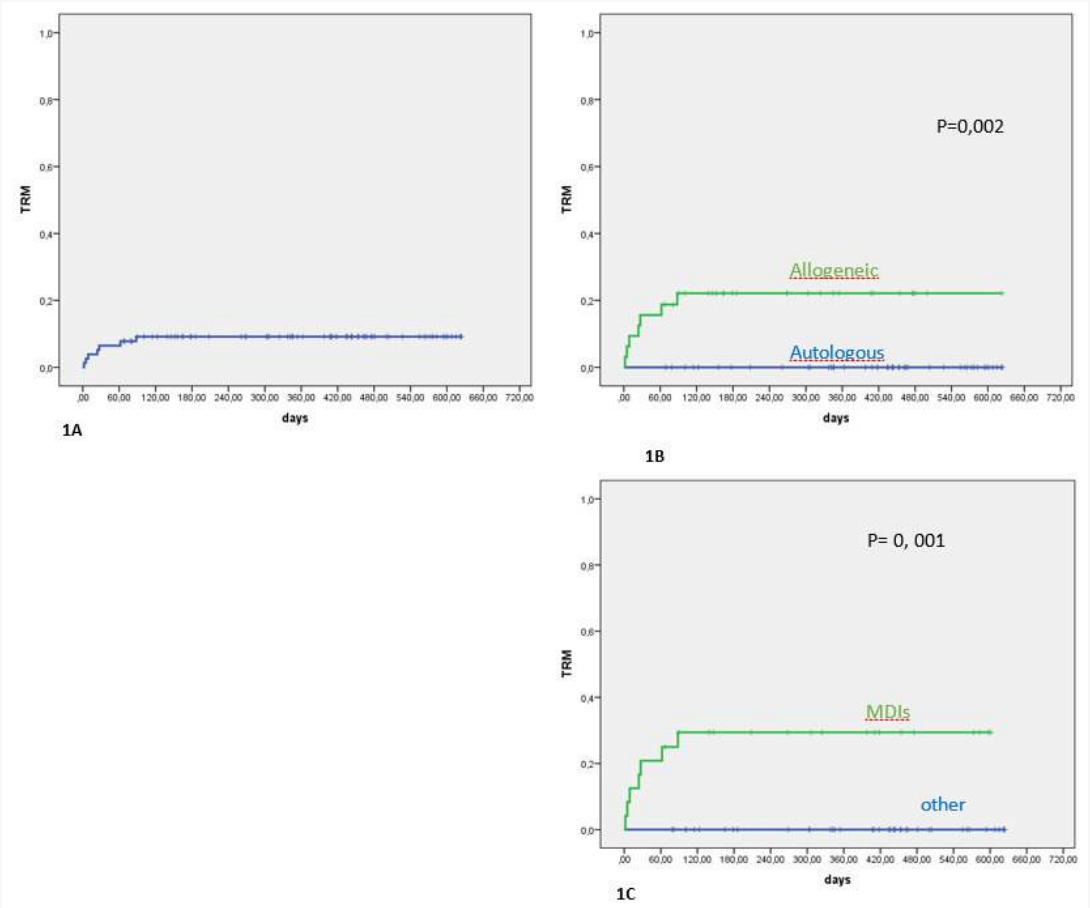

Figure 1: TRM of patients; **1A:** overall; **1B:** in relation to the type of transplant; **1C:** in relation to the presence of microbiologically documented infections (MDIs).

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Red blood cell pathologies

STANDARDIZED FLOW CYTOMETRIC QUANTIFICATION OF CIRCULATING ERYTHROID PRECURSORS AS BIOMARKERS OF INEFFECTIVE ERYTHROPOIESIS IN TRANSFUSION DEPENDENT BETA THALASSEMIA

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Ineffective erythropoiesis (IE) is a hallmark of transfusion dependent beta thalassemia (TDT), but its direct assessment in clinical practice remains limited. Circulating erythroid precursors (CEPs) may represent a minimally invasive marker of erythropoietic stress.We performed standardized multiparametric flow cytometry, based on an EuroFlow-oriented approach, on peripheral blood samples from TDT patients (n=31) and healthy controls (n=11). Erythroid precursors were identified as CD45dim CD71+ CD235a+ cells and classified into polychromatic (PolyE) and orthochromatic erythroblasts (OrthoE).Healthy controls showed negligible levels of CEPs (CD45dim 0.002±0.004%), consistent with the absence of circulating erythroid precursors under physiological conditions. In contrast, TDT patients showed a clear expansion of these populations (CD45dim 0.83±1.9% in ICT=0 and 0.89±2.7% in ICT=1; p<0.001). OrthoE represented the predominant circulating population (0.82±1.9% and 0.87±2.6% vs 0.002±0.004% in controls; p<0.001), while PolyE, undetectable in controls, were detectable in TDT patients (0.01±0.01%; p=0.019).CEPs significantly correlated with markers of erythropoietic activity, including reticulocyte count and erythropoietin levels (p<0.001), and showed an inverse correlation with Ret-He. Overall, these data indicate that CEPs reflect both ineffective erythropoiesis and erythropoietic drive.Flow cytometric quantification of CEPs provides a robust, standardized and minimally invasive laboratory approach to assess ineffective erythropoiesis in TDT and may represent a clinically useful tool for disease monitoring and evaluation of treatment response. CEPs showed a clear discriminatory ability between TDT patients and healthy controls, supporting their potential role as diagnostic biomarkers. This approach may also enable dynamic monitoring of erythropoietic activity and early assessment of response to disease-modifying therapies. These findings support the integration of CEPs quantification into routine laboratory workflows, highlighting the potential of flow cytometry to bridge advanced cellular analysis with clinically actionable biomarkers in hematology.

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Red blood cell pathologies

LEUKEMIC RISK AFTER LONG-TERM HYDROXYUREA THERAPY IN SICKLE CELL DISEASE: AN INTEGRATED MORPHOLOGIC, CYTOGENETIC AND GENOMIC ASSESSMENT

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Background. Hydroxyurea remains the cornerstone disease-modifying treatment for sickle cell disease. However, the potential leukemogenic risk associated with very prolonged exposure continues to be debated, particularly in patients treated for more than two decades. Evidence combining bone marrow morphology, conventional cytogenetics and high-resolution genomic analyses in this setting is still limited. Moreover, the relative contribution of hydroxyurea exposure, chronic inflammatory and hemolytic stress, clonal hematopoiesis, and inherited predisposition to myeloid transformation remains incompletely defined.

Aims. This pilot study aimed to investigate marrow features, cytogenetic abnormalities and clonal molecular profiles in patients with sickle cell disease receiving long-term hydroxyurea, with particular focus on those exposed to treatment for 20 years or longer.

Methods. We conducted a single-center pilot analysis including 15 patients with sickle cell disease aged over 50 years and treated with hydroxyurea. Patients were stratified according to treatment duration: less than 20 years of exposure in 4 cases and 20 years or more in 11 cases. Bone marrow morphology, conventional karyotyping, array-CGH and targeted next-generation sequencing, including Indel and SNP calling, were performed. Analyses were descriptive. Authorization for the retrospective study was obtained from the Institutional Review Board.

Results. Among patients treated with hydroxyurea for at least 20 years, median bone marrow cellularity was 64%. Megakaryocytic dysplasia or atypia was observed in 8 of 11 patients, corresponding to 73% of this subgroup. Two cases of myeloid transformation were documented, both occurring in patients with hydroxyurea exposure of 20 years or longer. One patient developed a myelodysplastic neoplasm with excess blasts and was treated with decitabine, while another developed MDS/AML with marrow fibrosis and carried a likely pathogenic TP53 variant, consistent with a high-risk CHIP-associated driver.Targeted NGS revealed heterogeneous clonal patterns across the cohort. Detected variants included JAK2 V617F, with a variant allele frequency of 15%, as well as TP53 and BRCA2 variants. Additional variants were also found in genes not typically associated with classical CHIP, including PRSS1, HFE, CDCA8 and NCOA3. One clinically stable patient carried both JAK2 and BRCA2 variants without evidence of morphological disease progression.Of note, the patient with excess blasts had a sister showing an identical NGS profile despite shorter hydroxyurea exposure, below 20 years, and no hematologic transformation. This finding suggests a possible familial predisposition to clonal hematopoiesis or clonal evolution. Overall, prolonged hydroxyurea exposure was not associated with a clear increase in variant burden, nor with a consistent pattern of copy-number alterations or structural genomic complexity.

Conclusions. In this pilot cohort of older patients with sickle cell disease, very long-term hydroxyurea exposure was associated with isolated cases of myeloid transformation, but not with a reproducible genomic signature suggestive of cumulative treatment-related instability. The coexistence of CHIP-related drivers, heterogeneous molecular findings and familial mutational concordance supports the hypothesis that intrinsic clonal susceptibility, acting within the chronically inflamed and stress-activated hematopoietic environment typical of sickle cell disease, may play a more relevant role than hydroxyurea duration alone.These findings suggest that hydroxyurea may act more as a selective pressure on pre-existing or emerging clones than as a direct mutagenic trigger. Prospective longitudinal studies integrating marrow evaluation, molecular profiling and inflammation-related biomarkers are needed to better define leukemic risk and to move beyond treatment duration alone as a marker of risk stratification.

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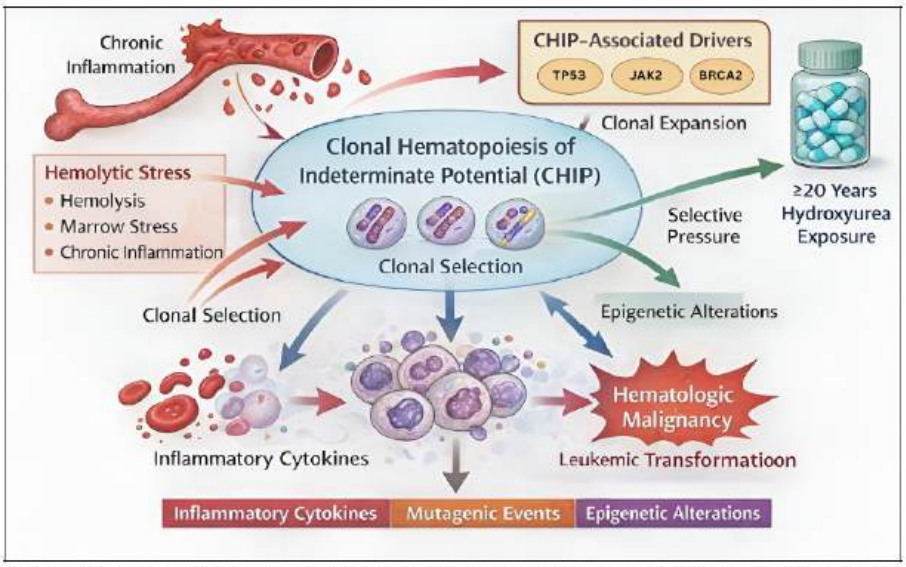

Integrated conceptual model of leukemic risk after ≥20 years of hydroxyurea exposure in SCD. Chronic inflammation, hemolytic/marrow stress and CHIP-associated drivers may promote clonal evolution; hydroxyurea may act as selective pressure rather than a direct mutagenic trigger.

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Red blood cell pathologies

DAPAGLIFLOZIN AS A POTENTIAL INTEGRATIVE THERAPY FOR CHRONIC ANEMIA IN B-THALASSEMIA: UNEXPECTED EMERGING EVIDENCE ON RED CELL AND IRON METABOLISM A MONOCENTRIC EXPERIENCE

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Introduction. Dapagliflozin (DAPA), a sodium-glucose transport protein 2 (SGLT2)- inhibitor, is not a standard treatment for β-thalassemia (Thal) but is increasingly used for common comorbidities such as type 2 diabetes, heart failure,and chronic kidney disease . Recent evidence (DELIGHT trial) suggests potential organ-protective effects in Thal patients, who are exposed to chronic iron overload and anemia.Additionally, SGLT2 inhibitors may influence erythropoiesis and iron metabolism, increasing EPO levels, stimulating red blood cell production.

Materials and Methods. We conducted a retrospective analysis of 8 transfusion-dependent β- Thal patients treated with DAPA 10 mg at our Center, followed over the period 2000-2026. Three patients were excluded from statistical analysis due to short follow-up (only 4 months).Hemoglobin (Hb) levels, renal function, transfusion interval, and ferritin were evaluated. One patient received the fixed combination metformin/dapagliflozin (Xigduo). Outcomes were compared over 110 weeks before and after treatment initiation. Statistical analysis was performed using an independent two-sample t-test ($p < 0.05$).

Results. DAPA use was associated with a reduction in transfusion burden, an increase in transfusion interval (mean +13 days), and higher pre-transfusion Hb levels (+1.75 g/dL over the last 2 years compared with the previous 2 years). One patient with Thal intermedia achieved transfusion independence after 76 weeks. Ferritin levels significantly decreased (median −350 ng/mL), likely also reflecting reduced transfusion requirements. The albumin/creatinine ratio decreased (mean 44 mg/g), suggesting a nephroprotective effect. One patient with a severe aortic stenosis, died due to probable cardiac arrhythmia. The drug was well tolerated, with no significant adverse events.Discussion: DAPA (10 mg) appears to improve erythropoietic parameters (Hb, red blood cells count, hematocrit) and iron metabolism in β-Thal patients. Caution is warranted regarding the risk of urinary tract infections. These findings suggest a potential additional role of SGLT2 inhibitors in reducing organ damage and transfusion burden.

Conclusions. The small sample size, short duration, and its retrospective nature limit our study's ability to draw definitive conclusions. However, the consistency with emerging data in other populations supports a potential novel therapeutic approach in β-Thal. Larger prospective studies are needed to confirm these findings and clarify underlying mechanisms.

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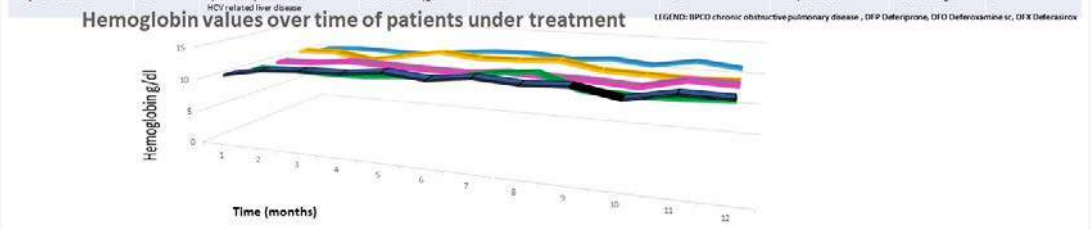
TABLE 1: CLINICAL AND LABORATORY FEATURES OF PATIENT COHORT TREATED WITH DAPAGLIZOLIM

DIAGNOSIS	AGE	COMORBIDITIES	GENOTYPE	ETHNICITY	Sex	Iron chelation	Blood group	Physician prescription	PATIENT NUMBER
Intermedia ß-thalassemia	62 years old	Splenectomy,BPCO, Nocturnal Apnoeas , Restrictive pulmonary disease, Ischemic heart attack Cardiac stent , Gastritis	IVS 1-6	Caucasian	M	DFP	O Rh pos	Cardiologist	1
Hereditary spherocytosis=Ilete microcytemia	73 years old	Aortic stenosis, Diabetes ,BPCO Bile lithiasis, Cholecystectomy	NA 3 Band levels reduced	Caucasian	F	DFP	B Rh pos CCee kk	Cardiologist	2
Major ß-thalassemia	55 years old	Splenectomy, Bile lithiasis Cholecystectomy ,Pulmonary hypertension, Atrial fibrillation	NA	Caucasian	F	DFO		Cardiologist	3
Intermedia ß-thalassemia	79 years old	BPCO (IV stage),Chronic congestive heart failure, Chronic respiratory failure, Bile lithiasis, Cholecystectomy Splenectomy	Cod 39 plus alpha tripled	Caucasian	M	DFX	Ab Rh neg	Cardiologist	4
Major ß-thalassemia	51 years old	Diabetes, Splenectomy, Bile lithiasis Cholecistectomy, Previous transfusional reactions, Hypotiroidism	Cod 39 homozygosis	Caucasian	F	DFX	A Rh POS CCDee kk	Diabetologist	5
Major ß-thalassemia	51 years old	Bile lithiasis, Cholecistectomy, Chronic congestive heart failure Ischamic stroke, Splenectomy ,Ectopic erytropoiesis , Diabetes	IVS II 745	Caucasian	M	DFO	A Rh Pos CcDee kk	Diabetologist	6
Major ß-thalassemia	61 years old	Diabetes,Pulmonary hypertension, Splenectomy, Hypotiroidism, Pulmonary embolism	ND G6PDH deficiency	Caucasian	F	DFO	O Rh pos	Our Center	7
Major ß-thalassemia	63	Splenectomy HCV related liver disease	Cod 39 homozygosis	Caucasian	F	DFO	A Rh pos CcDeekk	Endocrinologist	8

LEGEND: BPCO chronic obstructive pulmonary disease , DFP Deferiprone, DFO Deferoxamine sc, DFX Deferasirox



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Myelodysplastic syndromes

LONG-TERM OVERALL SURVIVAL AND SAFETY OUTCOMES FROM THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 IMERGE TRIAL OF IMETELSTAT FOR LOWER-RISK MYELODYSPLASTIC SYNDROMES

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In the primary analysis of the Phase 3 IMerge trial (NCT02598661), IME showed greater ≥8-wk, ≥24-wk, and ≥1-y (primary, secondary, and post hoc endpoints, respectively) red blood cell (RBC) transfusion independence (TI) vs PBO, but data were immature to assess survival. Here, we present long-term safety, time to acute myeloid leukemia (AML) progression, median OS (mOS), and progression-free survival (PFS). Patients (pt) with LR-MDS RBC transfusion-dependent anemia (TD), relapsed or refractory to/ineligible for erythropoiesis-stimulating agents were randomized to 7.1 mg/kg IME active dose or PBO.At data cutoff (05/10/2025), median follow-up was 45 mo for 118 IME-treated pts and 60 PBO pts in the intention-to-treat (ITT) population. Subsequent anticancer therapy (tx) was received by 57 (48.3%) of 118 IME-treated pts and 35 (59.3%) of 59 PBO pts in the safety analysis set, with 41 (34.7%) and 18 (30.5%), respectively, receiving luspatercept, and 12 (10.2%) and 12 (20.3%), respectively, receiving a hypomethylating agent (HMA). No new safety signals emerged; 2 pts in the IME group and 1 pt in the PBO group died from adverse events (sepsis, myocardial infarction, and aortic stenosis, respectively) ≤30 days of their last dose. Progression to AML remained low at 1.7% for IME vs 3.3% for PBO (hazard ratio [HR], 0.45 [95% CI, 0.06-3.23]). In the ITT population, mOS (95% CI) was 47.8 mo (38.3-not estimable [NE]) for IME and 44.8 mo (37.4-NE) for PBO (HR, 0.82 [95% CI, 0.48-1.38]). Censoring at start of subsequent tx yielded an HR of 0.84 (95% CI, 0.37-1.94), with HRs of 0.76 (95% CI, 0.41-1.41) and 0.83 (95% CI, 0.47-1.48) when censored only for subsequent luspatercept or HMA, respectively. Among IME-treated pts, mOS was longer for responders achieving ≥8-wk, ≥24-wk, ≥1-y RBC-TI, or hemoglobin rise ≥1.5 g/dL lasting ≥8 wk, vs nonresponders; results were maintained when censored for subsequent tx. Subgroup mOS analyses generally favored IME over PBO regardless of ring sideroblast or International Prognostic Scoring System status, and in other subgroups.In summary, although the analysis was not powered for statistical significance, IME resulted in a favorable trend in mOS, PFS, and time to progression to AML vs PBO. OS favored IME vs PBO in most subgroups, and mOS was longer in IME responders vs nonresponders. The survival benefits with IME were maintained in pts who received subsequent tx. These analyses support the clinical benefit of IME in pts with RBC-TD LR-MDS.

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Myelodysplastic syndromes

ENERGETIC FAILURE OF HEMATOPOIESIS: PRELIMINARY EVIDENCE OF MITOCHONDRIAL AND GLYCOLYTIC DEFECTS IN PEDIATRIC IBMFS AND MDS

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Introduction. Altered utilization of key energy substrates, particularly affecting the balance between glycolysis and mitochondrial oxidative phosphorylation, has been reported in rare hematological disorders of childhood such as inherited bone marrow failure syndromes (IBMFS) and myelodysplastic syndromes (MDS). However, the metabolic phenotype of hematopoietic cells in these conditions remains poorly defined.

Aim. To characterize the metabolic profile of hematopoietic cells in IBMFS and MDS pediatric patients.

Methods. Bone marrow and peripheral blood mononuclear cells (PBMCs) from IBMFS and MDS patients were isolated by Ficoll density gradient. Mitochondrial and glycolytic metabolism, as well as cellular energetic phenotype, were assessed using the Seahorse XFe96 platform. Peripheral blood from age- and sex-matched healthy subjects and bone marrow samples from patients with autoimmune thrombocytopenia were used as controls.

Results. Samples from seven Shwachman-Diamond syndrome (SDS), two Fanconi Anemia (FA), and three pediatric MDS patients were analyzed. Compared with controls, bone marrow cells from IBMFS and MDS patients showed significantly reduced basal and maximal mitochondrial oxygen consumption rate ($p \leq 0.0001$), spare respiratory capacity ($p \leq 0.0001$ and $p=0.0001$, respectively), and ATP production ($p=0.001$; $p=0.01$). Basal and compensatory glycolysis were also markedly impaired in patients ($p \leq 0.0001$). No significant differences in mitochondrial or glycolytic metabolism were observed between IBMFS and MDS. The total ATP production was reduced in both groups, affecting both mitochondrial ($p=0.0001$) and glycolytic ($p \leq 0.0001$) pathways, although glycolytic ATP production was higher in IBMFS than in MDS ($p=0.01$). In contrast, PBMCs from SDS patients showed increased mitochondrial respiration ($p \leq 0.0001$), compensatory glycolysis ($p=0.01$), and total ATP production ($p \leq 0.0001$), compared with controls.Discussion BM cells in IBMFS and MDS exhibit markedly impaired mitochondrial respiration and glycolytic activity, suggesting a state of energy deficiency that may compromise cellular function and survival, especially under oxidative stress. These findings support a contributory role for metabolic dysfunction in disease pathogenesis and suggest potential target for metabolic intervention. The increased ATP production observed in PB cells, potentially reflecting cellular activation, proliferation, or adaptive functional responses, warrants further investigation.

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Acute myeloid leukemia

ALIDHE: A PHASE 3B STUDY ASSESSING IVOSIDENIB + AZACITIDINE IN ADULTS WITH NEWLY DIAGNOSED *MIDH1* ACUTE MYELOID LEUKAEMIA WHO ARE INELIGIBLE FOR INTENSIVE INDUCTION CHEMOTHERAPY

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Background. Ivosidenib (IVO) is an oral targeted small molecule inhibitor of isocitrate dehydrogenase 1 (*IDH1*) mutations (*mIDH1*) with activity in patients (pts) with AML. The AGILE trial demonstrated that IVO + azacitidine (AZA) provides long-term clinical efficacy with a favourable safety profile in pts with newly diagnosed mIDH1 (nd *mIDH1*) AML who are ineligible for intensive chemotherapy (ICIE). ALIDHE is a single-arm, open-label phase 3b study conducted in a real-world setting in ICIE pts with nd *mIDH1* AML (NCT05907057).

Methods. ALIDHE is enrolling pts aged ≥18 years with *mIDH* AML. Treatment (tx) comprises IVO (500 mg) once daily and AZA (75 mg/m2/day) for 7 days in 28-day cycles. The primary aim is to assess the safety of IVO+AZA. Secondary endpoints include event-free survival (EFS) and disease response. Measurable residual disease (MRD; optional consent) and biomarker correlations with clinical outcomes are exploratory endpoints. ALIDHE is a post-approval study, designed with the Acute Leukemia Advocates Network, putting patient needs, experiences, and perspectives first.

Results. At Nov 3, 2025 (data cut off), 124 pts from 9 countries had been enrolled and treated; 84 pts remained on tx. Median age was 75.5 years; 62.1% of pts had de novo AML. Median tx duration was 6.2 months (IQR: 2.7; 11.3). Overall, IVO+AZA had a favourable safety profile (Table 1). Fifteen (12.1%) pts had grade ≥2 differentiation syndrome and 10 (8.1%) had grade ≥3 QT prolongation, neither of which led to tx discontinuation.The objective response (OR) rate in the overall patient population was high (62.9%); rates of complete remission (CR) and CR with partial haematologic recovery were 46.0% and 8.1%, respectively. Responses were observed across the full range of co-occurring mutations, including CRs in 76.2% of pts with *NPM1m* and 30.3% in pts with mutations in the RTK pathway. Median durations of OR and CR were 18.2 months and 16.1 months, respectively. Over 24 cycles, haemoglobin and platelet counts increased, neutrophil counts stabilised, and mean bone marrow blasts decreased. During tx, 103 (83.1%) and 78 (62.9%) pts were red blood cell and/or platelet transfusion-free for ≥8 and ≥16 weeks, respectively. Of the 25 MRD-evaluable pts in CR, 11 (44.0%) were MRD-negative by flow cytometry, with >80% reaching MRD negativity by cycle 6.Summary/conclusion: These data from the ongoing ALIDHE study confirm the IVO+AZA efficacy and safety profile seen in the pivotal AGILE study.

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Table 1. Safety outcomes (N=124)

TEAEs	n (%)
Any TEAE	118 (95.2)
Grade ≥3 TEAE	105 (84.7)
Treatment-related TEAEs (IVO and/or AZA)	94 (75.8)
Serious TEAEs	72 (58.1)
TEAEs leading to death[a]	8 (6.5)[a]
TEAEs leading to discontinuation of IVO+AZA	8 (6.5)
AESI	24 (19.4)
Grade ≥2 differentiation syndrome	15 (12.1)
Grade ≥3 QT prolongation	10 (8.1)

[a]None were considered related to treatment.

AESI, adverse event of special interest; AZA, azacitidine; IVO, ivosidenib; TEAE, treatment-emergent adverse event.

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Acute myeloid leukemia

DIVERGENT CLONAL TRAJECTORIES UNDER PARP-INHIBITORS: FROM CHIP TO THERAPY-RELATED MYELOID NEOPLASMS

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PARP inhibitors (PARPi) are used as maintenance therapy in epithelial ovarian cancer (EOC) after platinum-based chemotherapy, but this combination has been associated with increased risk of therapy-related myeloid neoplasms (t-MNs). In our previous work, we reported an 8.7% incidence of t-MNs in PARPi-treated patients. Moreover, chemotherapy may increase the occurrence of clonal hematopoiesis (CH), an age-related condition defined by the presence of somatic mutations in hematopoietic cells without evidence of disease. We aimed to characterize CH dynamics during PARPi exposure and to identify features associated with leukemic evolution in this setting. We performed high-sensitivity targeted sequencing (limit of detection= 0.1% variant allele frequency, VAF) with a custom CHIP-UMI gene panel on longitudinal peripheral blood samples from 59 EOC patients (EOC cohort) before and during PARPi treatment, every 6 months and up to 2 years. CH profiles were compared with those of 22 EOC patients who subsequently developed t-MNs after similar therapeutic exposure (t-MN cohort, median PARPi exposure 24.6 months). At baseline, in the EOC cohort, CH was in 92% patients, with high clonal complexity (median 4 mutations/patient), mostly involving DNMT3A, PPM1D and TP53. 90% (572/632) of variants had VAF<2%, indicating a predominantly subclinical CH landscape. During PARPi treatment (up to 2 years), the number of CH mutations remained stable, while their VAF significantly increased, with the most pronounced and persistent expansion of PPM1D-mutated clones. Moreover, half of patients developed CHIP or CCUS during PARPi therapy. In contrast, all patients of the t-MN cohort had CH with clear clonal dominance. 95% of patients harbored TP53-mutated clones with significantly higher VAF compared to EOC cohort (16.8% vs 0.3%), whereas PPM1D-mutated clones were less common (59% of patient) with low VAF values (median VAF 0.9%). These data show a shift from PPM1D-driven clonal expansion in pre-leukemic phases to TP53-driven clonal dominance at t-MN onset, suggesting that PARPi exposure promotes expansion of specific CH clones, that are not responsible per se to drive leukemic transformation. Rather, progression to t-MNs appears to be associated with emergence and dominance of TP53 mutated clones. Our study highlights the importance of longitudinal CH monitoring in PARPi treated patients and supports the role of CH profiling as a potential tool for early risk stratification of t-MNs.

Acute myeloid leukemia

EARLY SEVERE INFECTIONS IN ACUTE MYELOID LEUKEMIA TREATED WITH AZACITIDINE–VENETOCLAX: DEVELOPMENT OF A BASELINE RISK PREDICTION MODEL

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Introduction. Azacitidine/Venetoclax (aza/ven) is a standard treatment for acute myeloid leukemia (AML) but is often complicated by early severe infections. Identifying high-risk patients may help guide inpatient versus outpatient management.

Aim We aimed to assess baseline factors predicting severe infections within 60 days of treatment in order to develope a baseline risk prediction model.

Methods. We retrospectively analyzed 250 AML patients treated with aza/ven across multiple centers. Baseline clinical and laboratory data were collected. Severe infection within 60 days was the primary endpoint and logistic regression identified predictors of early infections. Variable weighting in the score was based on the estimated regression beta coefficients.

Results. Baseline characteristics are reported in Table 1. With a median follow up of 27 months, relapsed/refractory (RR) disease (p=0.017) and absence of antiviral (AV) prophylaxis (p=0.047) were associated with higher early infection risk (grade >=3 infections). Charlson Comorbidity Index, complex karyotype, and ELN 2024 risk approached significance, suggesting larger cohorts are needed to clarify their impact. A model including these variables, age, baseline blood counts, and TP53 status predicted 60-day infection risk with high accuracy (AUC 0.916). Early severe infection increased 60-day mortality by 57%, without reaching statistical significance (Figure 1; Table 2).

Conclusions. In this exploratory multicenter analysis, we developed a predictive model for severe infections within 60 days of azacitidine/venetoclax initiation, integrating readily available baseline clinical, laboratory, and disease-related variables. The model showed high discriminative performance, supporting its potential role in early risk stratification. Relapsed/refractory disease and absence of antiviral prophylaxis emerged as factors associated with increased infection risk, although the latter may reflect underlying immunosuppression and should be interpreted cautiously. With further validation in larger cohorts, this predictive model could support clinical decision-making by identifying patients who may benefit from closer monitoring, prophylactic strategies, or inpatient rather than outpatient treatment during the early phases of therapy.

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Table 1: Baseline characteristics

Median age	73.0 [61.7-84.3]
White Blood Count (/uL)	3200 [100-33064]
Platelets (/uL)	72000 [1000-146000]
LDH (U/L)	250 [125-482]
Bone marrow blasts	40% [13.1-66.9]
Sex, Male	136 (54.4%)
Infectious event prior to therapy	25 (10%)
ECOG ≥2	85 (34%)
CCI ≥6	114 (45.6%)
Line of therapy	
TN	184 (73.6%)
RR	66 (26%)
Prophylaxis	
antifungal	224 (89.4%)
antibacterial	133 (53.2%)
antiviral	67 (26.8%)
Karyotype	
Normal	109 (43.6%)
Altered	62 (4.8%)
Complex	49 (19.6%)
TP53	
Mutation	26 (10.4%)
NV	141 (56.4%)
ELN 2024 risk	
Favourable	64 (25.6%)
Intermediate	20 (8%)
Unfavourable	25 (10.0%)
NV	141 (56.4%)
ORR	163 (65.2%)
Median time to CR/MLFS	2 [1.9-3] months
DOR	15 [12-22] months

Figure 1: Overall survival in patients with (red line) and without (blue line) infectious events within the first 60 days of therapy

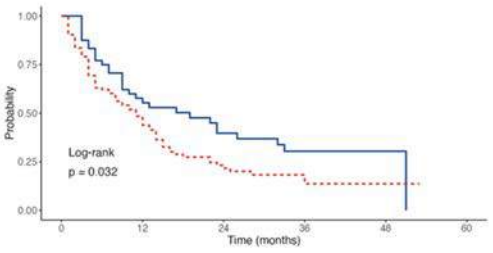

Table 2: Proposed risk score for predicting early severe infection to guide inpatient versus outpatient management (cut-off ≥10)

	Proposed score
Infectious event prior to therapy	2
CCI ≥6	1
ECOG ≥2	1
cytogenetic alterations	2
TP53	12
ELN 2024 risk unfavourable	12
relapsed/refractory disease	4
antiviral/antibacterial/antifungal prophylaxis	2
PLTs < 50x10^9/L	1
WBC > 10x10^9/L	1

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Acute myeloid leukemia

FOUNDER PERSISTENCE, CLONAL PRUNING, AND MOLECULAR EVOLUTION IN ACUTE MYELOID LEUKEMIA RELAPSE AFTER ALLOGENEIC TRANSPLANTATION

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Relapse after allogeneic transplant is a major cause of treatment failure in AML. However, the molecular architecture of relapse post-transplant, including stability of molecular lesions and patterns of molecular relapse are incompletely characterized.We analyzed 20 AML patients from our center with paired NGS data at diagnosis and post-transplant relapse. Relapse was defined as early (<6 mos.) or late (>6 mos.). Putative founder lesions were evaluated based on mutation type and VAF. Patients were assessed for reacquisition/loss of founder lesions, pruning, and acquisition of new lesions associated with signaling escape or non-signaling clonal evolution (Table). FLT3 status, which was based on PCR, was integrated as a mechanism of signaling escape. Exploratory analyses were performed using Fisher Exact test.17/20 patients had a founder lesion at diagnosis: of these, all but one retained the founder at post-transplant relapse. While founders were mostly retained, patients frequently showed a dynamic molecular relapse, which included signaling escape mutations in 4/20 and non-signaling clonal evolution in 5/20. Additionally, pruning was observed in 8/11 patients with >1 NGS mutation at diagnosis (Table).Patients without a dynamic molecular relapse had a tendency for earlier relapse (median 4 mos. vs. 8 mos., p=0.18).An association was found between lack of dynamic molecular relapse and myeloablative conditioning (MAC): Excluding one patient with sequential MAC- and reduced-intensity conditioned (RIC) transplants due to graft failure, 0/6 of the relapses following MAC were a dynamic molecular relapse, compared with 8/13 for RIC transplants (p=0.02).All patients with signaling escape had a related donor (matched related or haplo) and TBF-based RIC, while patients with non-signaling clonal evolution were enriched for unrelated donor (8/8 and 7/8) and modified Baltimore-based RIC.AML post-transplant relapse was associated with persistence of founder lesions, which frequently coexisted with pruning and acquisition of lesions associated with signaling escape or non-signaling clonal evolution. Exploratory analyses suggest a pattern of later molecular dynamic relapse following RIC, which may relate to survival of multiple subclones subject to post-transplant selection. Early relapse following MAC may relate to re-emergence of a treatment-resistant clone with less pressure for molecular evolution. These findings warrant validation in an expanded cohort.

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Molecular feature	Criteria for classification	N (%)
Putative founder lesion	Presence of molecular lesion(s) associated with founder/myeloid ancestry (eg, ASXL1, DNMT3A, EZH2, SRSF2, TET2, ZRSR2), AML-defining (eg, CEBPA, RUNX1), or resistance-associated (eg, TP53, WT1)	17/20 (85%)
Reacquisition of founder	Same founder lesion(s) detectable at post-transplant relapse	16/17 (94%)
Loss of founder	Loss of founder lesion at post-transplant relapse	1/17 (6%)
Pruning	Loss of ≥1 molecular lesion at post-transplant relapse (among patients with ≥2 molecular lesions at diagnosis)	8/11 (73%)
Signaling escape	Acquisition of lesion(s) associated with signaling escape at post-transplant relapse (eg, CBL, FLT3*, KIT)	4/20 (20%)
Non-signaling clonal evolution	Acquisition of lesions associated with non-signaling clonal evolution at post-transplant relapse (eg, CEBPA, EZH2, SRSF2, TP53, ZRSR2)	5/20 (25%)
Lack of dynamic molecular relapse	No acquisition of molecular lesion associated with signaling escape or non-signaling clonal evolution at post-transplant relapse	11/20 (55%)

*FLT3 status was determined by PCR-based assay rather than NGS panel

Acute myeloid leukemia

NGS-BASED GENOMIC PROFILING IN ACUTE MYELOID LEUKEMIA: IMPACT ON PROGNOSTIC RISK STRATIFICATION AND THERAPEUTIC STRATEGIES ACROSS DIFFERENT AGE GROUPS

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Acute myeloid leukemia (AML) is a heterogeneous malignancy associated with variable outcome, poorer in elderly patients. With a progressively aging population, understanding molecular basis of age-related differences in AML is increasingly relevant. Advances in Next-Generation Sequencing (NGS) have enhanced the characterization of mutational landscapes, improved prognostic stratification according to the European LeukemiaNet (ELN) guidelines, and expanded therapeutic options.The aim is to investigate by NGS the genetic differences between younger and older AML patients, in order to refine risk stratification and support therapeutic strategies.NGS data from 402 AML patients diagnosed in 2025 were analyzed. DNA and RNA were extracted from bone marrow using the Maxwell CSC 48 system. Sequencing was performed with the Oncomine Myeloid Assay GX V2 on the Ion Torrent Genexus platform, enabling rapid detection of point mutations and gene rearrangements in 24 hours. Variants with coverage >1000× were evaluated using ClinVar, COSMIC, and Franklin Genoox databases; only pathogenic variants were considered.Among all patients, 299 (74.4%) were over 60 years old. Only 12.7% of older and 18.4% of younger patients showed no genomic alterations. Older patients (>60 yrs) showed more frequently mutations in epigenetic regulators (ASXL1, TET2, IDH1/2), splicing factors (SRSF2, SF3B1, U2AF1), transcriptional regulators (RUNX1, BCOR), tumor suppressor/genomic stability genes (TP53, STAG2), and signaling genes (JAK2). In contrast, younger patients showed higher frequencies of FLT3, NPM1, NRAS, KRAS, and WT1 mutations. Median number of alterations was higher in older patients (3 vs 2). Frequencies significantly differed (Aged<60 vs ≥60; p<0.05) for ASXL1, TET2, IDH1, SRSF2, FLT3, NPM1, and NRAS mutations. Among rearrangements, KMT2A-PTD (p=0.005) was significantly enriched in older patients, whereas inv (16) (p=0.0039) in younger ones (Fig. 1A–B). When stratified according to ELN 2022 risk categories, higher risk was enriched in older AML patients (Fig. 1C).NGS analysis revealed marked age-related differences in AML genomic profiles at diagnosis. ELN 2022 stratification showed a higher prevalence of adverse-risk features in older patients; younger patients were more evenly distributed across prognostic groups. These findings highlight the biological impact of age in AML and support the implementation of age-tailored genomic assessment to guide prognosis and targeted therapy.

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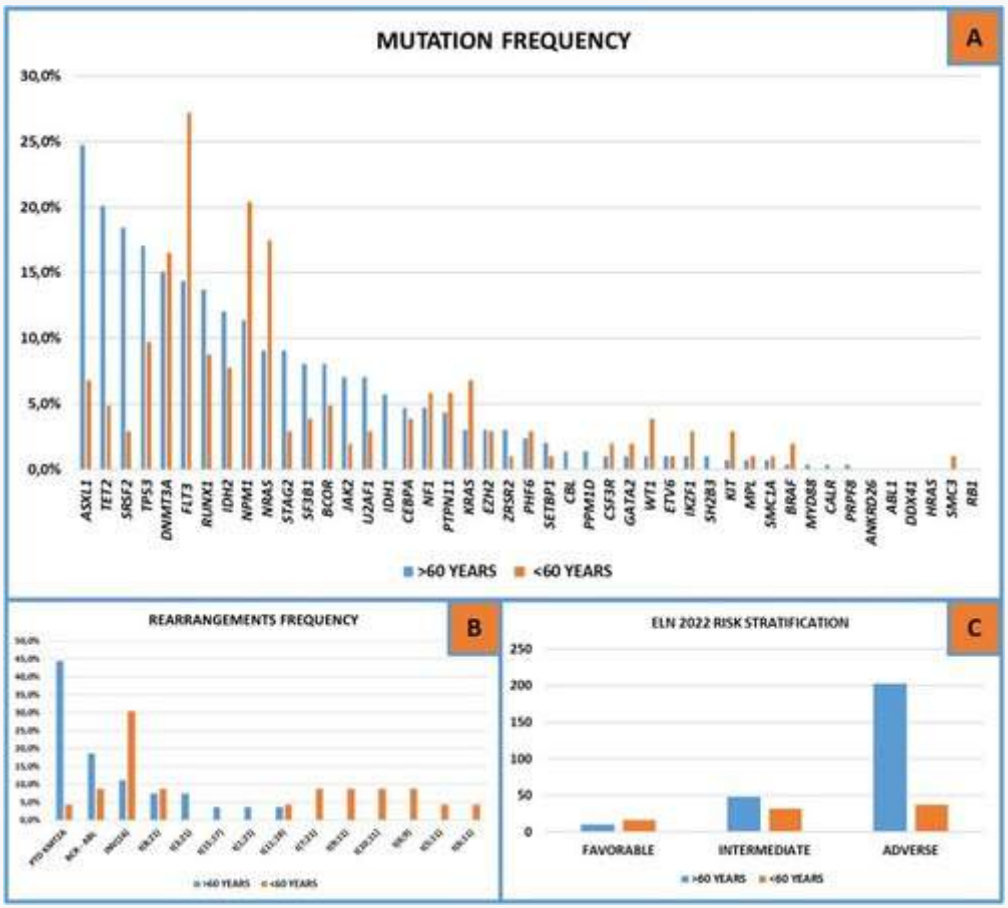
Acute myeloid leukemia



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Acute myeloid leukemia

EXPLORING CD135, CLEC2A AND FOLR1 AS CANDIDATE LEUKEMIA-ASSOCIATED MARKERS IN AML: EXPRESSION ON LEUKEMIC CELLS AND IMMUNE MICROENVIRONMENT ACROSS DISEASE PHASES

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Acute myeloid leukemia (AML) is a biologically heterogeneous disease with a high risk of relapse. Multiparametric flow cytometry (MFC)-based minimal residual disease (MRD) monitoring is an established independent prognostic tool; however, identifying reliable and informative markers remains a challenge. This study evaluates the expression of three underexplored leukemia-related markers, CD135 (FLT3 receptor), CLEC2A (C-type lectin family receptor 2A), and FOLR1 (Folate Receptor α), on leukemic cells and key immune subsets (B cells, $CD4^+$, $CD8^+$ and NK-like T cells, NK cells, monocytes) in AML patients (n=24) at diagnosis and during follow-up (25 MRD^+, 15 MRD^-).CD135 expression (percentage and mean fluorescence intensity (MFI)) on leukemic cells was significantly reduced in MRD^- compared to diagnosis, correlating positively with leukemic burden. Adverse-risk patients showed significantly lower CD135 expression than intermediate- and favorable-risk groups ($p<0.05$), with significantly reduced levels in TP53-mutated versus IDH1/2- or FLT3-mutated AML patients, suggesting a link with disease biology. Within the immune microenvironment, CD135+ monocytes (~60% at diagnosis) progressively decreased during follow-up, reaching significance (MFI) only in MRD^+ samples. B cell CD135 expression, minimal at diagnosis, was significantly increased in MRD^+ versus MRD^- and correlated with leukemic burden, indicating that the bone marrow immune microenvironment may reflect residual disease. A similar association was observed in $CD135^+$ NK cells.CLEC2A expression on leukemic cells was low (<5%) but significantly reduced in MRD^- versus diagnosis; MRD^+ samples showed higher MFI than MRD^-, supporting an association with persistent disease. Adverse-risk MRD^- patients also exhibited lower CLEC2A expression compared to diagnosis. No significant differences were observed across immune subsets.FOLR1 expression did not show any significant variation across disease phases, risk groups, or cell populations.No significant changes were observed for the evaluated markers in $CD4^+/CD8^+$ T cells or NK-like T cells.Overall, CD135 and CLEC2A emerge as promising indicators of leukemic burden and disease biology, reflecting both disease phase and mutational landscape. Also, CD135 expression across immune subsets highlights the relevance of microenvironmental analysis in MRD assessment. Thus, integrating leukemia-associated markers with immune profiling may improve MFC-based MRD monitoring in AML.

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Acute myeloid leukemia

A PHASE 3 STUDY OF REVUMENIB PLUS VENETOCLAX/AZACITIDINE IN ADULTS WITH NEWLY DIAGNOSED *NPM1*-MUTATED OR *KMT2A*-REARRANGED ACUTE MYELOID LEUKEMIA INELIGIBLE FOR INTENSIVE CHEMOTHERAPY (EVOLVE-2/HO177/AMLSG35-24/ACT-HOV-AML-002): TRIAL IN PROGRESS

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Background. Treatment for patients (pts) with acute myeloid leukemia (AML) unfit for intensive chemotherapy (IC) is challenging and depends on pt and disease characteristics and pt preference. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction, which disrupts multiple key drivers of leukemogenesis (lysine methyltransferase-2A rearrangement [*KMT2A*r], nucleophosmin-1 mutation [*NPM1*m], and *NUP98* rearrangement. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy showed clinically meaningful responses and was generally well tolerated in relapsed/refractory *NPM1*m AML or *KMT2A*r acute leukemia pts. To improve outcomes, combination regimens are being studied as front-line therapy for newly diagnosed (ND) pts. In the phase 1b Beat AML study (NCT03013998), revumenib plus venetoclax/azacitidine (VEN/AZA) led to deep responses in pts ≥60 years (y) of age with ND *NPM1*m or *KMT2A*r AML. EVOLVE-2 will assess whether revumenib plus VEN/AZA prolongs overall survival (OS) and improves complete remission (CR) rates in ND *NPM1*m or *KMT2A*r AML pts ineligible for IC.

Methods. EVOLVE-2 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT06652438/EU-CT 2024-512733-32-00). Eligible pts are ≥75 y of age (18–74 y with comorbidities), have centrally confirmed ND *NPM1*m or *KMT2A*r AML, are ineligible for IC, and are AML treatment-naive. Pts will be randomized 1:1 to revumenib or placebo plus VEN/AZA and stratified by age (<75 vs ≥75 y), genotype (*NPM1*m vs *KMT2A*r), and region (Europe vs Australia vs United States). In Cycle (C) 1, VEN is given QD on Days (D) 1–28 and AZA QD on D1–7, ± revumenib BID on D1–28. In C2+, responders (per 2022 European LeukemiaNet criteria) may adjust VEN based on remission status/count recovery. Dual primary endpoints are OS and CR rate. Key secondary endpoints include event-free survival and rate of CR/CR with partial hematologic recovery (CRh). Other endpoints include rates of CRh and CR/CR with incomplete hematologic recovery (CRi), measurable residual disease (MRD) negativity, time to/duration of response, adverse events, time to hematopoietic recovery, and incidence of platelet and RBC transfusions. Overall, 448 pts will be enrolled. As of April 30, 2026, the study is open to enrollment.©2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting. All rights reserved.

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Acute myeloid leukemia

TSPYL5 IN ACUTE MYELOID LEUKEMIA FUNCTIONAL AND METABOLIC CHARACTERIZATION OF A CANDIDATE DRIVER OF MITOCHONDRIAL REPROGRAMMING

E. Espina Barroso[1], G. Pasqualini[1|2], A. Zaza[1], E. De Marinis[3|4], T. Ottone[5], P. Niscola[6], S. Perrone[7], R. Palmieri[5], D. Armiento[8], E. Santinelli[8], A. Brunetti[9], F. Buccisano[5], L Maurillo[7], S. Galimberti[9], A. Venditti[5], M. t. Voso[1|5], G. Catalano[1|5], C. Nervi[3], N. i. Noguera[1|5]

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Background. Metabolic reprogramming is a hallmark of cancer and is critical in acute myeloid leukemia (AML), where leukemic stem cells rely on mitochondrial metabolism for survival and therapy resistance. We previously identified AML subgroups with high oxidative phosphorylation (OXPHOS) and proton leak (PL), associated with poor outcome, but the underlying molecular drivers remain unclear.Objective: To identify transcriptional regulators of the high OXPHOS/PL phenotype and define their role in metabolic rewiring.

Methods. RNA-seq and GSEA were performed on primary AML blasts with high (n=6) vs low (n=6) OXPHOS/PL. Gene expression was validated by RT-PCR and Western blot, and localization by immunofluorescence. TSPYL5 was silenced (e-siRNA) in OCI-AML3 and HL60 cells. Mitochondrial respiration, proton leak, and glycolysis were assessed by Seahorse XF.

Results. High OXPHOS/PL samples showed enrichment of adipogenesis, fatty acid oxidation, OXPHOS, and ROS pathways, defining a distinct metabolic signature (Fig 1A). TSPYL5 emerged among the top upregulated genes (Fig 1B), and, in TCGA AML database, higher expression was associated with worse outcome (p=0.05) in line with our results. TSPYL5 displayed nuclear and cytoplasmic localization. Expression analyses showed a consistent trend toward higher levels in high OXPHOS/PL cases (Fig 1C). Functionally, TSPYL5 silencing significantly reduced mitochondrial respiration and proton leak indicating a role in sustaining oxidative metabolism (Fig. 1D). Western blot analysis revealed reduced expression of SDHB, a member of mitochondrial complex II (siTSPYL5 0.7 ± 0.2vs Sc-control 1,5± 0.08; p = 0.005) (Fig. 1E), supporting the OXPHOS downregulation observed.In addition, TSPYL5 knockdown impaired glycolytic capacity (Fig. 1F) and reduced PKM2 levels in OCI-AML3 cells (siTSPYL5 0.4 ± 0.05 vs Sc-control 0.8± 0.1; p = 0.05) (Fig. 1G), supporting a role for TSPYL5 in metabolic rewiring.

Conclusions. TSPYL5 is a novel regulator of metabolic adaptation in AML, contributing to the maintenance of a high-OXPHOS and glycolytic phenotype. It may represent both a biomarker of adverse metabolic features and a potential therapeutic target to exploit metabolic vulnerabilities in AML.

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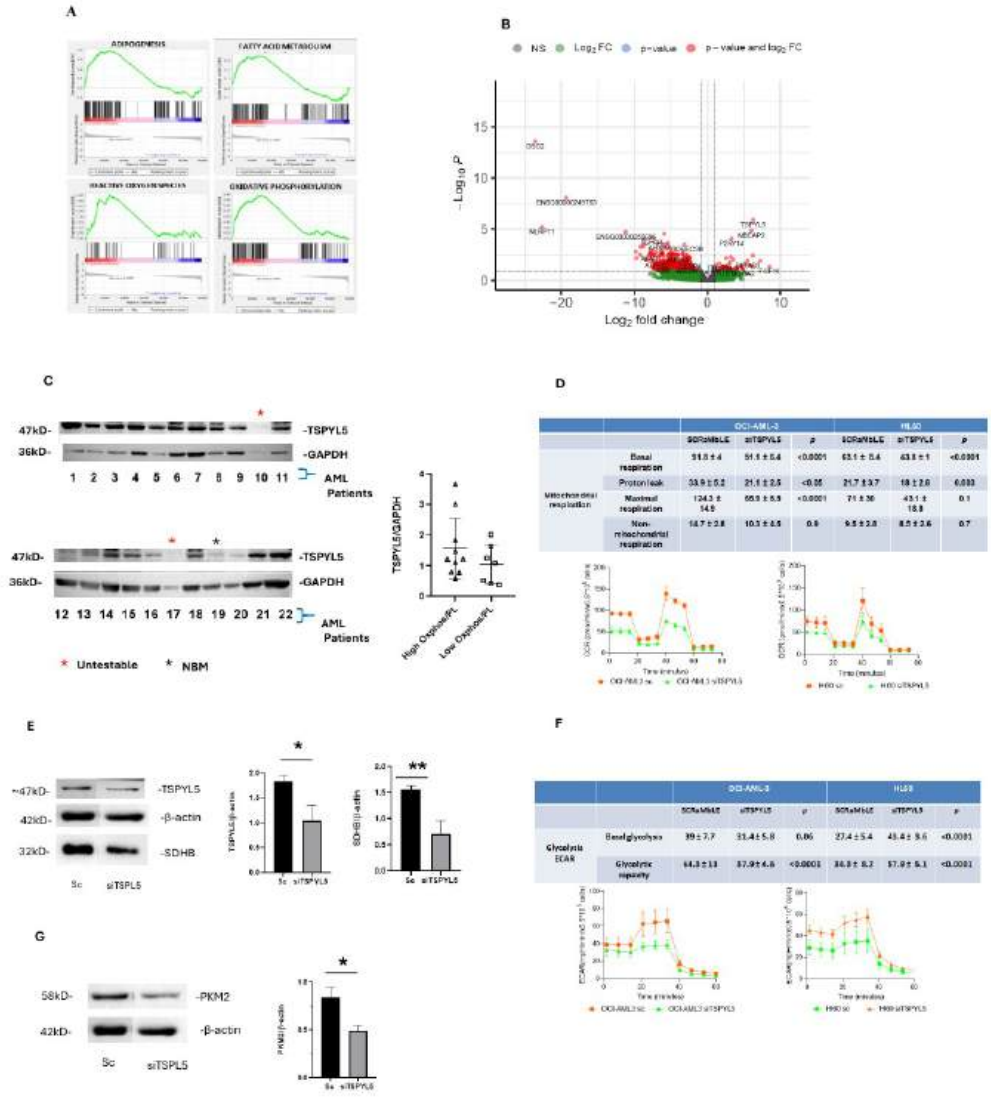

Figure 1. **A** GSEA enrichment plot in high OXPHOS/PL patients.**B** RNA sequencing on blast cells from patients with opposite metabolic phenotypes. **C** TSPYL5 expression in AML patients. **D** Mitochondrial respiration in *TSPYL5* silencing AML cells. **E** TSPYL5 and electron transport chain complex II SDHB subunit expression in *TSPYL5*- knockdown OCI-AML3 cells. **F** Glycolityc function in *TSPYL5* silencing AML cells. **G** pyruvate kinase M2 expression in *TSPYL5*- knockdown OCI-AML3 cells

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Acute myeloid leukemia

TP53-MUTATED ACUTE MYELOID LEUKAEMIA: REAL-WORLD OUTCOMES FROM A SINGLE-CENTER RETROSPECTIVE COHORT

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Acute myeloid leukaemia (AML) with TP53 mutation is recognized as a distinct nosologic entity by ICC22 classification and is associated with a dismal prognosis. Both intensive and non-intensive treatment (n-iT) provide limited benefits. Allogeneic stem cell transplantation (SCT) remains the only potentially curative option, although it is associated with a high relapse rate (RR). Herein we present the clinical outcome of 50/581 AML patients (pts) (8.6% of all newly AML cases) with TP53-mutation, diagnosed between Jan 18 and Dec 25 at our institution. Overall survival (OS) was estimated using the Kaplan–Meier method.Median age was 71 years (range:48-88); 50% had de novo AML. A complex karyotype was present in 98% (49/50) of cases. Intensive chemotherapy (IT) (3+7, FLAI, CPX-351) was administered to 21/50 (42%) pts, n-IT (hypomethylating agents and venetoclax-HMA±ven) to 20/50 (40%), and best supportive care (B-SC) to 9/50 (18%). The overall response rate (ORR) for IT and non-IT was 52% (11/21) and 70% (14/20) (p=0.3 - complete remission [CR] 33% vs 30%), respectively. Within the n-IT group, ORR was similar in HMA and HMA+ven treated pts [64% (9/14) vs 83% (5/6); p=0.6], while CR rate was better in HMA+ven group (14% vs 67%; p=0.037). The RR among responding pts was 88% (22/25). The median duration of response was 6.6 months (m) (range:2-35) without differences according to intensity of treatment. Median OS in the overall population was 8.2 m (9.9, 6.8, and 2 m in IT, n-IT, and BSC groups, respectively); log-rank $p < 0.001$ for treated vs BSC. No significant OS difference between IT and n-IT (p=0.3)(Fig1A) was noted. Overall, 28/50 (56%) were considered eligible for SCT, 63% (12/20) of pts treated with IT and 62.5% (5/8) of those treated with n-IT proceeded to SCT, with no significant differences in post-transplant outcome (9.9vs12.2 m; p=0.11). The use of SCT was associated with an advantage of survival (12.2vs5.5 m; p<0.001)(-Fig1B). The RR after SCT was 62% (10/16), with a median time to relapse of 7m (range: 2-35).In our cohort, TP53-mutated AML showed a poor prognosis. SCT remains the only strategy to improve OS, with no significant differences based on pre-transplant treatment intensity. In pts not eligible for transplantation, both n-IT approaches (HMA±ven) yield comparable outcomes and are associated with improved survival compared to BSC, although the optimal treatment strategy in this setting remains to be established.

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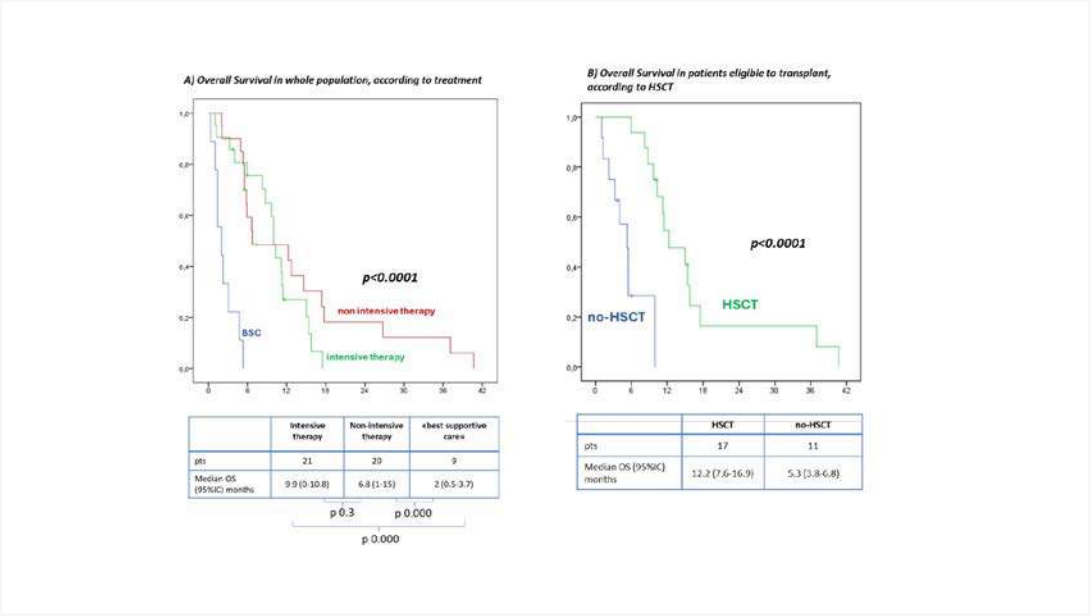
Acute myeloid leukemia



	Intensive therapy	Non-intensive therapy	«best supportive care»
pts	21	20	9
Median OS (95%IC) months	9.9 (0-10.8)	6.8 (1-15)	2 (0.5-3.7)

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	HSCT	no-HSCT
pts	17	11
Median OS (95%IC) months	12.2 (7.6-16.9)	5.3 (3.8-6.8)

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IMPACT OF INTENSIVE CHEMOTHERAPY AND HYPOMETHYLATING AGENTS-BASED REGIMENS IN MOLECULARLY DEFINED SECONDARY-TYPE AML: A REAL-LIFE STUDY THE FROM CAMPANIA REGION

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Introduction. According to ELN 2022, mutations in *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1* or *ZRSR2* define secondary-type AML (sAML), an adverse-risk category irrespective of prior MDS. However, the impact of different treatments in this subset remain underexplored.

Aims. To evaluate the efficacy of different treatments in molecularly defined sAML.

Patients and methods. Data from 126 patients treated across 6 Hematology Divisions in Campania were collected. Molecular analysis was centralized at CEINGE; cytogenetics and flow cytometry were performed locally. Patients were stratified by age (<65 vs ≥65 years) and treatment (intensive chemotherapy, including 3+7-based, FLAG-IDA-based regimens and CPX-351; HMA-ven; HMA single agent; and BSC. Response, MRD, relapse and survival were analyzed.

Results. Median age was 70 years [IQR 58–77]; 49 patients (39.2%) were <65 and 76 (60.8%) ≥65 years. Males were 66 (55%). Median comorbidities were 1 [IQR 0–2] and median WBC 7,960/µL [IQR 2,695–38,400]. Cytogenetics was evaluable in 94 patients: normal karyotype in 50.0%, complex karyotype in 13.8%, and chromosome 5/7 abnormalities in 11.7%. Patients ≥65 years had more comorbidities (2 vs 1; p=0.0006), whereas younger patients had higher WBC (21,400 vs 6,585/µL; p=0.017). Overall, 44 patients received intensive chemotherapy (35.2%), 31 HMA-ven (24.8%), 19 HMA single agent (15.8%), and 31 BSC/other (23.2%). Treatment allocation differed by age (p<0.0001), with HMA combinations in older patients. Overall CR rate was 51.2%. Among patients ≥65 years, CR rates were 50.0% with intensive chemotherapy, 56.5% with HMA-ven, and 28.6% with HMA single agent (p=NS). CR MRD-negativity was achieved in 40.5%, 23.1%, and 25.0% of intensive-chemotherapy, HMA-ven, and HMA single-agent patients, respectively, and was associated with lower relapse rate (8.3%; p<0.05). Median OS was 16.1 months (95% CI 9–NR) with intensive chemotherapy and 10.7 months (95% CI 8.5–NR) with HMA-ven. Adverse cytogenetics was associated with inferior OS (HR 2.26, 95% CI 1.02–5.00; p=0.044).

Conclusions. In sAML, treatment allocation was age-dependent. HMA-ven showed meaningful activity, with CR rates comparable to intensive chemotherapy. Adverse cytogenetics retained independent prognostic relevance for OS. These data support HMA-ven as an effective lower-intensity option, particularly for older or less fit patients.

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Acute myeloid leukemia

AMONG S-AML PATIENTS RECEIVING CPX-351 WITHOUT HSCT CONSOLIDATION, IDH2 BUT NOT IDH1 MUTATIONS ARE RELATED WITH A LONGER SURVIVAL

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Background. Secondary acute myeloid leukemia (s-AML) is associated with poor prognosis due to advanced age at diagnosis and a high frequency of adverse-risk mutations.In this setting, allogeneic hematopoietic stem cell transplantation (HSCT) after complete remission (CR) remains the only potentially curative option.CPX-351 has demonstrated improved efficacy compared to conventional chemotherapy, both in patients undergoing HSCT and in those not eligible for consolidation. However, prognostic stratification remains challenging, as most patients fall into the adverse ELN 2022 risk category. Among elderly patients receiving less intensive treatments such as HMA-VEN, newer risk scores have been developed, with IDH mutations associated with improved outcomes.

Aims. To evaluate the prognostic role of IDH1 and IDH2 mutations in s-AML patients treated with CPX-351, with or without HSCT consolidation.

Methods. A total of 96 s-AML patients (median age 69 years, range 38–77) were treated with CPX-351 at our center. Next-generation sequencing was performed on bone marrow samples using a 34-gene panel. Minimal residual disease (MRD) was assessed in all patients by multiparameter flow cytometry.

Results. According to ELN 2022, 82.3% of patients were classified as adverse risk.IDH1 and IDH2 mutations were detected in 9.3% and 13.5% of cases, respectively.After induction, 80.2% of patients achieved CR, with MRD negativity in 57% of responders. IDH mutations did not influence CR rate or MRD negativity.After a median follow-up of 43 months, median overall survival (OS) was 14 months. Only MRD-negative CR was associated with significantly longer OS (29 vs 10 months, $p<0.001$).HSCT was performed in 37.7% of CR patients and represented the strongest predictor of survival. No variables impacted survival among transplanted patients.Conversely, among non-transplanted CR patients, IDH2 mutations were associated with significantly longer OS (45 vs 15 months, for patients not receiving HSCT with or without IDH2 mutations, respectively; Fig.1), whereas IDH1 mutations showed no prognostic impact.

Conclusions. HSCT remains the only curative strategy in s-AML.However, for patients not eligible for transplantation, IDH2 mutations identify a subgroup with improved outcomes following CPX-351. These findings support the investigation of CPX-351 in combination with IDH2 inhibitors and suggest that HMA-VEN may represent an effective subsequent therapeutic option for this population.

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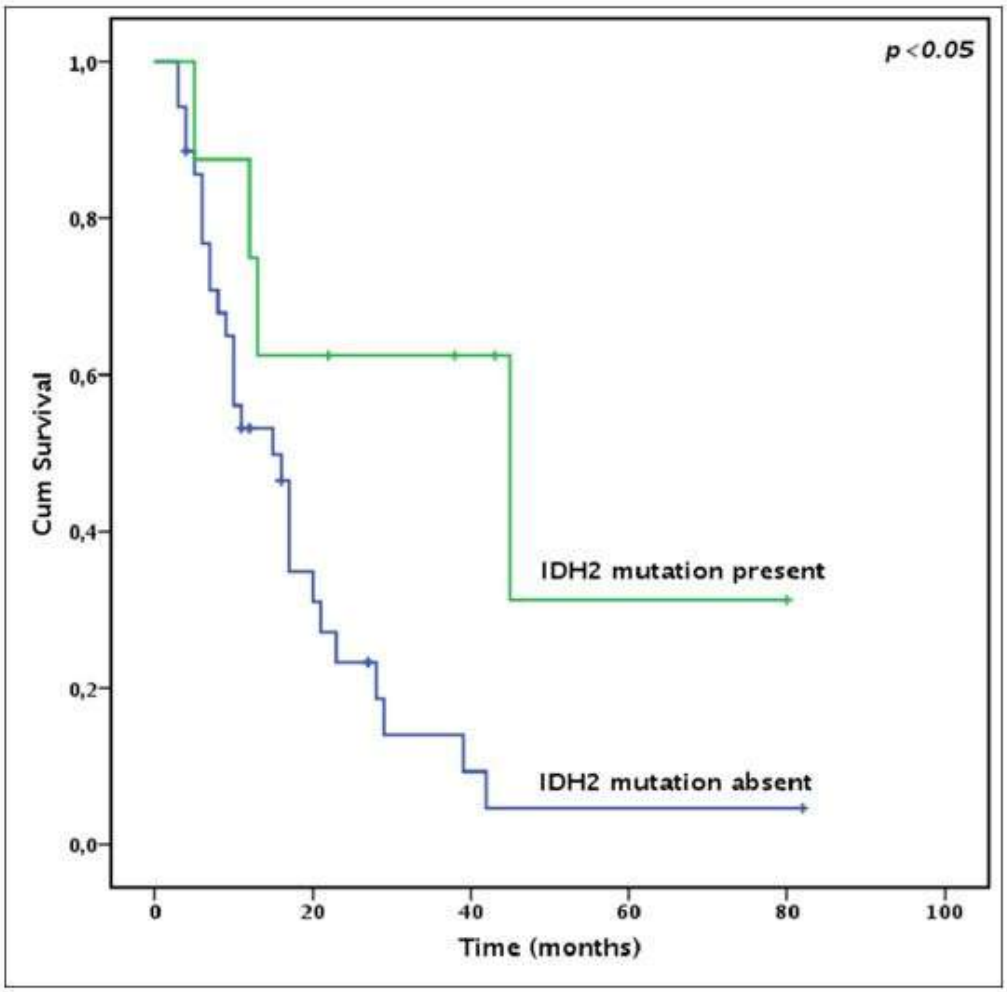

Figure 1: Overall Survival according to IDH2 mutational status in CR patients not receiving HSCT consolidation

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Acute myeloid leukemia

THERAPY RELATED ACUTE MYELOID LEUKEMIA: CLINICAL FEATURES AND OUTCOME IN A REAL- WORLD ITALIAN COHORT

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Background. therapy related acute myeloid leukemia (t-AML) develops as a consequence of prior cancer treatments (chemotherapy and/or radiation therapy). It is often characterized by adverse cytogenetic and/or molecular alterations, partially explaining an overall poorer prognosis compared to de novo and secondary AML. Intensive chemotherapy (IC) followed by hematopoietic stem-cell transplantation (HSCT) represents the gold standard treatment for the best eradication of the disease. However because of patients' (pts) related issues (i.e. previous treatments, fitness, age, comorbidities), the majority of t-AML pts are not eligible for this clinical approach.

Aims and Methods. we retrospectively collected data from a real-world cohort of pts with t-AML treated at two Italian Hematology Centers (Ematologia Univesitaria and Ematologia Ospedaliera, Città della Salute e della Scienza. Molinette, Torino) between January 2017 and February 2026. Data on demographics, type and treatments of the neoplasia prior to the development of t-AML, clinical and biological data of t-AML were collected. The aim was to describe the clinical features and outcome of t-AML in a real-life setting. Results: the final cohort comprised 76 pts. Median age of t-AML at diagnosis was 67.2 years (yrs) (range: 41-88): 43 females, 33 males. The preceding neoplasia was a solid tumor in 48.7%, a hematological malignancy in 51.3% of the cases. Risk stratification according to 2022 ELN was intermediate-high in 93.1% of the cases. 64 pts (84.2%) of the entire cohort received an active treatment for t-AML: 34 (53.1%) received IC, 13 (20.3%) a hypomethylating agent plus venetoclax (HMA+VEN), 17 HMA alone; 12 pts (15.8%) received best supportive care (BSC). Complete remission was achieved in 67.6% of pts in IC, 69.2% of pts in HMA-VEN and 23.5% of pts in HMA alone (overall: p.0.027; IC versus HMA-VEN: p. 0.83; HMA-VEN versus HMA alone: p.0.05). 15 of 76 pts (19.7%) underwent HSCT: 1/15 (6.7%) treated with HMA-VEN; 14/15 (93.3%) treated with IC. After a median follow up of 38 months (mo) (95% CI: 33-43), median overall survival (OS) in the entire cohort was 13 mo: 20 mo in pts treated with IC, 14 mo in pts treated with HMA-VEN and 13 mo in pts treated with HMA alone (p. 0.045); OS in pts receiving BSC was 1 mo (p. <0.001).

Conclusions. in the adverse- risk setting of t-AML, HMA-VEN provides meaningful remissions comparable to IC. Consolidation with HSCT is feasible only in a minority of cases.

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Acute myeloid leukemia

VALIDATION OF PROGNOSTIC RISK STRATIFICATION ACCORDING TO THE HARMONY MODEL IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

R. Marnoni[1|2], B. De Marco[1], L. Masina[1|2], D. Bertoli[3], C. Cattaneo[1], E. Cerqui[1], M. Oberti[1], E. Olivari[1], C. Giupponi[3|4], S. Bagnasco[1], E. Accorsi Buttini[1], G. Biasiotto[3|4], M. Malagola[2], A. Tucci[1], E. Borlenghi[1]

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Acute Myeloid Leukemia (AML) with NPM1 mutation (mut) is a distinct biological and prognostic group, generally considered favorable. Emerging evidence suggests that additional co-mut may refine prognostic stratification. The Harmony study proposed a model incorporating recurrent co-mut, including FLT3-ITD, DNMT3A, TET2, and IDH1/2. We analyzed a real-world cohort of 190 patients (pts) with NPM1--mutated AML, diagnosed and intensively treated at our center between 2006 and 2025. Among them, 86 had available next-generation sequencing (NGS) data and were stratified according to the Harmony model. We compared the prognostic value of the ELN22 classification and the Harmony model. Among the 190 pts (median age: 56y), 64 (34%) had FLT3-ITD co-mut. According to ELN22, 5-y Overall Survival (OS) was 70% in favorable (fav) and 57% in intermediate (int) risk group (p=0.1), whereas median Leukemia Free Survival (LFS) was significantly better in the fav one [34vs18 months (m); p=0.029]. Allogeneic stem cell transplantation (SCT) was performed in 56/190 pts (29.5%). In the NGS cohort (n=86), the most frequent co-mut were DNMT3A (50%), TET2 (28%), FLT3-ITD (28%), NRAS (23%), IDH1 (17%), and IDH2 (17%). According to ELN22, 72% of pts were classified as fav (n=62), whereas, based on the Harmony model, 54% (n=47) were fav, 34% (n=29) int, and 12% (n=10) adverse (adv) risk. No statistically significant difference in OS was observed among the Harmony-defined risk groups; by contrast, median LFS was 19.9, 15.7, and 5m in pts with fav, int, and adv risk, respectively, with significantly shorter LFS in the adv group (p=0.028)[Fig1A]. According to ELN22, 5-y LFS was barely significant between fav and int risk group (70%vs50%, p=0.046) with a median LFS of 18.9 and 13m, respectively (Fig1B). SCT was performed in 31/86 pts (36%). In our cohort, ELN22 stratified prognosis only in terms of LFS, while no difference was observed in OS, likely due to the impact of SCT, which may mitigate the negative prognostic effect of relapse. In line with the Harmony study, pts classified as adv —NPM1, FLT3-ITD, DNMT3A co-mut—showed poorer outcome and a higher relapse risk, worthy of SCT consolidation. However, in our cohort, the Harmony model did not significantly stratify OS. Larger prospective studies are warranted to validate the prognostic value of this molecular classification, especially in light of the availability of new drugs (e.g., Menin and FLT3 inhibitors), which may modify pts outcome.

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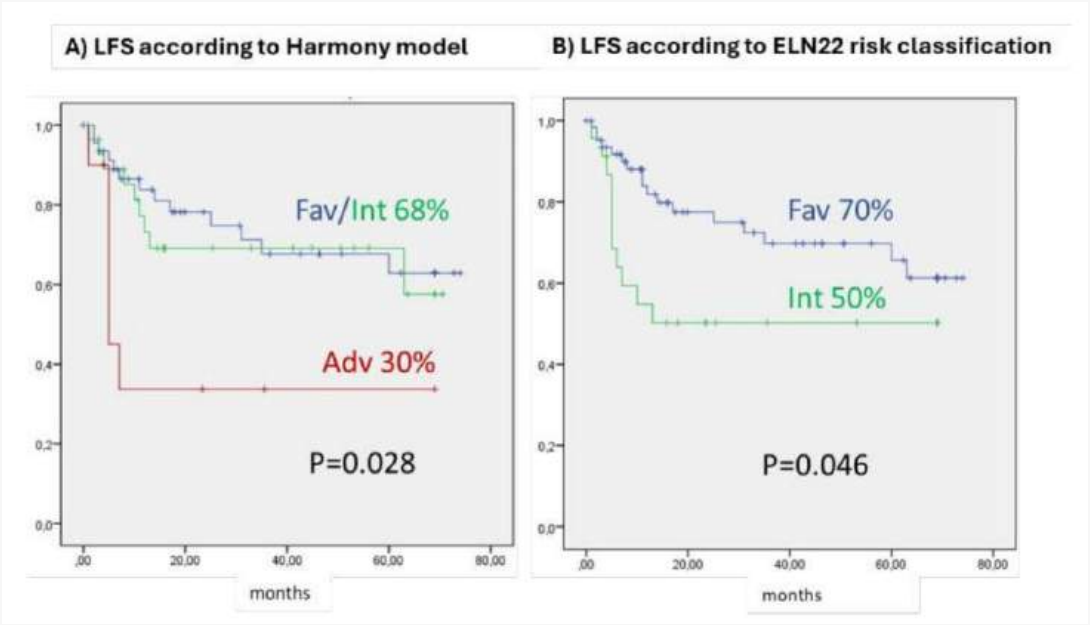

Myeloproliferative Neoplasms

DURABLE EFFICACY AND LONG-TERM SAFETY WITH PELABRESIB PLUS RUXOLITINIB IN JAK INHIBITOR–NAÏVE MYELOFIBROSIS: 96-WEEK RESULTS FROM THE PHASE III MANIFEST-2 STUDY

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Background. Janus kinase inhibitor (JAKi) monotherapy is the standard of care for myelofibrosis (MF) but provides limited depth and durability of response. Pelabresib (PELA), an inhibitor of bromodomain and extraterminal (BET) proteins, acts complementarily with the JAK1/2 inhibitor ruxolitinib (RUX) by modulating inflammatory pathways driven by BET-mediated gene expression involved in MF pathogenesis.
Methods. MANIFEST-2 (NCT04603495)[1] is a randomized, double-blind phase III trial in patients with JAKi-naïve MF that demonstrated superior spleen volume reduction with PELA plus RUX compared with RUX alone. Patients were randomized 1:1 to PELA once daily or placebo (PBO) with RUX twice daily. We report updated efficacy and safety outcomes at week 96, including spleen volume reduction ≥35% (SVR35), total symptom score (TSS), hemoglobin response, safety, and survival outcomes.[2]
Results. As of March 2, 2025, 56.5% of patients in the PELA+RUX arm and 59.3% in the PBO+RUX arm completed 96 weeks of treatment. Median follow-up (FUP) was 115.9 weeks. Approximately half of patients remained on treatment (48.6% vs 48.1%, in PELA+RUX and PBO+RUX, respectively). The most common reasons for discontinuation were adverse events (AEs) (21.0% vs 13.4%), physician decision (7.5% vs 14.8%), withdrawal of consent (10.3% vs 6.0%), and disease progression (5.1% vs 6.9%) in PELA+RUX and PBO+RUX, respectively.Higher response rates were observed with PELA+RUX vs PBO+RUX: SVR35, 91.5% vs 57.5%, in evaluable patients, respectively; ≥50% reduction in TSS from baseline (TSS50), 36.9% vs 28.2%, respectively; dual SVR35 and TSS50 responses, 31.8% vs 15.7%; hemoglobin response, 17.8% vs 11.6%. These data demonstrate durable responses in symptom improvement (Table 1).AEs were mainly low grade and comparable between arms (any grade AEs occurred in 99.5% vs 98.1%; Grade ≥3, 67.5% vs 70.1%). Leukemic transformation occurred in 5.1% vs 3.7% of patients.
Conclusions. This is the longest FUP to date from a randomized combination trial in MF. After 96 weeks of FUP, PELA+RUX showed deep and durable improvements in splenic response, symptom burden, dual SVR35/TSS50 response, and anemia vs PBO+RUX. The safety profile remained manageable and comparable between arms. Combining BET and JAK inhibition may provide clinically meaningful benefits and potential disease modification in MF.

References

1. Rampal RK. et al. Nat Med. 2025.
2. Rampal RK. et al. Blood 2025. © ASH (2025) Reused with permission

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Table 1. Summary of long-term outcomes as of the data cut-off date, March 2, 2025.

Outcome	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
SVR35 response at week 96, % (n/evaluable patients)	91.5% (97/106)	57.5% (65/113)
Difference, %	34.0%	
SVR35 (intent-to-treat)	45.3% (97/214)	30.1% (65/216)
Difference, %	15.2%	
Absolute change in TSS at Week 96	−15.07	−12.48
Difference (95% CI)	−2.59 (−5.23 to 0.05)	
TSS50 response at Week 96, %	36.9% (79/214)	28.2% (61/216)
SVR35/TSS50 dual responders at Week 96, %	31.8% (68/214)	15.7% (34/216)
Hemoglobin response	17.8% (38/214)	11.6% (25/216)
Red blood cell transfusions, % (n/evaluable patients)	33.1% (44/133)	39.9% (57/143)
Leukemic transformations, %	5.1% (11/216)	3.7% (8/214)

CI, confidence interval; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

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Myeloproliferative Neoplasms

BENEFIT OF RUSFERTIDE MAINTAINED IN PATIENTS WITH LOW-RISK OR HIGH-RISK POLYCYTHEMIA VERA: EFFICACY AND SAFETY SUBGROUP ANALYSIS FROM THE RANDOMIZED CONTROLLED PHASE 3 VERIFY STUDY

A. Vannucchi[1], V. García-Gutiérrez[2], A. Bankar[3], N. Pemmaraju[4], K. Pettit[5], J. Shatzel[6], A. Lucchesi[7], J. Mayer[8], A. Yacoub[9], H. Gill[10], A. Hlusi[11], D. Sasca[12], J. Scandura[13], D. Ross[14], F. Palandri[15], M. Fox[16], S. Koschmieder[17], J. -J. Kiladjian[18], P. Morello[19], P. Dinh[19], H. Goli[19], G. Vosganian[19], S. Khanna[19], A. Molina[19], A. Kuykendall[20]

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Background. VERIFY (NCT05210790) assessed standard-of-care with rusfertide or placebo (PBO) in phlebotomy (PHL)-dependent PV. VERIFY met its primary endpoint and all four key secondary endpoints (Kuykendall AT, et al. J Clin Oncol. 2025;43(S17):LBA3).

Aims. Post-hoc comparison of low-risk PV (<60 years [yrs] old and no thromboembolic event [TE] prior to study entry) vs high-risk PV (≥60 yrs old and/or TE prior to study entry) in the rusfertide and PBO arms.

Methods. Pts requiring frequent PHL with or without cytoreductive therapy (CRT) to achieve/maintain hematocrit (Hct) <45% were randomized (1:1) to once-weekly rusfertide or PBO, receiving rusfertide or PBO treatment at baseline to week (wk) 32. After 32 wks, pts could continue open-label rusfertide. Primary endpoint was clinical response (absence of PHL eligibility) during wks 20-32. Key secondary endpoints (baseline–wk 32) were mean PHLs, proportion with Hct <45%, and mean change in PROMIS Fatigue SF-8a and MFSAF version 4.0 PRO scores.

Results. As of 10 December 2025, of 293 pts (median age, 57 yrs), 156 had low-risk PV and 137 high-risk PV. During wks 20-32, more pts achieved clinical response with rusfertide vs PBO regardless of risk and CRT status (Table). Irrespective of risk group, rusfertide improved mean PHLs received, percentage pts with Hct <45%, and PRO scores. Treatment-emergent AEs in rusfertide-treated were similar in high-risk (96.1%) and low-risk (94.2%); serious AEs were more common in high-risk (14.7%) vs low-risk (6.4%). From baseline to wk 32, TEs were similar irrespective of risk (0 TEs in pts with high-risk PV in each arm; 1 TE [rusfertide arm] in a pt with low-risk PV). In rusfertide-treated pts during the open-label period, TEs were observed in 3 pts with low-risk PV and 3 pts with high-risk PV.

Conclusions. Rusfertide benefit was maintained vs PBO irrespective of baseline risk group, with statistically significant improvements in the primary endpoint and the first two key secondary endpoints, and numeric (non statistically significant) improvements in the remaining two key secondary endpoints (PROs).*2026 European Hematology Association (EHA). Reused with permission. This abstract was previously accepted and presented at the 2026 EHA Annual Meeting. All rights reserved.*

	Randomized N=293			
	High Risk n=137		Low-Risk n=156	
	Rusfertide	PBO	Rusfertide	PBO
With Or Without Concurrent CRT, n	66	71	81	75
Responders, n (%)	47 (71.2)	22 (31.0)	65 (80.2)	26 (34.7)
Concurrent CRT, n	50	52	32	28
Responders, n (%)	36 (72.0)	17 (32.7)	23 (71.9)	9 (32.1)
No concurrent CRT, n	16	19	49	47
Responders, n (%)	11 (68.8)	5 (26.3)	42 (85.7)	17 (36.2)

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Myeloproliferative Neoplasms

REFINING THROMBOTIC RISK STRATIFICATION IN ESSENTIAL THROMBOCYTHEMIA: IMPACT OF EUROPEAN LEUKEMIANET CLINICAL SIGNS AND SYMPTOMS

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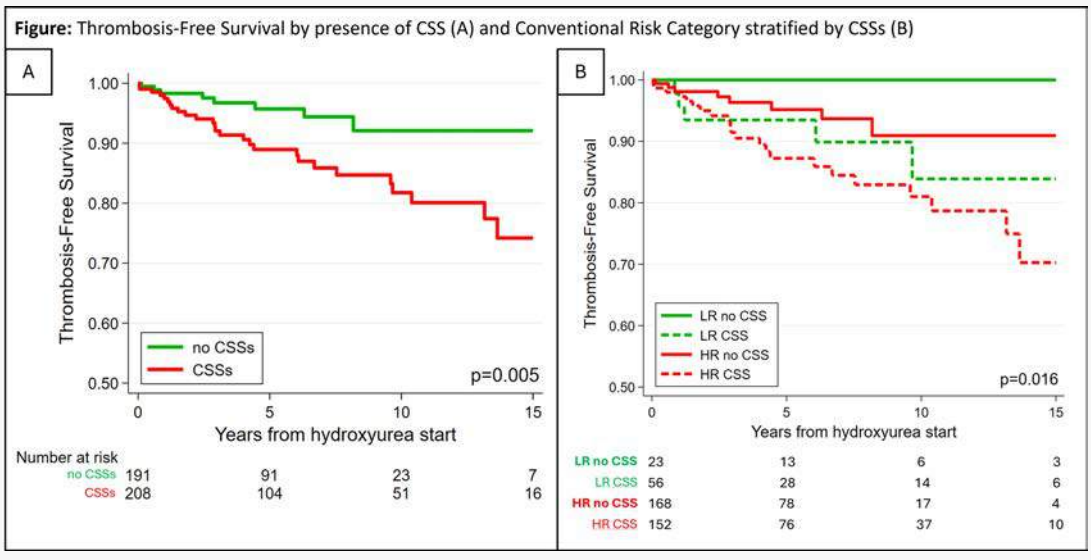
Background. Essential thrombocythemia (ET) carries a relevant thrombotic risk, traditionally stratified by age and prior thrombosis and refined by the revised IPSET-thrombosis (rIPSET) score. The prognostic role of ELN-defined clinical signs and symptoms (CSSs), recently validated in polycythemia vera, has not been explored in ET.

Methods. We retrospectively analyzed 399 WHO-defined ET patients treated with first-line hydroxyurea (2010–2024) to assess the prevalence of ELN CSSs and their association with thrombosis across conventional and rIPSET categories. CSSs included progressive splenomegaly, persistent/progressive leukocytosis, extreme thrombocytosis, severe pruritus, elevated hematocrit (>45% but below PV thresholds with normal EPO) and relevant cardiovascular risk factors (CVRFs, defined as concomitant active smoking and hypertension). Thrombosis-free survival was analyzed from HU start using Kaplan–Meier while thrombotic risk with Cox models with frailty terms.Results Overall, 71.4% of patients were aged ≥60 years, 65.7% carried JAK2V617F and 21.3% had prior thrombosis. By conventional criteria, 19.8% were low risk (LR) and 80.2% high risk (HR); rIPSET classified 19.8% as LR, 15.8% as intermediate (IntR), and 64.4% as HR. CSSs were present in 52.1%, mainly elevated hematocrit (35.8%) and extreme thrombocytosis (14.5%), and were significantly more frequent in LR than in IntR or HR groups (p<0.001).During HU, 50 thrombotic events occurred in 38 patients [incidence rate (IR) 1.97%py], with higher IR in CSS-positive patients (2.74 vs 0.93%py; p=0.001).By conventional risk stratification, HR pts with CSSs had higher IR than those without (3.02 vs 1.11%py; p=0.003). Consistently with rIPSET, CSSs identified higher risk across strata: IR 2.99 vs1.17%py in HR (p=0.01) and 2.89 vs 1.07%py in IntR (p=0.04). In both conventional and rIPSET LR groups, events occurred only in CSS patients (IR 2.01 and 2.80%py).In MVA, including also age≥60 and presence of JAK2V617F, ≥1 CSS (HR 3.01; p=0.002) and prior thrombosis (HR 1.76; p=0.038) independently predicted thrombosis. Among individual CSSs, relevant CVRFs (HR 4.0; p<0.001) and high HCT (HR 1.7; p=0.05) retained significance.

Conclusions. ELN-defined CSSs identify ET patients at higher risk of thrombosis during HU therapy, across conventional/rIPSET risk categories. Their integration may improve risk stratification and enable more individualized management in ET, mirroring advances in PV.



Myeloproliferative Neoplasms

UPDATE FROM THE PHASE 2 RESTORE TRIAL OF ELRITERCEPT IN PATIENTS WITH MYELOFIBROSIS RECEIVING RUXOLITINIB

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Anemia is common in patients (pts) with MF and is associated with fatigue, transfusion dependence, impaired quality of life, and reduced survival. JAK inhibitors such as ruxolitinib are standard of care for MF but can exacerbate anemia, limiting optimal dosing. Elritercept is an investigational, modified activin receptor type IIA ligand trap designed to bind select TGF-β superfamily ligands, including activin A/B, GDF8/11, to restore hematopoiesis.RESTORE (NCT05037760) is an open-label, phase 2 study of elritercept monotherapy or with ruxolitinib in pts with MF and anemia. Eligible pts are transfusion-dependent (TD; ≥3 RBC units/12 wks) or non-transfusion-dependent (NTD; <3 RBC units/12 wks with Hgb <10 g/dL). We report data for pts receiving elritercept starting at 3.75 mg/kg every 4 wks with ruxolitinib. Primary endpoint is safety/tolerability; other endpoints include hematologic parameters, spleen size, MF-SAF TSS, and gene mutations.As of July 2025, 38 pts receiving ruxolitinib were enrolled and treated with elritercept ≥3.75 mg/kg. Baseline: median age 71 years (45-80); 27 (71%) had spleen volume ≥450 cm^3; median Hgb 8.5 g/dL and platelets 121×10^9/L; median RBC transfusion requirement 4 units/12 wks (0-17), with 23 (61%) TD. Median elritercept exposure was 10.9 months (1.2-20.6) and 21 (55%) up-titrated to 5 mg/kg. Common adverse events were diarrhea (24%, none grade ≥3), thrombocytopenia (18%, grade 3 in 10.5%), and fatigue (18%, grade 3 in 5%). By wk 24, 8 (35%) TD pts achieved RBC transfusion independence (TI) ≥12 wks, 13 (57%) had ≥50% RBC transfusion reduction over consecutive 12 wks, and 4 (17%) achieved TI with concurrent mean Hgb increase ≥1.5 g/dL. Among 14 NTD pts, 5 (36%) and 7 (50%) achieved mean Hgb increases ≥1.5 and ≥1 g/dL over any 12-wk period. By wk 24, 16/38 (42%) had mean platelet increase ≥30×10^9/L over any 12-wk period. Spleen volume reduction ≥25% occurred in 5/24 (21%) evaluable pts and MF-SAF TSS reduction ≥50% in 13/27 (48%). JAK2 V617F variant allele frequency reduction ≥50% was observed in 3/19 pts at wk 24 and was sustained at wk 52.Elritercept add-on to ruxolitinib showed improvements in transfusion burden, spleen volume, platelet counts, and symptoms in pts with MF, supporting further evaluation.*2026 European Hematology Association (EHA). Reused with permission. This abstract was previously accepted and presented at the 2026 EHA Annual Meeting. All rights reserved*

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Myeloproliferative Neoplasms

ESTIMATED PULSE WAVE VELOCITY IS ASSOCIATED WITH MAJOR ADVERSE CARDIOVASCULAR EVENTS AND ARTERIAL THROMBOSIS IN ESSENTIAL THROMBOCYTHEMIA AND POLYCYTHEMIA VERA

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Cardiovascular (CV) morbidity is a major issue in essential thrombocythemia (ET) and polycythemia vera (PV). Estimated pulse wave velocity (ePWV), a surrogate of arterial stiffness, predicts cardiovascular risk in the general population and in cancer patients (pts), but its role in MPN needs to be defined. The aims of this study were to assess the association of baseline ePWV with major adverse cardiovascular events (MACE), thrombosis, and overall survival (OS) in ET and PV. We conducted a retrospective, single-center cohort study including 664 pts (ET 71.8%; PV 28.2%). Baseline ePWV was calculated using a validated equation from age and mean blood pressure (Greve et al. 2016). Time-to-event analyses were performed using Cox models; cause-specific Cox and Fine–Gray models were applied for non-fatal outcomes. Multivariable models adjusted for clinical covariates not included in ePWV. ePWV was analyzed as a continuous variable and categorized using the early vascular aging (EVA) threshold (≥9.4 m/s) (Vishram-Nielsen et al. 2020). Outcome-driven cutoffs were identified using maximally selected rank statistics (maxstat). Median age was 64.0 y (IQR 51.0–74.1); median ePWV 11.1 m/s (IQR 9.2–12.9). During a median follow-up of 67.4 mos, 57 MACE (8.6%), 52 thrombotic events (7.8%; AT 5.9%; VTE 2.0%), and 57 deaths (8.6%) occurred. ePWV showed a linear association with outcomes. Each 1 m/s increase in ePWV was associated with higher MACE risk (adjusted HR 1.16, 95% CI 1.01–1.32; p=0.032) and inferior OS (adjusted HR 1.79, 95% CI 1.53–2.10; p<0.001). Associations with thrombosis were attenuated after adjustment (p=0.054); no association was observed for venous thromboembolism (p= 0.519). The EVA threshold did not significantly discriminate MACE, whereas maxstat identified cutoffs (12.92 m/s for MACE; 11.23 m/s for OS) with significant risk stratification, identifying subgroups at markedly increased risk (HR 2.96 for MACE; HR 14.84 for OS; both p<0.001). Among *JAK2*-mutated patients, *JAK2* V617F variant allele fraction showed a significant correlation with ePWV (r = 0.13; p = 0.024). In comparative models, ePWV retained independent prognostic value for MACE, whereas age did not, while for OS the association was driven by age. In ET and PV, ePWV is associated with arterial but not venous thrombotic risk and provides incremental prognostic information beyond chronological age for CV outcomes, supporting its role as a clinically relevant marker of vascular risk in MPN.

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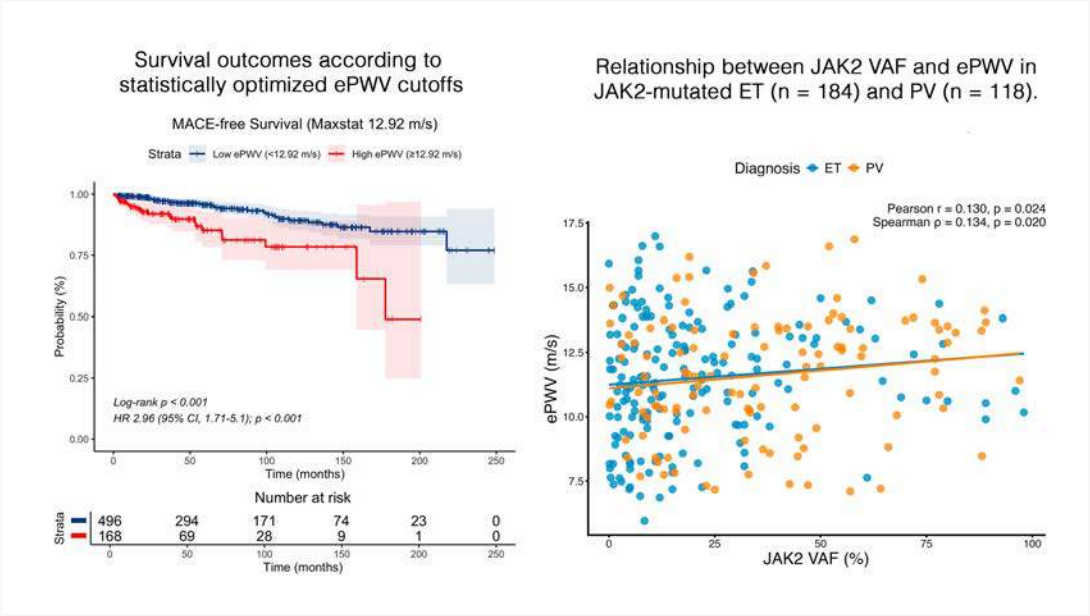

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Myeloproliferative Neoplasms

CAN AI PREDICT JAK2 MUTATION? A MACHINE LEARNING APPROACH IN SUSPECTED MPN

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Background. JAK2 V617F mutation is a key molecular driver in chronic myeloproliferative neoplasms (MPN), and its testing is central to the diagnostic workup. However, it is often requested in patients with nonspecific clinical suspicion, leading to suboptimal use of healthcare resources. Artificial intelligence (AI) may improve diagnostic accuracy by identifying predictive patterns based on clinical and laboratory data.

Aim and Methods. This study aimed to develop and evaluate AI models capable of predicting JAK2 mutation positivity in pts with suspected MPN and to assess their potential role as decision-support tools.212 pts who underwent JAK2 testing were included and 12 clinical-laboratory variables were analyzed. Statistical comparisons between JAK2 positive and negative pts were performed using Kruskal–Wallis and Pearson's chi-square tests, with statistical significance defined as $p \leq 0.05$. 23 machine learning models were trained to identify parameters mostly associated with mutation status and to estimate the probability of JAK2 positivity, using a stratified 5-fold cross-validation. Mean AUC, accuracy, precision, recall and F1-score evaluated performance. The selected best-performing model was compared with Logistic Regression Model. Interpretability was assessed using SHAP, a model-agnostic explainable AI framework that quantifies each feature's contribution to model predictions. SHAP values indicate both the magnitude and direction of feature effects, with positive values increasing and negative values decreasing the predicted outcome.

Results. Figure 1 summarizes all variables reporting descriptive statistics for the overall cohort and stratified according to JAK2 mutation status.Among the evaluated models, the ExtraTreesClassifier achieved the best overall performance.ROC curve of the best-performing model highlighted the superior discriminative ability of the former compared to the Logistic Regression baseline (Fig1).SHAP analysis (Fig1) showed that reduced EPO, LDH, thrombocytosis and splenomegaly were variables most strongly associated with the detection of JAK2 mutation positivity.

Conclusions. This model may serve as a simple and reliable clinical tool to identify patients most likely to benefit from JAK2 mutation testing and to optimize allocation of health care resource. Further refinement may improve predictive performance and patients' selection. Similar approaches could be extended to other disorders requiring costly diagnostic evaluation

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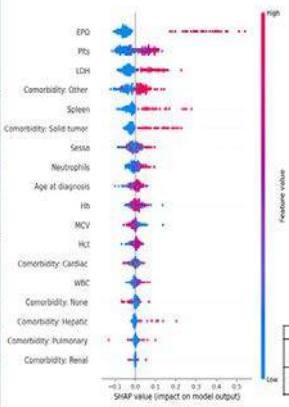
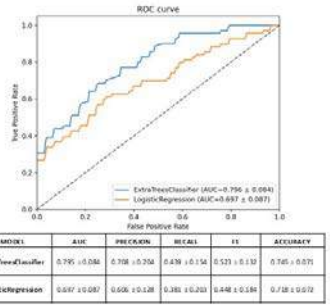
A

Features	Overall (n = 212)	JAK2 negative (n = 143)	JAK2 positivity (n= 69)	p-value
Age at diagnosis	65.0 (54.0-74.0)	65.0 (54.0-74.0)	66.0 (59.0-74.0)	0.498
Comorbidities 0: None 1: Cardiac 2: Hepatic 3: Pulmonary 4: Renal 5: Solid tumor 6: other	41 (19.3%) 87 (41.0%) 13 (6.1%) 23 (10.8%) 9 (4.2%) 34 (16.0%) 108 (50.9%)	28 (19.6%) 61 (42.7%) 9 (6.3%) 18 (12.6%) 6 (4.2%) 18 (12.6%) 68 (47.6%)	13 (18.8%) 26 (37.7%) 4 (5.8%) 5 (7.2%) 3 (4.3%) 16 (23.2%) 40 (58.0%)	1.00 0.568 1.00 0.349 1.00 0.077 0.202
EPO Normal Reduced	74 (34.9%) 29 (13.7%)	59 (41.3%) 5 (3.5%)	15 (21.7%) 24 (34.8%)	<0.05
Hct	48.2 (41.3-53.0)	48.2 (41.0-53.0)	46.9 (43.6-52.2)	0.857
Hb	15.5 (13.0-17.3)	15.6 (12.9-17.6)	15.3 (13.5-17.2)	0.902
LDH Normal Increased	105 (49.5%) 63 (29.7%)	77 (53.8%) 32 (22.4%)	28 (40.6%) 31 (44.9%)	<0.05
MCV	90.0 (86.2-95.5)	91.2 (87.0-96.0)	88.1 (84.0-92.2)	<0.05
Neutrophils	4840.0 (3475.0-6490.0)	4195.0 (3225.0-6005.0)	5740.0 (4320.0-7760.0)	<0.05
Plts	278.0 (198.0-408.0)	246.0 (178.0-412.0)	440.5 (277.8-600.5)	<0.05
Sex Male Female	130 (61.3%) 82 (38.7%)	94 (65.7%) 49 (34.3%)	36 (52.2%) 33 (47.8%)	0.080
Spleen 0 Normal 1 Enlarged	129 (60.8%) 37 (17.5%)	91 (63.6%) 19 (13.3%)	38 (55.1%) 18 (26.1%)	<0.05
WBC	8060.0 (6270.0-10200.0)	7620.0 (5422.5-9865.0)	8560.0 (7000.0-11110.0)	<0.05





MODEL	AUC	PRECISION	RECALL	F1	ACCURACY
ExtraTreesClassifier	0.795 ± 0.084	0.708 ± 0.204	0.439 ± 0.154	0.533 ± 0.132	0.745 ± 0.071
LogisticRegression	0.697 ± 0.087	0.606 ± 0.128	0.381 ± 0.203	0.448 ± 0.184	0.718 ± 0.072

1A. Continuous variables are presented as median (IQR), and categorical variables as absolute frequencies (percentages). p-value was calculated using Kruskal–Wallis for continuous variables and Pearson's chi-square test for categorical variables. EPO: Erythropoietin, Hct: Haematocrit, Hb: Haemoglobin, LDH: Lactate Dehydrogenase, MCV: Mean Corpuscular Volume, PLT: Platelet count, WBC: White Blood Cell count.
1B. SHAP values showing the impact of each feature on the output of the best-performing model.
1C. ROC curve of the best model, ExtraTreesClassifier, against Logistic Regression. The AUC values are reported as the mean over 5-fold cross-validation, with the standard deviation.

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Myeloproliferative Neoplasms

A REAL-WORLD COMPARISON OF SAFETY AND TOLERABILITY BETWEEN PEGYLATED INTERFERON ALFA-2A AND ROPEGINTERFERON ALFA-2B IN CHRONIC PH-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

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Background and Aim. Pegylated interferon alfa-2a (pegIFN) and ropeginterferon alfa-2b (ropegIFN) are used to treat Ph–negative myeloproliferative neoplasms (MPN). However, comparative data on their efficacy and toxicity remain limited. We aim to compare their safety profiles in a real-world setting.

Methods and Results. We retrospectively analyzed 99 consecutive MPN pts. treated at our center with pegIFN (n=57) or ropegIFN (n=42) for at least six months since 2011. To focus on safety, inclusion criteria did not depend on MPN phenotype. According to prescribing rules, all pts. on ropegIFN had polycythemia vera (PV), while those on pegIFN had PV (n=24), essential thrombocythemia (n=31), or pre-myelofibrosis (n=2). Sex, age, JAK2 V617F frequency, prior thrombosis, and comorbidities were balanced between groups.Total patient-years were 204.2 for pegIFN and 70.7 for ropegIFN. The incidence rate per 100 patient-years (IR % pt-yrs) of hematologic toxicity was similar for pegIFN and ropegIFN in cases of anemia (2.0 vs 4.2, p=0.38), leukopenia (2.0 vs 1.4, p=1.00), and thrombocytopenia (2.4 vs 2.8, p=1.00). There were no significant differences in the IR % pt-yrs of flu-like symptoms (10.3 vs 7.1, p=0.65), gastrointestinal symptoms (4.4 vs 1.4, p=0.46), neuropsychiatric effects (5.4 vs 9.9, p=0.27), dermatologic reactions (6.4 vs 7.1, p=0.79), thyroid disorders (8.3 vs 15.6, p=0.13), or autoimmune disorders (1.0 vs 1.4, p=1.00). Liver enzyme elevations were more frequent with ropegIFN (IR %pt-yrs 4.9 vs 12.7, p=0.04). Six pts. experienced major thrombosis on pegIFN (IR %pt-yrs 2.9, arterial/venous 3/3), while none occurred on ropegIFN.All adverse events were grade 1 or 2, except for one case of grade 3 immune thrombocytopenia on pegIFN.To address differences in follow-up duration, pegIFN observation was limited to 4.4 years, matching the maximum observation time for ropegIFN. No differences in adverse events, including liver toxicity, were observed. Twenty-four pts. discontinued pegIFN and six discontinued ropegIFN due to toxicity or intolerance, resulting in a lower discontinuation rate for ropegIFN (Hazard Ratio 0.40, 95% CI 0.16–1.00; p=0.042) (Figure).

Conclusions. The safety profiles of pegIFN and ropegIFN were similar, with most adverse events being mild or moderate. RopegIFN demonstrated better tolerability, as indicated by a lower discontinuation rate. Further studies are needed to confirm whether ropegIFN is more effective in preventing thrombosis.

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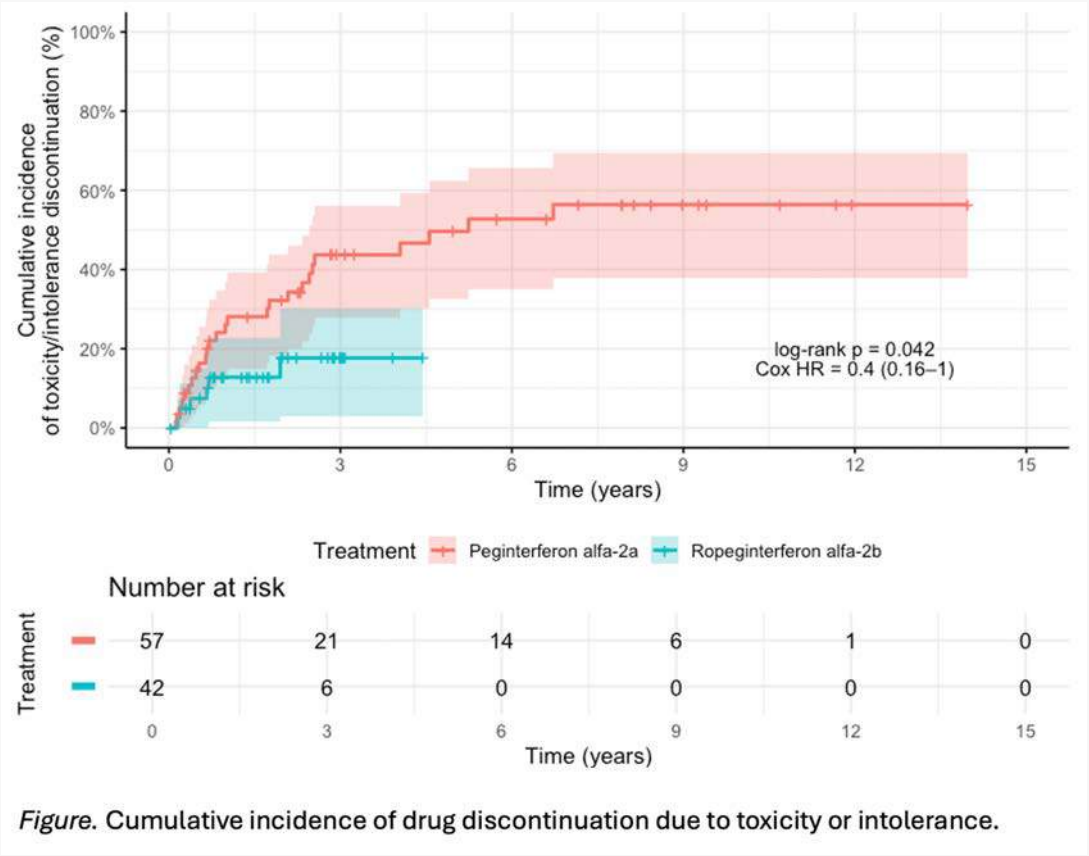

Figure. Cumulative incidence of drug discontinuation due to toxicity or intolerance.

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Myeloproliferative Neoplasms

CLONAL HEMATOPOIESIS, AUTOIMMUNITY, AND CLINICAL OUTCOME IN MYELOID NEOPLASMS: A SINGLE-CENTER ANALYSIS

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Department of Clinical and Experimental Medicine

Introduction. Myeloid neoplasms are heterogeneous clonal disorders increasingly defined by their molecular landscape, which also appears to influence immune dysregulation. This study investigated the association between somatic mutations, autoimmune diseases (AID), and clinical outcomes in 107 patients with myeloid neoplasms.Patients: The cohort included acute leukemia (33.6%), MF/CMML (25.2%), myeloproliferative neoplasms (22.4%), and myelodysplastic syndromes (18.7%). Autoimmune manifestations were observed in 25.2% of patients, including 7.5% with systemic and 17.8% with organ-specific AID.

Results. Systemic AID were significantly enriched in the MF/CMML subgroup (44.4%) compared to acute leukemia (19.4%), MPN (12.5%), and MDS (25.0%) (p=0.041). Molecular analysis identified TET2 (46.7%), ASXL1 (34.6%), DNMT3A (31.8%), and JAK2 (28.0%) as the most frequently mutated genes. Patients with AID had a significantly higher frequency of ASXL1 (51.9% vs 28.8%; p=0.037), RUNX1 (33.3% vs 10.0%; p=0.012), and PTPN11 mutations (18.5% vs 5.0%; p=0.043). A composite mutational profile (ASXL1/DNMT3A/TET2) was associated with increased prevalence of AID (30.5% vs 8.0%; p=0.033), particularly in MF/CMML (57.9% vs 12.5%; p=0.043). Co-occurrence of ASXL1 and RUNX1 mutations further increased AID frequency (54.5% vs 21.9%; p=0.028). Survival analysis showed no significant impact of AID on overall survival (OS: 178.9 vs 162.6 months; p=0.188; HR 1.74, 95% CI 0.82–3.70) or progression-free survival (PFS: 169.7 vs 130.2 months; p=0.283; HR 1.50, 95% CI 0.75–3.02). In contrast, the ASXL1/DNMT3A/TET2 profile was associated with significantly inferior OS (127.6 vs 284.0 months; p=0.004; HR 10.23, 95% CI 4.53–23.11), while PFS was not significantly different (p=0.188). Similarly, ASXL1/RUNX1 co-mutated patients showed reduced OS (37.4 vs 175.4 months; p=0.021), without significant differences in PFS (p=0.593).

Conclusions. autoimmunity is common and enriched in MF/CMML, but does not independently affect survival. Instead, specific mutational profiles—particularly ASXL1/DNMT3A/TET2 and ASXL1/RUNX1—are strongly associated with both autoimmunity and poor prognosis, highlighting the central role of clonal genetic background in shaping immune dysregulation and clinical outcomes.

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Myeloproliferative Neoplasms

PERFORMANCE OF SCORE2/OP, QRISK3 AND PREVENT IN PREDICTING CARDIOVASCULAR AND SURVIVAL OUTCOMES IN *BCR::ABL1*-NEGATIVE MPN

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Patients (pts) with *BCR::ABL1*-negative myeloproliferative neoplasms (MPN) are at increased risk of cardiovascular and thrombotic events. The performance of general-population cardiovascular risk models in this setting remains uncertain. The aim of this study was to evaluate and compare the predictive performance of SCORE2/OP, QRISK3, and PREVENT for arterial thrombosis (AT), venous thromboembolism (VTE), any thrombosis, and overall survival (OS) in essential thrombocythemia (ET) and polycythemia vera (PV). We retrospectively analyzed a monocentric cohort of Italian MPN pts. Risk scores were evaluated in eligible subjects according to score-specific applicability criteria. AT included myocardial infarction, ischemic stroke, or peripheral arterial thrombosis; any thrombosis was defined as the composite of AT and VTE. Associations were assessed using Cox regression; Fine-Gray (FG) models were used for non-fatal outcomes with death as competing event. Discrimination was evaluated by Harrell's C-index. The cohort included 682 pts (ET, n=485 [71.1%]; PV, n=197 [28.9%]). Median age was 64 y (IQR 51–74), 49.9% were male, and median follow-up was 5.26 y. Applicability rates were 64.5% for SCORE2/OP, 55.9% for QRISK3, and 55.1% for PREVENT. In applicable subsets, first thrombosis events were 31, 24, and 27 for SCORE2/OP, QRISK3, and PREVENT, respectively; corresponding AT events were 22, 16, and 19. SCORE2/OP was associated with AT (HR 2.37, p=0.0037) and OS (HR 3.29, p<0.001), with a trend for any thrombosis (HR 1.50, p=0.090). QRISK3 showed the most consistent performance, being associated with AT (HR 1.06, p=0.005), any thrombosis (HR 1.04, p=0.032), and OS (HR 1.11, p<0.001), confirmed in FG models for AT (p=0.0019) and any thrombosis (p=0.030). PREVENT was associated only with OS (HR 1.06, p=0.0016). None of the scores showed significant associations with VTE. Discrimination for OS was highest for QRISK3 (C-index 0.840). In ET, all scores associations were restricted to OS. In PV, QRISK3 was associated with AT, any thrombosis, and OS, with consistent FG results; PREVENT also showed associations with AT, any thrombosis, and OS, whereas SCORE2/OP retained prognostic value mainly for OS. In conclusion, QRISK3 showed the most consistent predictive performance across outcomes, with stronger prediction for arterial and overall thrombotic events than for VTE.

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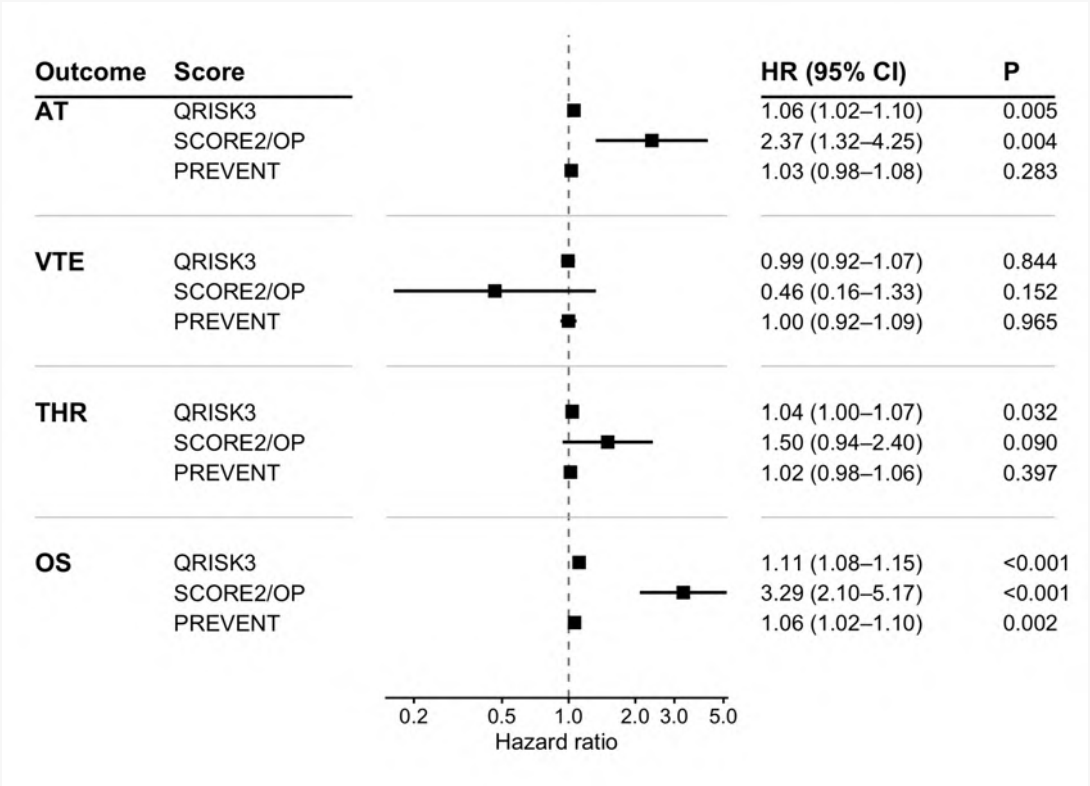
Myeloproliferative Neoplasms



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Chronic myeloid leukemia

IMPACT OF BASELINE BCR/ABL LEVELS AND PONATINIB DOSE ON TREATMENT RESPONSE IN CML

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Background. Ponatinib is currently used as a 2nd and 3rd line treatment in patients (pts) with chronic myeloid leukemia (CML). The PACE and OPTIC studies demonstrated the possibility of managing adverse events through progressive dose reduction. There are no studies correlating response with baseline transcript levels, but an OPTIC subanalysis, show that pts with baseline BCR/ABL >10% have lower response rates and that the 45 mg dose remains the most effective also for this group.

Patients and Methods. 47 pts (median age- 44 years, range- 26-79) treated with Ponatinib were evaluated. All were resistant to prior therapy. Response at 3 months (mths) was defined as at least a 1-log reduction in BCR/ABL. At 12 mths, the proportion achieving at least MR3 was osserved.

Results. -14 pts started Ponatinib at 15 mg, 16 at 30 mg and 17 at 45 mg.19 pts were in MR2, while 28 had BCR/ABL greater than 1%. In the overall cohort, 57,4% achieved a 1-log reduction at 3 mths, while 57,8% reached at least MR3 at one year. Table 1 reports results according to the different Ponatinib doses. At the start of Ponatinib therapy, 47,3% of pts who were in MR2 obtained response at 3 mths and 76,4% achieved at least MR3 at 12 mths. Table 2a presents the results for pts in MR2 at baseline according to dose. Pts with baseline BCR/ABL >1% achieved a response in 64,2% of cases at 3 mths, and at least MR3 in 47,6% at 12 mths, Table 2b summarizes the results for these pts.

Conclusions. Despite the limitations related to the small sample size,our study confirms that higher doses of Ponatinib lead to greater reductions in BCR/ABL at both 3 and 12 mths. This finding, already observed in PACE and OPTIC studies appears independent of baseline BCR levels. However it may be interesting to note that, while the one-year assessment shows a higher number of major and deep responses in pts who are already in MR2 at baseline, the early response at 3 mths,evaluated as a one-log reduction, seems to be better in pts with baseline BCR/ABL >1%.This finding could suggest that the speed of the drug's action is related to dosage and the sensitivity of the neoplastic cells, rather than to the disease burden.

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Ponatinib dosage	Number of patients	% -1 log at 3 months	% ≥ MR3 at 12 months
15 mg	14	46,8	46,1
30 mg	16	56,2	53,8
45 mg	17	70,15	75
Tot	**47**	**57,4**	**57,8**

Table 1 – Molecular response according different Ponatinib dosage

Ponatinib dosage	Number of patients	% -1 log at 3 months	% ≥ MR3 at 12 months
15 mg	5	20	50
30 mg	8	50	75
45 mg	5	66,6	100
Tot	**18**	**47,3**	**76,4**

Table 2a – Patients in MR2 at the start of Ponatinib therapy

Ponatinib dosage	Number of patients	% -1 log at 3 months	% ≥ MR3 at 12 months
15 mg	9	55,5	44,4
30 mg	8	62,5	30 *
45 mg	12	72,7	71,4
Tot	**29**	**64,2**	**47,6**

Table 2b – Patients with BCR/ABL >1% at the start of Ponatinib therapy

* In this group, the one-year assessment is unavailable for 3 patients

Allogeneic, Autologous transplant

POST-TRANSPLANT CYCLOPHOSPHAMIDE DOSE MODULATION BASED ON AGE, COMORBIDITIES AND CARDIOVASCULAR RISK FACTORS: RESULTS FROM A PROSPECTIVE PILOT STUDY

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Background. Post-transplant Cyclophosphamide (pTCy) prophylaxis of GVHD has become current clinical practice in haploidentical and mismatched unrelated donor (MMUD) stem cell transplantation. Age, pluritreated patients, and comorbidities (cardiovascular diseases, especially), may limit the use of pTCy standard dose (100 mg/kg total dose). Previous studies demonstrated the efficacy of reduced pTCy dose mainly in the haploidentical setting.

Aim. To evaluate the efficacy of pTCy dose modulation in haploidentical and MMUD transplantation, we performed a prospective pilot study on 49 patients, in which pTCy dose was reduced on the basis of patient characteristics.

Methods. From September 2024, the total dose of pTCy was reduced to 70-80 mg/kg for patients who met at least one of the following criteria: age > 60 years, HCT-CI >/=3, cardiovascular disease, pre-transplant ferritin levels>1000 ng/ml, lines of therapy >/=3, or a history of severe infectious complications. Patients without any of these criteria received the standard total dose of 100 mg/kg. Median age of patients was 55 years (range, 19-75) and 40% had HCT-CI >/=3, 14% with cardiovascular comorbidities.

Results. pTCy was reduced in 34 patients. A trend to better OS was observed in the group of reduced pTCy (1y: 73 vs 55%; p=0.08) likely due to lower TRM (1y: 11 vs 38%; p=0.03), whereas the incidence of relapse was not significantly different (1y: 31 vs 20%; p=0.50). Incidence of acute GVHD did not differ between the 2 groups (28 vs 44%; p=0.24) and chronic GVHD was lower in the pTCy-reduced groups (0 vs 17%; p=0.04). Early bacterial infections were reduced in this group as well (12 vs 46%; p=0.02). The rate of cardiotoxicity was comparable between the two groups (4% pTCy-reduced vs 7% pTCy-standard; p=0.9).

Conclusions. Reduced pTCy dose seems not only to offset the unfavorable characteristics of "unfit" patients but also to give a certain advantage in OS, by reducing bacterial infections, chronic GVHD, and TRM. The decreased toxicity could not be the single mechanism involved. Distinct effects on PD-1+T cell subsets of reduced versus standard dose of pTCy, such as increased PD1+ CD4+ and CD8+ cells, could explain the efficient immunoregulatory activity and GVHD-prophylaxis efficacy. Further trials with more patients and immuno-reconstitution analysis could confirm our findings.

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Allogeneic, Autologous transplant

COMPARABLE OUTCOMES BETWEEN DOSE REDUCED AND FULL DOSE POST-TRANSPLANT CYCLOPHOSPHAMIDE IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

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Background Post-transplant cyclophosphamide (PT-Cy) for GvHD prophylaxis after allogeneic HSCT has expanded the access to haploidentical transplantation and improved outcomes with unrelated or related donors. PT-Cy can be associated with relevant toxicities, so that reduced-dose strategies are currently explored to preserve GvHD control while improving safety, especially in elderly or frail patients.
Methods. We retrospectively compared reduced versus standard dose PT-Cy-based GvHD prophylaxis in adult patients transplanted between January 2021 and December 2024 in our Unit. Patients were stratified into a standard--dose (SD, 100 mg/kg overall on days +3 and +4) and a reduced-dose group (RD, 50-80 mg/kg on days +3 and +4, according to clinical judgment).Primary endpoint was the cumulative incidence of grade II–IV aGvHD. Secondary endpoints included cumulative incidence of cGvHD, 1-3 year OS, 1-2 year GRFS, 1-3 year PFS, and 1-year NRM.
Results. 82 patients were included, 36 in the RD and 46 in the SD. AML was the main diagnosis (43%), and donor was haploidentical in 61% of the cases. RD showed older age (p<0.001), more cardiac comorbidities (p= 0.043) and bacterial colonization (p=0.04).aGvHD occurred in 34 (41%) patients and cGvHD in 18 (22%), without a significant difference in incidence between the two dose-groups. In multivariable analysis, PT-Cy dose reduction was not an independent risk factor for aGvHD (p=0.64).After a median follow-up of 490 days, outcomes were not significantly different between the two cohorts, including OS (62.1 vs. 69.6%), GRFS (32.9 vs. 30.1%) (figure 1), PFS (60.4 vs. 67.8%), NRM (25 vs. 25%) (all 1-year estimates; RD vs. SD, respectively). In Cox analysis having ≥2 comorbidities were associated with impaired OS [HR 3.52 (1.15-10.78), p=0.02].RD was associated with faster neutrophil [median days 18 (16-21) vs 24.4 (21-28), p=0.01] and platelet engraftment [19(14-22) vs 24 (19-31), p=0.08]. Infectious complications did not differ significantly, and no PT-Cy related toxicities were observed.
Conclusions. Reduced-dose PT-Cy emerged as a safe and effective strategy, with survival outcomes and GvHD incidence comparable to standard-dose, while engraftment was significantly faster, supporting dose reduction as a valid option especially in older or frail patients. Prospective multicenter studies are needed to define optimal dose cut-offs and refine patient selection.

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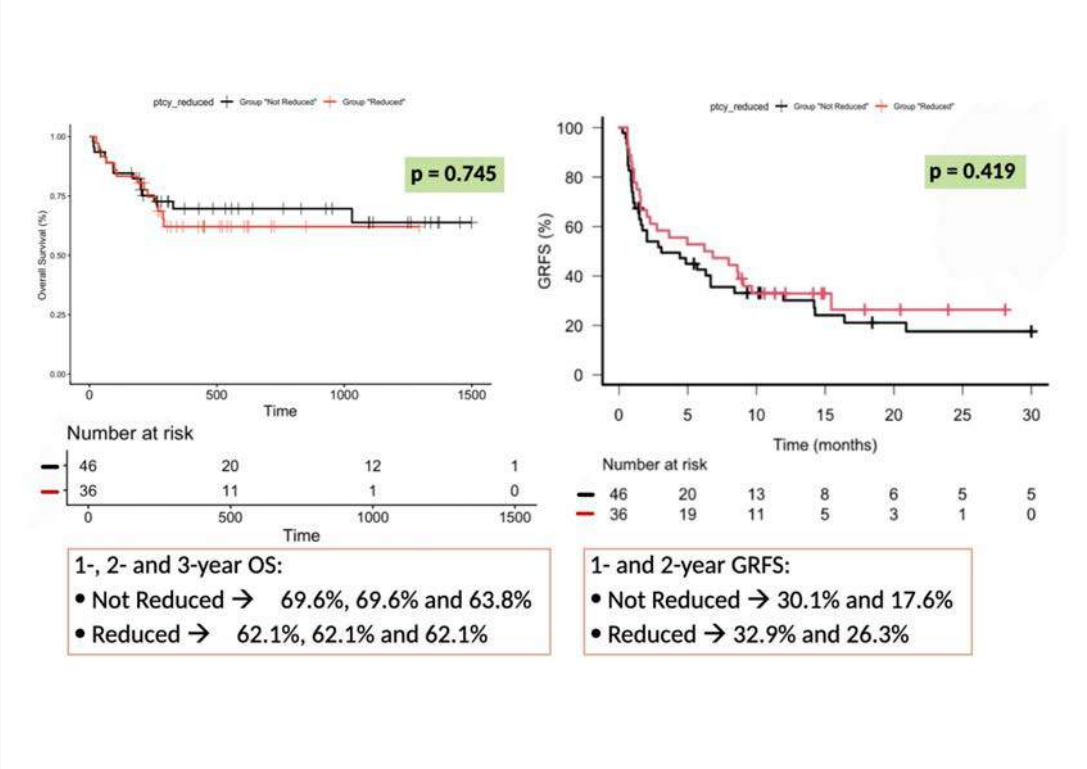

Allogeneic, Autologous transplant

IMPACT OF STEM CELL INFUSION TIMING ON THE INCIDENCE OF ACUTE GRAFT-VERSUS-HOST DISEASE IN UNRELATED DONOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

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Introduction. Circadian rhythms seem to play a crucial role in regulating immune responses and hematopoietic homeostasis. Recent studies have suggested that later timing of stem cell infusion in allogeneic hematopoietic cell transplantation (alloHCT) may negatively affect the risk of acute graft-versus-host disease (GvHD). We evaluated the impact of infusion timing on clinical outcomes after alloHCT using peripheral blood stem cell grafts from unrelated donors (UD).

Methods. We conducted a single-center retrospective study including consecutive UD alloHCT recipients transplanted at IRCCS San Raffaele Hospital between August 2018 and September 2025 who received post-transplant cyclophosphamide (PTCy) as GvHD prophylaxis. Infusion timing was primarily determined by the logistics of stem cell product arrival and was analyzed as a dichotomous variable using an exploratory cutoff derived from the literature and further confirmed by receiver operating characteristic (ROC) curve analysis. Primary endpoint was the incidence of acute GvHD within 100 days after transplantation. Secondary endpoints were GvHD/relapse-free survival (GRFS) and the incidence of chronic GvHD.

Results. Among 272 patients undergoing UD alloHCT during the study period, 246 (90%) had infusion timing data available and were included in the study. Median follow-up among survivors was 58 months (range, 2-191). ROC analysis identified 12:00 as the best exploratory threshold, although with modest discriminatory performance (AUC 0.60). Patients were therefore classified into early (N=80, 33%) and late (N=166, 67%) infusion group. Baseline clinical and transplant characteristics were balanced between groups. The only significant difference concerned grade 1 skin-only acute GvHD, which was less frequent in the early infusion group (10% versus 24.6%, $p<0.01$). No differences were observed in the incidence of grade 2-4 acute GvHD and any grade chronic GvHD. Unexpectedly, the early infusion group showed lower GRFS compared with the late one (45% versus 55% at 2 years; $p=0.02$).

Conclusions. In line with recent findings in the setting of UD alloHCT with rabbit anti-thymocyte globulin-based GvHD prophylaxis, our results confirm that stem cell infusion timing does not significantly influence the risk of clinically relevant acute GvHD in the PTCy setting. These findings highlight the complex nature of GvHD and suggest that infusion scheduling may continue to be primarily guided by logistical considerations.

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A MULTI-COUNTRY RETROSPECTIVE STUDY ON THE EFFECTIVENESS OF BELUMOSUDIL FOR CHRONIC GRAFT VERSUS HOST DISEASE (ROCKREAL II STUDY)

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Background. Chronic graft-versus-host disease (cGVHD) remains a major cause of long term morbidity and impaired quality of life following allogeneic hematopoietic stem cell transplantation, with many patients requiring prolonged systemic therapy. Belumosudil, a selective ROCK2 inhibitor, is approved for refractory cGVHD, however evidence across varied European clinical practice is limited. This study evaluates the effectiveness of belumosudil in patients with refractory cGVHD treated in Europe.

Methods. ROCKreal II is a retrospective chart review study aimed to collect real-world data on patients receiving belumosudil across Spain, Italy and United Kingdom, with a target enrolment of 150 patients. The study aims to include patients from Spain and Italy (receiving belumosudil through early access / compassionate programs) and the UK (receiving treatment under approved label). Study eligibility criteria include patients aged ≥12 years with a diagnosis of cGVHD who had received belumosudil. Data collection for this interim analysis occurred between August 2025 and January 2026. The primary outcome, was 6-month overall response rate (ORR), defined as the proportion of complete or partial responses based on 2014 National Institutes of Health consensus criteria, supplemented by a hierarchical algorithm incorporating the treating physician's assessment or a ≥50% reduction in corticosteroid dose without progression of cGVHD.

Results. A total of 44 patients were included in the interim analysis, with enrolment from Spain (75%) and Italy (25%). Median age at cGVHD diagnosis was 46 years (IQR 30.0–55.5), and 65.9% were male. Median time from cGVHD diagnosis to belumosudil initiation was 26 months (IQR 13.1–50.5), with the median age at initiation being 48.5 years (IQR 36.0–57.0). The average number of LOTs prior to Belumosudil was 3 (IQR 2.0-4.0). Two-thirds of patients received belumosudil as third- or fourth-line therapy, and 82% had been previously treated with ruxolitinib. Among those with evaluable response at 6 months (n=32) the overall response rate at six months following belumosudil initiation was 56.3% (18/32). Additional analyses are currently ongoing to characterize the study cohort.

Conclusions. Despite a heavily pretreated population—with 80% having received prior ruxolitinib and two-thirds initiating belumosudil at third or fourth line—more than nearly half of evaluable patients achieved a clinical response at six months. *This study was funded by Sanofi*

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DOES REDUCING METHOTREXATE IMPROVE GVHD PROPHYLAXIS? A SINGLE-PROGRAM EXPERIENCE

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Background. Methotrexate (MTX) is standard prophylaxis for GVHD in matched allogeneic HSCT, but optimal dosing remains debated. A retrospective study at AORN Cardarelli (Naples) compared two MTX schedules to evaluate effects on acute and chronic GVHD incidence/severity, infections, gastrointestinal (GI) toxicity and grading, overall survival (OS), time to discharge, engraftment, non-relapse mortality (NRM), and time to relapse (TTR).

Methods. We assessed safety and efficacy of 4 MTX doses (N=59) versus 3 doses (N=29) (15 mg/m² day +1; 10 mg/m² days +3, +6, and +11 only in the 4-dose group) using target trial emulation on real-world AML/MDS and ALL cohorts. Baseline differences were evaluated by standardized mean differences (SMD), with ≥|0.10| indicating imbalance. Variables above this threshold informed propensity scores to generate inverse probability of treatment weighting (IPTW), creating a balanced pseudo-population.Weighted logistic regression analyzed GVHD, infections, and GI toxicity (reported as odds ratios, OR). Weighted Cox models assessed time-to-event outcomes (reported as hazard ratios, HR). NRM and TTR were analyzed with Fine–Gray competing risk models, considering relapse or other death as competing events for NRM, and NRM for TTR.

Results. After IPTW, baseline characteristics were balanced (all SMD<|0.07|). GI toxicity and its maximum grade were significantly lower in the 3-dose group (OR 0.17, 95% CI 0.06–0.47, p<0.01; max grade: OR 0.17, 95% CI 0.04–0.77, p=0.01). No significant differences emerged for aGVHD (OR 1.19, 95% CI 0.39–3.65, p=0.79; max grade: OR 1.10, 95% CI 0.11–10.48, p=0.93), cGVHD (OR 2.64, 95% CI 0.93–7.45, p=0.18; max grade: OR 1.17, 95% CI 0.32–4.24, p=0.85), time to discharge (HR 1.19, 95% CI 0.75–1.89, p=0.45), or engraftment (HR 1.40, 95% CI 0.91–2.14, p=0.13).Overall mortality was 28.4%, NRM 7.9%, and median survival was not reached. No differences were observed in OS, NRM, or TTR (HR 0.76, 95% CI 0.25–2.28, p=0.62; SHR 1.38, 95% CI 0.21–8.96, p=0.74; SHR 0.55, 95% CI 0.16–1.91, p=0.35).

Conclusions. In this single-center adult transplant program, 3 versus 4 MTX doses for GVHD prophylaxis showed no significant differences in transplant outcomes, including engraftment, NRM, TRM, OS, or GVHD incidence/severity. However, reducing MTX may decrease severe mucosal injury, lowering both occurrence and intensity of GI toxicity.

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Table 1. Baseline characteristics

	Baseline population				Weighted pseudopopulation			
	4 doses	3 doses	p value	Test SMD	4 doses	3 doses	p value	Test SMD
N	59	29			57.21	28.64		
Age (mean (SD))	44.6 (14.4)	46.9 (16.4)	0.516	0.144	45.32 (15.05)	44.85 (14.40)	0.900	-0.0308
Sex n (%): F M	30 (50.8) 29 (49.2)	13 (44.8) 16 (55.2)	0.761	0.121	28.4 (49.7) 28.8 (50.3)	12.7 (44.5) 15.9 (55.5)	0.724	0.0518
Diagnosis n (%): ALL AML/MDS HR	17 (28.8) 42 (71.2)	6 (20.7) 23 (79.3)	0.577	0.189	15.2 (26.6) 42.0 (73.4)	6.2 (21.9) 22.4 (78.1)	0.709	0.0465
Donor n (%): MUD 8/8 Sibling	24 (40.7) 35 (59.3)	22 (75.9) 7 (24.1)	0.004	0.764	30 (52.4) 27.2 (47.6)	16.9 (59.1) 11.7 (40.9)	0.656	-0.0672
Conditioning regimen n (%): -low intensity -high-moderate intensity	14 (23.7) 45 (76.3)	16 (55.2) 13 (44.8)	0.007	0.679	17.4 (30.4) 39.8 (69.6)	8.6 (30.2) 20 (69.8)	0.983	0.0026

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RUXOLITINIB AS TREATMENT FOR CENTRAL NERVOUS SYSTEM ATYPICAL MANIFESTATION OF GRAFT-VERSUS-HOST DISEASE

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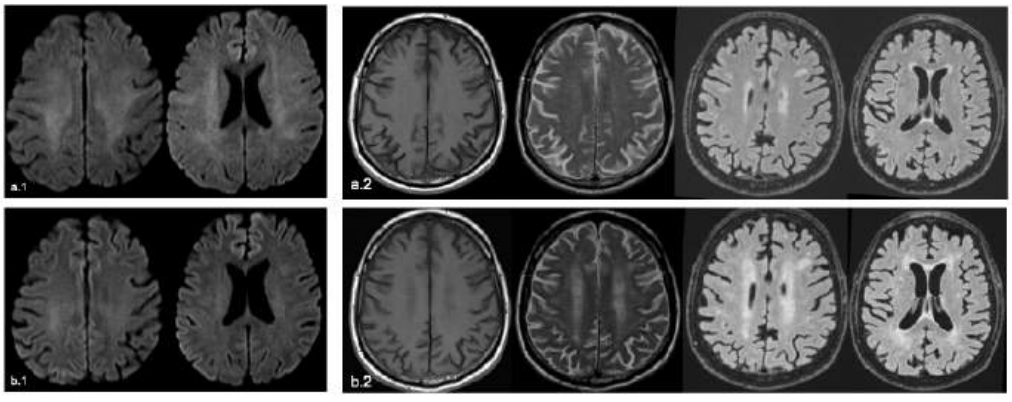
Central nervous system(CNS) can be involved in some cases as atypical manifestation of GVHD following allogeneic hematopoietic stem cell transplantation(HSCT), but diagnosis and treatment are challenging. In this retrospective study, we identified all patients(pts) that developed immune-mediated CNS manifestations after an HSCT performed at our institution between January 2020 and Decembrer 2024, among the spectrum of atypical chronic GVHD (cGVHD) manifestations, as proposed by the 2020 NIHcGVHD Consensus Project. Of 328HSCT at our Center, 147(45%) pts developed acuteGVHD and 84(26%) cGVHD. Two pts(0,6%)developed atypical CNS-GVHD with similar neurological symptoms, Magnetic-Resonance(MRI) features, proinflammatory cytokine patterns in blood and cerebrospinal fluid(CSF), and steroid refractoriness. The first case was a 31-year-old man with B-acute lymphoblastic leukemia who underwent HSCT from a matched unrelated donor in complete remission. At day+45,severe upper Gastrointestinal(GI) GVHD appeared with associated tremor, cortical myoclonus, transient Lhermitte's sign. MRI showed bilateral subcortical/deep white matter T2hyperintensities; CSF pleocytosis, proinflammatory cytokine pattern without infection or relapse. Steroids induced GIremission and partial neurological benefit. During tapering, neurological worsening occurred with behavioral changes, cognitive impairment (Montreal Cognitive Assessment-MoCA test25/30), tremor, postural instability, and apraxia, along with MRI progression, and Electroencephalogram(EEG) abnormalities. Ruxolitinib(15-10mg/day due to cytopenia) led to rapid recovery and normalization. The patient is still alive, in remission, and off steroids. The second case was a 74-year-old man with relapsed follicular lymphoma undergoing HSCT from a fully matched unrelated donor. After steroid-responsive acute GVHD, he developed GI cGVHD with neuropsychiatric signs associated. MRI, CSF, and EEG supported CNS-GVHD involvement. Steroids induced transient benefit, but symptoms worsened during tapering. Ruxolitinib(15mg/day) achieved rapid normalization. At follow-up, patient remains in remission, neurologically intact, and steroid-free. In our series only 2(0,6%) patients developed CNS-GVHD both steroid refractories. These two cases highlight the complexity of managing CNS-GVHD, from diagnosis to treatment. Ruxolitinib resulted effective leading to a rapid and durable clinical response, normalization of EEG and amelioration of MRI features.

Figure 1 Immaging of CNS-GVHD patients a1) Case 1 widespread subtle hyperintensity in Diffusion Weighted Images (DWI) in the white matter of the corona radiata and centra semiovalia at diagnosis of CNS-GVHD involvement b1) Case 1 DWI progressive reduction in the extent of the signal abnormality after ruxolitinib. a2) Case 2 Baseline scan prior to HSCT and b2) at diagnosis of CNS-GVHD involvement a moderate increase in the extent of T2/FLAIR signal abnormality is observed in the periventricular region, the corona radiata and centra semiovalia.



Allogeneic, Autologous transplant

AZACITIDINE AS POST-TRANSPLANT MAINTENANCE THERAPY IN ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROMES: EFFICACY, SAFETY AND IMMUNE RECONSTITUTION DYNAMICS

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Background. Disease relapse after allogenic hematopoietic stem cell transplantation (HSCT) is a major adverse prognostic event in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Post-transplant maintenance strategies have been introduced to mitigate this risk. Azacitidine (AZA) is currently the only available maintenance option for high-risk MDS and adverse-risk AML without FLT3 mutations, although evidence remains inconsistent. We conducted a single-center retrospective study to compare survival, safety, and immune reconstitution in patients receiving or not receiving post-HSCT AZA.

Methods. We analyzed 83 adult patients undergoing HSCT in our center between September 2019 and November 2024. Patients were grouped as follows: AZA+ (n=25), receiving AZA 32 mg/m^2/day subcutaneously for 5 days every 28 days (planned 12 cycles), mostly with adverse-risk AML or high/very high-risk MDS; AZA− (n=42), not receiving AZA, with heterogeneous risk; and FLT3+ (n=16), receiving Sorafenib or Gilteritinib.Patients' baseline characteristics are summarized in the table below. Immune reconstitution was assessed by lymphocyte subsets at days +60, +120, +180, +365, and +730.

Results. AZA was not associated with increased acute or chronic GvHD (20% vs 36%, p=0.26; 20% vs 24%, p=0.77), infections (64% vs 79%, p=0.25), CMV (32% vs 40%, p=0.65), or EBV reactivation (36% vs 43%, p=0.61), compared with AZA− patients. Median overall survival (OS) and progression-free survival (PFS) were not reached in either group (p=0.68; p=0.73). Median GvHD-free/relapse-free survival (GRFS) was longer in AZA+ patients (16 vs 14 months), with a trend toward improved 1-year GRFS (p=0.19). AZA+ patients showed early higher NK-cell counts compared with AZA− patients (1-year post-HSCT median NK-cell counts: 298/µL vs. 220/µL, p = 0.11) and, at 1 year, significantly higher total T cells (1768 vs 1121/µL, p=0.03), CD8$^+$ T cells (731 vs 387.5/µL, p=0.04), and NK cells (298 vs 170.5/µL, p=0.01) compared with FLT3+ patients.

Conclusions. Post-HSCT AZA maintenance is safe and well tolerated. Despite higher baseline risk, AZA-treated patients achieved OS and PFS comparable to untreated patients, with signals of improved GRFS and enhanced immune reconstitution, supporting its use in high-risk AML and MDS.

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	Total (N=83)	AZA⁺ (N=25)	AZA⁻ (N=42)	FLT3⁺ (N=16)
Sex - N° (%) Males Females	 43 (52%) 40 (48%)	 12 (48%) 13 (52%)	 24 (57%) 18 (43%)	 7 (44%) 9 (56%)
Median Age at Diagnosis, yrs. (range)	56 (48-63)	55 (49.50-63.50)	60.50 (53-63.25)	48 (36.50-57)
Diagnosis - N° (%) MDS AML	 24 (29%) 59 (71%)	 8 (32%) 17 (68%)	 16 (38%) 26 (62%)	 0 16 (100%)
ELN Risk Profile - N° (%) Favorable Intermediate Adverse	 11 (19%) 14 (23%) 34 (58%)	 1 (6%) 2 (12%) 14 (82%)	 10 (38%) 5 (19%) 11 (43%)	 0 7 (44%) 9 (56%)
IPSS-R Risk Score - N° (%) Very Low Low Intermediate High Very High	 2 (8%) 2 (8%) 7 (29%) 5 (21%) 8 (34%)	 1 (12%) 1 (13%) 3 (38%) 1 (12%) 2 (25%)	 1 (6%) 1 (6%) 4 (25%) 4 (25%) 6 (38%)	
Karyotype - N° (%) Normal Complex Others NE	 35 (42%) 10 (12%) 35 (42%) 3 (4%)	 6 (24%) 1 (4%) 16 (64%) 2 (8%)	 15 (36%) 8 (19%) 18 (43%) 1 (2%)	 14 (88%) 1 (6%) 1 (6%) 0
TP53 Mutation - N° (%)	13 (16%)	6 (24%)	7 (17%)	0
Additional Criteria - N° (%) MDS and AML Therapy-related AML Myelodysplasia-related sAML following MPN	 11 (13%) 17 (20%) 7 (9)	 4 (16%) 7 (28%) 3 (12%)	 6 (14%) 8 (19%) 4 (9%)	 1 (6%) 2 (13%) 0

Allogeneic, Autologous transplant

ALLOGENEIC TRANSPLANT IN RELAPSED/REFRACTORY T CELL LYMPHOMAS IN THE ERA OF NEW DRUGS FOR SALVAGE THERAPY

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Introduction. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative option for patients with relapsed/refractory T-cell lymphoma. The combination of new drugs to achieve remission before transplant and reduce intensity conditioning (RIC) might be the best strategy to maximize disease control and reduce non-relapse mortality (NRM).

Results. We report on sixteen patients, median age 53.5 (range 24-70), transplanted between 2014 and 2025. Histologic subtypes were: T-Follicular Helper (n=5, 2 angioimmunoblastic-type), Anaplastic Large Cell Lymphoma (n=3, 2 ALK+ and 1 ALK-), Peripheral T-cell lymphoma NOS (n=3) Extranodal NK/T (n=2), Hepatosplenic (n=2) and Mycosis fungoides (n=1).Patients underwent allo-HSCT after a median of 3 lines of therapy (range 2-8), with a new drug being the last line (Brentuximab, Duvelisib, Linprelisib, CKD 9-inhibitors, Valemetostat, Pembrolizumab, anti-CD94 antibody DR-01); most of them achieved complete remission before allo-HSCT (14/16, 87.5%), with only 1 partial remission and 1 stable disease.All patients received fludarabine-based reduced intensity conditioning (RIC) and three-drugs GVHD prophylaxis with calcineurin inhibitor + antimetabolite + ATLG (n=14) or PT-Cy (n=2). Donors were: 9 matched unrelated, 4 mismatched unrelated (HLA 7/8), 2 matched sibling, 1 haploidentical.Nine patients (56.2%) developed aGVHD, 6 (37.5%) grade II-IV and 2 (12.5%) grade III-IV; 6 (37.5%) developed cGVHD, 3 (18.8%) moderate-severe.At a median follow-up of 29 months (873 days), 3 patients died (18.8%) for drug-toxicity, infections and/or aGVHD. Only 1 (6.3%) with Mycosis fungoides relapsed and is currently alive, on treatment with donor lymphocyte infusion (DLI).One-year incidence of relapse and NRM are 6 % (95% C.I. 0%-25%) and 19.2% (95% C.I. 5%-41%), respectively.Disease free survival (DFS) and Overall Survival (OS) at 1 year are 74.5% (95% C.I. 45%-90%) and 81% (95% C.I. 51%-93%). No additional relapse or death events have been recorded beyond 1 year.

Conclusions. The combination of new drugs as bridge to allo-HSCT and RIC shows encouraging DFS and OS for patients with R/R T-cell lymphoma and may be a curative option for patients who achieve remission before transplantation.

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Allogeneic, Autologous transplant

IMPACT OF PULMONARY FUNCTION TESTING ON BRONCHIOLITIS OBLITERANS SYNDOME AND OUTCOME AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

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Background. Bronchiolitis obliterans syndrome (BOS) is a progressive small airway disease that can develop after hematopoietic stem cell transplantation (HSCT), often with poor therapeutic response and progression to respiratory failure. Diagnosis relies on pulmonary function testing (PFT).

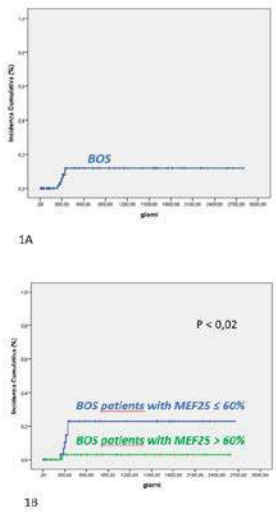
Aims. We investigated the role of PFT as a predictive marker in BOS and graft-versus-host disease (GvHD) after HSCT. Methods We retrospectively analyzed allogeneic HSCT recipients from January 2018 to May 2025 at Cardinale G. Panico Hospital (Tricase, Italy) with available baseline PFT. BOS was defined using modified 2005 NIH criteria. Mid-expiratory flow at 75% of forced vital capacity (MEF75), 50% (MEF50), 25% (MEF25), and the mid-expiratory flow range between 75% and 25% (MEF75–25) ≤60% predicted were evaluated as additional markers of small airway obstruction and as potential predictors of BOS and GvHD. Univariate and multivariate logistic regression were performed using SPSS 20.0. Kaplan–Meier estimates evaluated time-to-event outcomes.Results. Among 105 included patients (median age 56 years), 60% had a past or current smoking history, and 6% had pre-transplant chronic obstructive pulmonary disease (COPD). Acute leukemia was the most common indication for HSCT. Overall, 69% of patients received a matched unrelated donor transplant (table 1). BOS was diagnosed in 7 (7%) patients, at a median of 297 days (243-344) after HSCT; all had evidence of chronic GVHD at another site. Patients' clinical features, hematologic disease, transplant-related variables, smoking history and pre-transplant COPD diagnosis were not significantly associated with BOS (table 1). We analyzed the role of pre-transplant PFTs in the development of BOS, acute and chronic GvHD. Pre-transplant MEF25 ≤60% was significantly more frequent in BOS patients (86% vs 47%, p=0.05, table 1). MEF75 ≤60% was associated with acute GvHD (19% vs 3%, p=0.004), while no PFT parameter correlated with chronic GvHD.

Conclusions. We identified novel pre-transplant PFT abnormalities associated with the development of BOS and acute GvHD. These findings may help identify a high-risk population and guide preventive or early therapeutic interventions.

Table.1

	Total (n = 105)	With BOS (n = 7, 7%)	Without BOS (n = 98, 93%)	P value
Male patients, n (%)	64 (61)	2 (29)	62 (63)	0,75
Age (yr), median (range) > 65 yr, n (%)	56 (17-71) 17 (16)	55 (20-61) 0	56 (17-71) 17 (17)	0,67
Smoking, n (%) Current, n (%)	56 (60) 14 (15)	4 (57) 0	52 (60) 14 (16)	0,89
Pre-HSCT COPD, n (%)	6 (6)	0	6 (6)	0,493
Acute leukemia, n (%) Lymphoma, n (%) Others, n (%)	61 (58) 22 (21) 22 (21)	5 (71) 0 2 (29)	56 (57) 22 (22) 20 (20)	0,366
Complete remission at HSCT, n (%)	65 (62)	6 (86)	59 (60)	0,14
Matched-unrelated donor, n (%)	72 (69)	2 (29)	70 (71)	0,45
Myeloablative Conditioning regimen, n (%)	63 (60)	4 (57)	59 (60)	0,176
Antithymocyte globulin prophylaxis, n (%)	64 (61)	5 (71)	59 (60)	0,56
FEV_1 (%), median (range) ≤ 80 %, n (%)	103 (49-153) 9 (9)	98 (75-112) 1 (14)	103 (49-153) 8 (8)	0,59
FEV_1/FVC, median (range) ≤ 70 %, n (%)	80 (58-96) 5 (5)	82 (75-89) 0	80 (58-95) 5 (5)	0,53
MEF75 (%), median (range) ≤ 60 %, n (%)	100 (37-149) 6 (6)	108 (91-125) 0	99 (37-145) 6 (6)	0,43
MEF50 (%), median (range) ≤ 60 %, n (%)	85 (28-174) 14 (14)	89 (64-98) 0	85 (28-174) 14 (15)	0,27
MEF25 (%), median (range) ≤ 60 %, n (%)	61 (12-203) 51 (50)	52 (48-103) 6 (86)	63 (12-203) 45 (47)	0,05
MEF75-25 (%), median (range) ≤ 60 %, n (%)	78 (21-168) 20 (20)	74 (60-95) 1 (14)	81 (21-168) 19 (20)	0,71

Figure.1A -1B



1A

1B

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Allogeneic, Autologous transplant

VIRAL REACTIVATION DURING CHRONIC GRAFT VERSUS HOST DISEASE INCREASES THE RISK OF NON-RELAPSE MORTALITY FOLLOWING CURATIVE ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANT A MONOCENTRIC, RETROSPECTIVE STUDY

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Background. Allogeneic haematopoietic stem cell transplantation(allo-HSCT) is a potentially curative option for patients with high-risk haematological malignancies, but outcomes are significantly impaired by disease relapse and immunological complications. Chronic graft-versus-host disease (cGVHD)per se and its treatment are known risk factors for opportunistic infections and viral reactivations. Herein we evaluated the prevalence and impact ofCMV,HHV6,EBV and Adenovirus reactivations following the diagnosis of cGVHD.
Methods. Between2002 and2024, 618adult patients underwent allo-HSCT at the Adult Bone Marrow Transplant Center of the Spedali Civili di Brescia; 169 patients(27%) developed cGVHD and were considered eligible for the analysis.The primary objective of the study was the impact of viral reactivations on non-relapse mortality (NRM). Overall survival, cumulative(OS), incidence of relapse (CIR),progression-free survival (PFS)and disease-related death(DRD) were assessed as endpoints.
Results. Fifty-nine percent of cGVHD patients developed a viral reactivation. The 2-year and 5-year OS for cGVHD patients with viral reactivations and without was 83.7% and72.4%, 90% and 78.5%, respectively(p = 0.11).PFS showed no differences between the two subgroups, resulting in 83% at 2 years and 79.4% at 5 years in both groups(p = 0.72). Similarly, the CIR at 2 and 5 years showed no significant differences between the two groups: 8.6% and 11.7% in patients with viral reactivations compared to 11.3% and 16.9% in patients without viral reactivations (p = 0.606). The 2-year and 5-year NRM was higher following viral reactivations compared to cGVHD patients who never developed this complication(11.3% and 19.1%, vs 3.9% and 9.5%, respectively– p = 0.021 – Figure 1). The disease-related death was comparable within the two groups of cGVHD patients.
Discussion and Conclusions. This study shows that occurrence of viral reactivations is not associated with a statistically significant reduction in OS or PFS. The occurrence of viral reactivations in patients with cGVHD represents a clinically relevant complication, significantly associated with an increased NRM. Although these events do not appear to directly impact overall survival or progression-free survival, they likely reflect a state of profound immune dysregulation and vulnerability. These findings underscore the importance of careful virological monitoring and optimized management of immunosuppression in cGVHD patients.

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Allogeneic, Autologous transplant

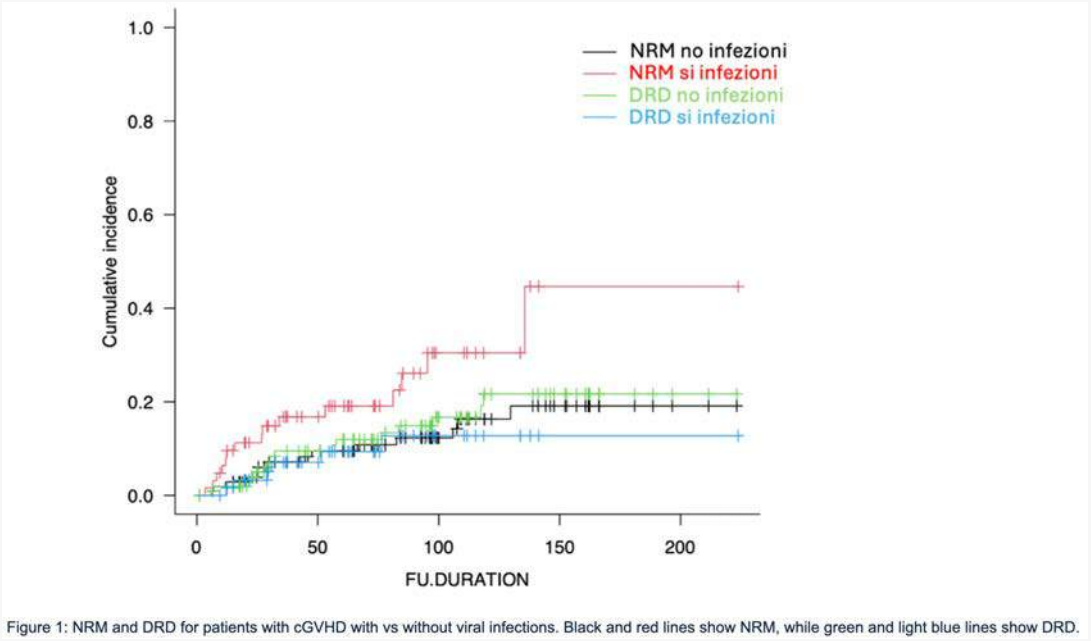

Figure 1: NRM and DRD for patients with cGVHD with vs without viral infections. Black and red lines show NRM, while green and light blue lines show DRD.

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Myeloma and other monoclonal gammopathies

MRD-NEGATIVE CONVERSION WITH DARATUMUMAB MONOTHERAPY IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS IN VGPR/MRD-POSITIVE AFTER FIRST-LINE THERAPY: FINAL ANALYSIS OF THE OPEN-LABEL, SINGLE-ARM MULTICENTRIC PHASE 2 TRIAL DART4MM

A. Gozzetti[1], P. Pacelli[1], F. Caroni[1], D. Raspadori[1], E. Bestoso[1], E. Antonioli[2], G. Buda[3], S. Ciofini[1], A. Santoni[1], P. Galieni[4], L. Puccetti[1], F. Bacchiarri[1], L. Pengue[2], D. Tocci[1], I. Attucci[2], M.L. Del Giudice[3], M. Ruggieri[4], A. Lombardo[5], A.M. Liberati[6], V. Candi[7], V. Sammartano[1], A. Cartocci[1], A. Sicuranza[1], S. Galimberti[3], A.M. Vannucchi[2], M. Bocchia[1]

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Background. Daratumumab is approved in frontline and relapsed myeloma therapy. Here, we evaluated daratumumab in newly diagnosed multiple myeloma patients already in ≥VGPR but MRD positive by NGF after first-line therapy, with the potential to eradicate the disease.

Methods. In this prospective, uncontrolled, open-label, single-arm phase 2 trial, between December 2018 and March 2022, we consecutively evaluated 110 eligible patients with newly diagnosed multiple myeloma for MRD positivity at 10-6 in the bone marrow and daratumumab naïve after a first-line therapy. Fifty patients were positive and were treated with 6 months daratumumab (16 doses). The primary endpoint was the response after 6 months: MRD-negative patients stopped treatment, while positive patients continued for a total of 24 months.

Results. At the primary endpoint 15/49 (31%) patients become MRD negative. At 24 months 11/39 (30%) evaluable patients were still MRD negative. At a median follow-up of 50 months (31-73), 29 (58%) patients relapsed (15 before 24 months). Median PFS is reached at 45 months (3-64), and OS is not reached. Achieving at least one-time MRD negativity was significant (progression-free survival of 61 vs 26 months, HR 0.24 CI 0.10 to 0.56; p=0.0009). 21/50 patients did not progress at a median time of 44 months (range 31-73) and 4 of the relapsed patients are still in duration of response, untreated.

Conclusions. Daratumumab improved MRD-negative conversion rate in NDMM patients in 30% of the patients and this rate was maintained over 24 months. PFS favored patients who achieved at least one MRD-negative timepoint. In newly diagnosed multiple myeloma, adding daratumumab as consolidation after a first-line therapy improved long-term overall response rates. The safety profile was good.Trial Registration. The trial was registered (EudraCT Number 2018-000386-36) .

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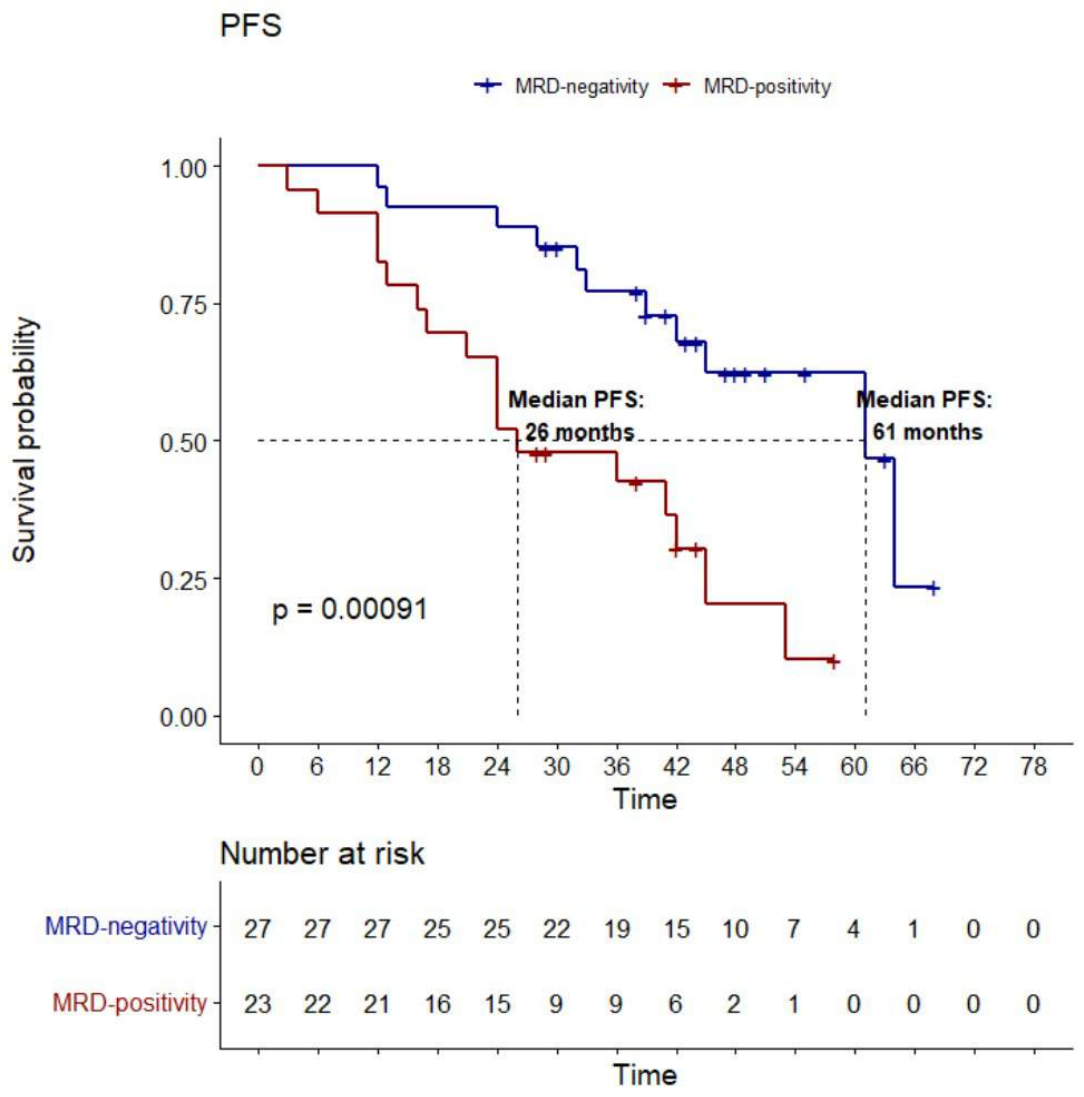
PFS
MRD-negativity
MRD-positivity
Survival probability
1.00
0.75
0.50
0.25
0.00
Median PFS:
26 months
Median PFS:
61 months
p = 0.00091
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time
Number at risk
MRD-negativity 27 27 27 25 25 22 19 15 10 7 4 1 0 0
MRD-positivity 23 22 21 16 15 9 9 6 2 1 0 0 0 0
Time

Myeloma and other monoclonal gammopathies

DARAVTD AND ASCT+ LENALIDOMIDE LED TO HIGH CR AND MRD NEGATIVITY RATES BY NGF: A REAL-WORLD STUDY OF THE TUSCAN MYELOMA NETWORK IN 228 PATIENTS

S. Ciofini[1], V. Venanzi[1], E. Antonioli[2], G. Buda[3], E. Bestoso[1], P. Pacelli[1], D. Raspadori[1], V. Candi[4], L. Pengue[2], Ml Del Giudice[3], A. Caremani[4], S. Moretti[5], G. Fontanelli[5], I. Attucci[2], Mt Pirrotta[5], C. Biagiotti[5], S. Birtolo[5], S. Grammatico[5], S. Pilerci[6], L. Notarfranchi[7], G. Tancredi[3], S. Galimberti[3], M. Bocchia[1], A. Gozzetti[1]

[1]Department of Medicine Surgery and Neuroscience Hematology, University of Siena; [2]Department of Hematology, Careggi Hospital and University of Florence; [3]Department of Clinical and Experimental Medicine, Hematology, University of Pisa; [4]Hematology Unit, Ospedale SDonato; [5]USL Toscana Centro, SOC Oncoematologia; [6]Hematology Ospedale della Versilia; [7]Hematology

Real-life DARA-VTD by the Multiple Myeloma Tuscan network (RTM) is an observational and retrospective, multicenter, no-profit clinical study that tested real-life data in patients with NDMM treated according to the DaraVTd induction regimen follow by ASCT, consolidation, and lenalidomide maintenance.

Methods. NDMM TE received induction treatment with Dara-VTD, after 4 cycles of therapy, CSE collection was performed. Following the administration of 4-6 cycles of therapy, patients underwent ASCT followed by consolidation with Dara-VTD (any missing cycles) and maintenance with Lenalidomide 10 mg/day. MRD analysis was performed using next -generation flow cytometry (NGF). FISH was done after plasmacells separation at diagnosis. HR was considered del17p, t4;14, t14,16, amp1q.

Results. 228 patients (M/F ,127/101) were enrolled with a median age of 62 years at diagnosis. Median follow up is 15 months(4-46). Grade 3-4 hematologic toxicities (anemia and/or leukopenia and/or thrombocytopenia) occurred in 7,4% of patients, while non-hematologic toxicities occurred in 21,9% of patients. 14 of 228 patients died (6,14%), including seven (3.07%) due to toxicity/sepsis during induction. Response after four cycles of Dara-VTD, showed 12.9% sCR, 11.29% CR, 52.15% VGPR, 19.35% 4.84% PD. Post -ASCT response was: 36,6% sCR, 17,65% CR, 36,6% VGPR, 5,88% SD, 3,27% PD (>CR 53%). The overall MRD negativity rate was approximately 51.8% pre-ASCT and 77.9% post-ASCT. MRD was tested on a total of 106 pre-ASCT patients, with a sensitivity of 10^-5 in 82 and 10^-6 in 24. Post-ASCT evaluation was performed on 82 patients, with a sensitivity of 10^-5 in 56 and 10^-6 in 26. The overall PFS at 12 months was 92.7%: 94.4% ISS stage I vs. 88.4% stage III (p=0.37); standard cytogenetic risk 96.4% vs. 88% high cytogenetic risk (p=0.05); beta2-microglobulin <3 mg/L 95% vs 87% in patients with a beta2-microglobulin value >5 mg/L (p=0.14); >VGPR post induction 93% vs 83% PR-PD (p=0.01); 96% >VGPR post ASCT vs 78% PR-PD (p=0.0026). Finally, we analyzed PFS stratified by patients who received or did not receive maintenance therapy with lenalidomide after autologous transplantation. A 12-month PFS of 94.9% was observed in patients who received this treatment versus 79.3% at 12 months in patients who did not receive maintenance therapy (p = 0.001).

Conclusions. Real-world data appear to align in terms of feasibility and survivals. MRD negativity and responses seem even deeper in the real-life setting.

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Myeloma and other monoclonal gammopathies

EFFECTIVENESS AND SAFETY OF DARATUMUMAB, POMALIDOMIDE, AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: PRELIMINARY RESULTS FROM THE MULTICENTER REAL-WORLD DARA-PD STUDY ON BEHALF OF EMN

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Background. The combination of daratumumab, pomalidomide, and dexamethasone (DPd) improved progression-free survival (PFS) and overall response rate (ORR) versus pomalidomide–dexamethasone in the phase III APOLLO trial. However, trial populations are highly selected, and real-world evidence in heterogeneous relapsed/refractory multiple myeloma (RRMM) remains limited. The Real-Life DARA-Pd study evaluates DPd effectiveness and safety in routine practice across Italian centers.

Aims. To assess ORR per IMWG criteria; secondary endpoints included PFS, overall survival (OS), depth of response, and safety.Methods:Multicenter retrospective–prospective observational study including consecutive RRMM patients (≥18 years) treated with DPd from January 2023 after ≥1 prior line with lenalidomide and a proteasome inhibitor. Data were collected via REDCap. Responses were assessed per IMWG criteria. PFS was defined from treatment start to progression or death; OS to death. Kaplan–Meier method was used.

Results. Ninety-three patients were included. Median age was 63 years (range 39–86); 53% male. DPd was used as second line in 49%, third in 37%, and ≥fourth in 14%. At initiation, 93% were treated at relapse (58% biochemical, 42% clinical), and 6.7% had refractory disease. Prior autologous transplant was reported in 74%. Previous regimens included VTD (49%), Rd (23%), and KRd (18%). No prior anti-BCMA or CAR-T therapy was reported. High-risk cytogenetics included del(17p) (9.7%), t(4;14) (2.2%), t(14;16) (5.4%), and 1q gain/amplification (14%). ISS stage was I 56%, II 26%, III 18%. ORR was 88%, with ≥VGPR 59% and CR/sCR 26%. Median time to best response was 4 cycles. After a median follow-up of 23 months, median PFS was 13 months (95% CI 11–22). CR/sCR was associated with longer PFS (29 vs 11 months). Median OS was 23 months (95% CI 16–28). No new safety signals emerged.

Conclusions. In this real-world multicenter RRMM cohort, DPd showed high response rates and meaningful survival outcomes, consistent with clinical trials. Depth of response correlated with longer PFS, supporting DPd as an effective option in routine practice.

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MYELOMA CELL-DERIVED EXTRACELLULAR VESICLES DELIVER THE LNCRNA MIAT TO BONE MARROW NICHES

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Background. Multiple myeloma (MM) is the second most common haematological malignancy and remains largely incurable due to relapse. Extracellular vesicles (EVs) released by MM cells (MM-EVs) can condition distant bone niches by reprogramming the pre-metastatic niche, carrying various cargos including long non-coding RNAs (lncRNAs). The lncRNA myocardial infarction associated transcript (MIAT) functions as a competitive endogenous. MIAT is upregulated in patient-derived MM cells, correlates with poor survival and is involved in Bortezomib resistance. However, its role in MM dissemination, bone niche reprogramming and its presence in MM-EVs remain uninvestigated. This study aims to determine whether MM-EVs reprogram the bone pre-metastatic niche by transferring MIAT to BM stromal cells.

Methods. Several MM cell lines were used to perform in vitro analysis. EVs isolation was performed through differential centrifugations and the quantity and quality of EVs were assessed with Colorimetric NANoplasmonic assay (CONAN). Digital droplet PCR (ddPCR) allowed the detection and quantification of MIAT in different samples. In vivo, Zebrafish embryos and NOD/SCID mice were used to investigate the homing of MM-EVs into BM niches.

Results. Preliminary data indicate that human MM cell lines express approximately 3 copies of MIAT per cell. Interestingly, MIAT is detectable in EVs isolated from MM cells, being preferentially packed into medium/large MM-EVs. Through CONAN and ddPCR analyses, we calculated that 10^{10} MM-EVs contain an average of 4.3 x 10^6 MIAT copies. Notably, a preliminary in vitro experiment revealed that 5x10^9 MM-EVs were able to transfer about 42 MIAT copies/-cell to murine endothelial cells. To investigate if MM-EVs could reach BM niches in vivo, we first injected intravenously GFP^+ EVs isolated from GFP^+ MM cells (GFP^+ MM-EVs) in Zebrafish embryos. GFP^+ MM-EVs were able to home into the Zebrafish BM-like caudal hematopoietic tissue niche 1 hour after EV injection. Next, GFP^+ MM-EVs were injected i.v. into mice and the levels of MIAT in the BM were analysed 1, 6 and 24 hours after EV injection. Interestingly, MM-EVs were able to transfer about 1.3 x 10^6 MIAT molecules to murine BM 6 hours after injection.

Conclusion These findings indicate that MIAT is a component of MM-EV cargo and can be delivered to BM niches. Ongoing studies are exploring whether MIAT contributes to bone niche reprogramming to support the homing and survival of metastatic MM cells.

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MAIN BIOLOGIC AND CLINIC FEATURES AT PRESENTATION AND TREATMENT RESULTS IN VERY ELDERLY PATIENTS (> 75 YEARS) WITH MULTIPLE MYELOMA: A MULTICENTRIC EXPERIENCE

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Multiple Myeloma (MM) is often diagnosed in patients (pts) >75 years. These pts are under-represented in clinical trials, with a diagnostic and biologic work-up reduced compared to youngers. In addition, a wide range of less intensive therapies is employed according to physician decision. In the present real-life multicentric study, clinic and biologic features, treatment choice and treatment results of 454 pts aged > 75 years newly diagnosed with symptomatic MM at 15 Italian Centres from 1/2018 to 06/2025 were analysed. Main clinical features at diagnosis are reported in the Table. FISH analysis was available in 204 pts (44.9%): 45 pts (22.1%) had a normal karyotype, while 159 pts (77.9%) had at least one alteration: the most frequent were gain/ampl(1q) in 47 pts (23.0%), t(11;14) in 29 pts (14.2%) and del(13q)/monosomy 13 in 27 pts (13.2%). High risk alterations were reported in 43/204 pts (21.0%). First-line treatments are reported in the Table. Among 443 pts fully evaluable for response, 21 (4.7%) achieved a stringent complete remission (sCR), 86 (19.5%) a CR, 146 (32.9%) a very good partial remission (VGPR) and 113 (25.5%) a partial remission (PR), with an overall response rate (ORR) of 82.6%: 38 pts (8.6%) had a stable disease (SD) and 39 pts (8.8%) a disease progression (DP). Among 366 pts with any type of response, 147 (40.1%) relapsed after a median time from 1st line start of 18.4 months (IQR 12.5 – 32.3). A 2nd line treatment was feasible in 120/147 relapsed pts (81.6%) and in 47/77 pts in SD/PD (61.0%). Dara-Rd was the most common 2nd line treatment (48/167 pts in 2nd line treatment, 28.7%). At the last follow-up, 275 pts (60.6%) are still alive, 25 (5.5%) were lost to follow-up and 154 (33.9%) died, mainly from MM progression (71 pts) or from infections (22 pts). Median overall survival (OS) of the entire cohort was 58.7 months (95%CI 49.6 – 72.3). At multivariate Cox analysis, elevated LDH [Odds Ratio (OR) 1.63, 95%CI 1.09-2.65, p=0.017], ISS classification (OR 1.31, 95%CI 1.01-1.69, p=0.035) and age ≥ 80 years (OR 1.80, 95%CI 1.28-2.52, p<0.001) had an independent prognostic value. Our data suggest that very elderly pts with MM can have a very good ORR to current treatments with a relatively long OS, and should be considered for the best available approaches irrespective from the age. In this setting, karyotype is very often missing: thus, ISS classification should be regarded as the best tool to evaluate prognosis in this subset.

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Table – Clinical features at MM diagnosis

N° of patients	454
M/F, n° (%)	221/233 (48.7/51.3)
Median age, years (IQR)	79.4 (76.8 – 82.7)
Patients aged ≥ 80 years, n° (%)	209 (46.0)
Median Hb, g/dl (IQR)	10.7 (9.4 – 12.1)
Previous monoclonal gammopathy, n° (%)	177 (39.0)
Type of MM, n° (%):	
IgG-k	175 (38.8)
IgG-λ	92 (20.4)
IgA-k	66 (14.6)
IgA-λ	45 (9.9)
Light chain k	35 (7.7)
Light chain λ	24 (5.3)
Other(IgD, IgM, double)	15 (3.3)
Not available	2
Hb < 10 g/dl, n° (%)	155 (34.1)
Creatinine ≥2 mg/dl, n° (%)	65 (14.3)
LDH > normal value, n° (%)	71 (15.6)
B2-microglobulin level, n° (%):	
< 3.5 mg/l	151 (35.8)
≥ 3.5 ≤ 5.5 mg/l	127 (30.1)
> 5.5 mg/l	144 (34.1)
Not available	32
ISS staging, n° (%):	
Stage I	118 (28.0)
Stage II	160 (37.9)
Stage III	144 (34.1)
Not evaluable (no β2-MG available)	32
R-ISS staging, n° (%):	
Stage I	60 (28.7)
Stage II	109 (52.2)
Stage III	40 (19.1)
Not evaluable (no FISH/LDH available)	245
First-line treatments, n° (%):	
VMP	116 (25.5)
Rd	110 (24.2)
Dara-Rd	140 (30.9)
Dara-VMP	31 (6.8)
VD/VP	19 (4.2)
MP	15 (3.3)
Other	23 (5.1)

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UPDATED SAFETY OF ISATUXIMAB SUBCUTANEOUS AT-HOME ADMINISTRATION BY ON-BODY INJECTOR IN RELAPSED/REFRACTORY MULTIPLE MYELOMA IN THE PHASE 3 IRAKLIA STUDY

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Background. At-home administration was studied in a subset of patients (pts) in IRAKLIA (NCT05405166), an ongoing, non-inferiority Phase 3 trial investigating isatuximab (Isa) subcutaneous (SC) versus intravenous (IV) administration plus pomalidomide and dexamethasone (Pd) in pts with relapsed/refractory multiple myeloma (RRMM). Isa SC is administered using an on-body injector (OBI), a wearable, automated injector with a small, retractable needle, which showed non-inferiority to Isa IV for efficacy and pharmacokinetics, higher patient satisfaction and lower infusion reactions as well as safety and feasibility of at-home. Here, we show updated results of at-home Isa SC OBI HCP administration with 93 additional injections.

Methods. Patients with RRMM (≥18 years, ≥1 prior LOT) were randomized 1:1 to Isa SC OBI (1400 mg; n=263) or IV (10 mg/kg; n=268) weekly in Cycle (C)1, then every 2 weeks, + P (4 mg/day, Day [D]1–21) + d (40 mg [20 mg if aged ≥75 years] weekly) in 4-week cycles. After 5 cycles, at-home HCP administration was optional for Isa SC OBI pts on D15 from C6 onward (D1 visits remained clinic based). At-home eligibility required absence of infusion reactions at C4–C5, hematology results (D1 of each C), investigator judgment, and patient willingness. HCPs applied and disposed of Isa SC OBI, evaluated injection site and vital signs, and completed documentation. For the first at-home Isa injection, an additional assessment was required 30 min post-injection. Thereafter, local tolerability was assessed at the end of injection.

Results. Overall, 16/263 pts treated with Isa SC OBI participated in at-home administration (cut-off: August 29, 2025; median follow-up: 21.75 months), with 148 injections performed (none interrupted). Most pts started at-home administration at C6 (n=7), while remaining pts started at C7+ (n=9). 68.8% switched to at-home administration and did not return to the hospital for subsequent D15 visits. Median injection duration was similar: clinic (13 min) vs at-home (12 min). No new safety signals with at-home administration, with a 100% completed injection rate. Injection-site reactions occurred in 1 pt (grade 1 site swelling, resolved same day). No other adverse events, infusion reactions, or device events were reported.

Conclusions. Updated IRAKLIA data demonstrated that at-home Isa SC OBI HCP administration is feasible, well tolerated, and maintains consistent injection times and success rates, supporting flexible MM patient care.

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LONG-TERM FOLLOW-UP OF USE OF POST-INDUCTION PET/DWI-MRI IN PATIENT WITH NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA IN THE ERA OF TRIPLETS: A SINGLE CENTER EXPERIENCE

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Imaging plays a crucial role in the diagnosis, staging, response assessment and prognostic stratification of multiple myeloma (MM). The [18F] FDG-PET/CT and diffusion-weighted MRI (DWI-MRI) technique are currently considered the standard method for evaluating response. To standardize definitions of metabolic response, the IMPeTUS criteria have been proposed; these include quantification of FDG uptake using the 5-point Deauville score (DS), combined with assessment of the anatomical distribution of FDG. The acquisition and interpretation of DWI images have been standardized through the introduction of the MY-RADS guidelines, which define 5 Response Assessment Categories (RACs). In this context, the hybrid [18F] FDG-PET/DWI-MRI technique has attracted interest for its ability to simultaneously acquire metabolic and morphological/functional data. The aim of this study is to retrospectively evaluate the prognostic role of PET and DWI-MRI acquired with hybrid [18F] FDG-PET/DWI-MRI technique after induction therapy in newly diagnosed transplant-eligible MM (NDTEMM), to predict post-autologous stem cell transplantation (ASCT) relapse. Between September 2015 and March 2022, 20 NDTEMM patients were treated in our Center and included in this study. All received induction treatment with the Bortezomib-Thalidomide-Dexamethasone regimen (4-6 cycles) and subsequently underwent one or two ASCT. Each patient underwent PET/MRI examinations at baseline and after induction. We consider “negative” patients with RAC1 and DS≤3. Patients who had a negative PET/MRI negative at diagnosis were not considered for the study. After induction, imaging showed: 1 PET+/MRI+, 8 PET-/MRI-, 1 PET+/MRI-, 10 PET-/MRI+. With a median follow-up of 83 months (range 12-117) the median PFS was 60 months with 12 patients experiencing a relapse. The patients PET-/MRI- showed a good prognosis, with an estimated median disease-free survival (DFS) not reached. In contrast, patients who had at least one of the two components (PET or MRI) still positive had a markedly worse prognosis, with a median DFS of 43 months. Among patients who relapsed after transplant (n=12), post-induction MRI was positive with a concomitant PET- 75% of them, suggesting a better sensitivity to predict relapse of pre-transplant MRI-DWI compared to PET. Future studies with larger cohorts of patients treated with current quadruplets regimens with immunotherapy with concomitant evaluation of MRD are needed to confirm these findings.

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CLINICAL EFFICACY OF ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: A RECENT UPDATE

D. De Novellis[1|2], D. Derudas[3], D. Vincelli[4], R. Fontana[1], R. Della Pepa[5], S. Palmieri[6], F. Accardi[7], F. Rotondo[8], E. Morelli[9], E. Gigliotta[10], D. Roccotelli[11], L. Marano[12], M. L. Barone[13], G. Cetani[14], D. Esposito[15], A. Lazzaro[16], G. Delle Cave[17], B. Serio[1], D. Morini[1], L. Settembre[1], M. Porrazzo[7], E. Urciuoli[12], C. Masucci[12], F. Fanelli[12], M. Rizzo[1], M. Arcamone[9], F. Trastulli[6], S. Rocco[6], A. Leone[5], R. Bianco[12], F. Salvatore[8], A. Idato[4], M. Sicari[4], P. Tosi[8], M. G. Rascato[15], M. Di Perna[13], A. P. Falcone[11], L. Morello[16], M. Carlisi[10], G. Svanera[17], G. R. Nunziata[15], M. Annunziata[6], F. Frigeri[14], C. Califano[13], A. M. Carella[11], G. Marcacci[9], F. Pane[5], A. M. Risitano[12], V. Giudice[1|2], C. Botta[10], C. Selleri[1|2]

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Introduction. Isatuximab, a novel anti-CD38 monoclonal antibody, has demonstrated significant efficacy in combination with carfilzomib and dexamethasone (Isa-KD) for relapsed/refractory multiple myeloma (RRMM) treatment, as documented in the phase III IKEMA trial. However, real--world evidence on its efficacy and safety remains limited.We present updated results from a multicenter retrospective observational study of Isa-KD in a real-life cohort of RRMM patients.

Methods. We enrolled 103 RRMM patients treated with Isa-KD between March 2022 and March 2024 across 16 Italian Hematology Units. All patients received Isa-KD outside of clinical trials and had undergone 1–3 prior lines of therapy. High-risk genetic abnormalities and lenalidomide refractoriness were defined according to International Myeloma Working Group (IMWG) criteria.

Results. Baseline characteristics are summarized in Fig 1A. Our cohort included 38% of patients with high-risk cytogenetic abnormalities and 16% with extramedullary disease (EMD). The median follow-up was 24 months (95% CI, 21–26). Isa-KD was administered as second-line treatment in 67% of cases (n = 69). Prior lenalidomide maintenance was reported in 61% of patients, with a median duration of 23 months. Lenalidomide-refractory and lenalidomide-exposed patients accounted for 19% and 71%, respectively. The overall response rate was 85%, including 18% of patients achieving stringent complete response (sCR) or complete response (CR), and 39% very good partial response. Median progression-free survival (PFS) was 28 months (95% CI, 19 -NE-; Fig.1B), and 24-month overall survival (OS) was 72% (95% CI, 62–81%). Among patients treated with second line therapies, median PFS was not reached (95% CI, 28–NE; Fig 1C), with 24-month PFS and OS of 63% (95% CI, 51–77%) and 75% (95% CI, 65–86%), respectively. Isa-KD was well tolerated with cardiac toxicity (hypertension, 14%; and tachyarrhythmia, 3%) and pneumonia (13%) as the most frequent serious adverse events observed.

Conclusions. Isa-KD demonstrates high efficacy and manageable toxicity in a real-world RRMM population, including those with adverse features such as high-risk cytogenetics, EMD, and lenalidomide resistance. These findings support the use of Isa-KD as an early-line option in routine practice, particularly for patients typically underrepresented in clinical trials.

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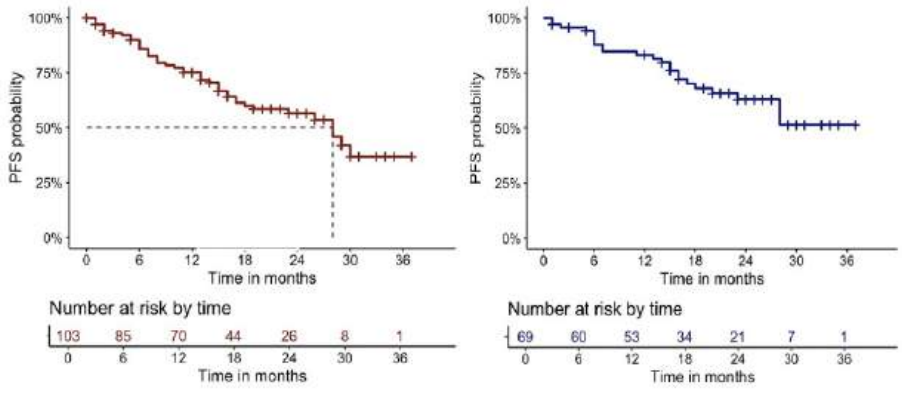
A

Characteristics	ITT cohort N = 103	2nd line cohort N =69
Median age, years (range)	64 (45-84)	63 (45-77)
Age > 75 years	13 (13)	4 (6)
ECOG scale, n (%)		
0-1	88 (86)	61 (88)
High genetic risk MM, n (%)	39 (38)	27 (39)
Extramedullary disease, n (%)	17 (16)	10 (15)
Revised international staging system, n (%)		
I	23 (22)	19 (27)
II	38 (37)	27 (39)
III	20 (19)	13 (19)
Previous ASCT, n (%)	78 (76)	58 (84)
Previous bortezomib treatment, n (%)	96 (93)	64 (93)
Previous anti-CD38 treatment, n (%)	15 (15)	4 (6)
Previous thalidomide treatment, n (%)	80 (78)	55 (80)
Lenalidomide exposed, n (%)	20 (19)	14 (20)
Lenalidomide refractory, n (%)	73 (71)	47 (68)
Previous lenalidomide maintenance, n (%)	63 (61)	54 (78)
Median duration of lenalidomide maintenance, months (range)	23 (2-62)	26 (2-62)
< 12 months of lenalidomide maintenance, n (%)	21 (20)	18 (26)
< 24 months of lenalidomide maintenance, n (%)	32 (31)	25 (36)
ORR, n (%)	**87 (85)**	**61 (88)**
sCR+CR	**19 (18)**	**14 (20)**
VGPR	**40 (39)**	**32 (46)**
PR	**28 (27)**	**15 (22)**
Time to best response, months, median (range)	3 (1-20)	2 (1-20)
Consolidation with ASCT, n (%)	13 (12)	10 (15)
Carfilzomib dose reductions, n (%)	23 (22)	18 (26)

B-C



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MOLECULAR LANDSCAPE OF PLASMA CELL DYSCRASIAS BY NEXT-GENERATION SEQUENCING: FROM MGUS AND SMOULDERING TO MULTIPLE MYELOMA

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Background. Clonal dynamics driving disease progression from pre-malignant plasma cell disorders to multiple myeloma (MM) is not fully defined, because there are limited data on bone marrow genomic landscapes in early disease, such monoclonal gammopathy (MGUS) and smouldering MM (SMM). Here, we aimed to characterize the molecular landscape across disease stages using NGS in a real-life setting.

Methods. A total of 127 consecutive patients with plasma cell disorders, since January 2024 to March 2026, were included, and molecular data from NGS was retrieved. The Custom Sophia panel included the following genes:ACTG1, ATM, BIRC2, BRAF, CCND1, CDKN1B, CDKN2C, CKS1B, CRBN, CYLD, DIS3, DUSP2, EGR1, FAM46C, FAT3, FGFR3, FMN2, HIST1H1E, HUWE1, IRF4, KLHL6, KRAS, LTB, MAF, MAX, MYC, NF1, NFKB2, NRAS, PPM1D, PRDM1, PRKD2, PTPN11, RASA2, RB1, ROBO1, SP140, TP53, TRAF2, TRAF3, UBR5, ZFHX4, ZNF292. Oncogenic mutations and variants of uncertain significance (VUS) were included and genes were grouped into biologically relevant pathways. Frequency and distribution of molecular alterations were compared between disease stages.

Results. In our cohort, 44 (35%) had pre-malignant conditions (MGUS, N=12; SMM, N=32) and 83 (65%) had newly diagnosed MM (NDMM, N= 71) or relapsed/refractory MM (RRMM, N=12). Alterations in MAPK pathway were more frequent in MM compared to pre-malignant cases (34% vs 14%, p=0.02), as well as DNA repair pathway-related gene mutations (43% vs 21%, p=0.01), largely driven by TP53 mutations (16% vs. 5%, p=0.02). Alterations involving RNA processing genes (DIS3, TENT5C/FAM46C) were observed only in MM (12% vs 0%, p=0.02), while no significant differences were found in cell cycle, NF-κB, cytoskeleton/adhesion, or ubiquitin-proteasome pathways. Transcription factor and MYC signalling-related abnormalities were slightly higher in MM (24% vs 11%, p=0.09), although not significant due to the limited number of patients. TP53-mutated patients showed enrichment for additive FISH abnormalities, including chromosome 17p deletion.

Conclusions. In this real-world study, our results showed progression from pre-malignant conditions to MM could be driven by genomic modifications in recurrent pathways, such as MAPK signalling, DNA repair alterations, and RNA processing genes. TP53 mutations identify a subset enriched for adverse cytogenetic features. These findings support a model of progressive genomic complexity and may have implications for disease stratification.

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A)

Features	Pre-malignant N= 44	Malignant N=83	P value
MAPK pathway (KRAS, NRAS, BRAF, NF1)	6 (14)	28 (34)	0.02
DNA repair (TP53, ATM, PPM1D) -TP 53 alone	9 (21) 2 (5)	36 (43) 13 (16)	0.01 0.02
Cell Cycle (RB1, CDKN1B, CCND1)	12 (27)	23 (28)	0.9
NF-κB pathway (TRAF2, TRAF3, NFKB2, CYLD, BIRC2)	6 (14)	10 (12)	0.8
RNA processing (DIS3, TENT5C/FAM46C)	-	10 (12)	0.02
Transcription factors / MYC axis (MYC, PRDM1, IRF4, MAF, MAX)	5 (11)	20 (24)	0.09
Cytoskeleton / adhesion (FMN2, FAT3, ACTG1, ROBO1)	18 (41)	37 (45)	0.7
Ubiquitin / proteasome (UBR5, HUWE1, CRBN)	1 (2)	4 (5)	0.5

B)

Fish features of TP53 mutated population	Pre-malignant N= 2	Malignant N= 13
Chromosome 17p deletion, n (%)	-	5
Chromosome 13q deletion, n (%)	-	6
Chromosome 1q gain/amp	-	2
Chromosome 14 abnormalities, n (%)	-	4
Overall FISH abnormalities, n (%) None 1 ≥2	 2 - -	 6 1 6

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Myeloma and other monoclonal gammopathies

CD20 POSITIVE MULTIPLE MYELOMA: IS IT A DIFFERENT ENTITY?

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Introduction. Expression of CD20 antigen is generally negative in patients (pts) with Multiple Myeloma (MM). However, a small number of MM pts (15-20%) can show CD20 positivity on neoplastic plasma cells (PC). The biologic and clinical features of pts with MM CD20+ are still a matter of debat.

Methods. From 1/2018 to 12/2023, all consecutive patients with MM newly diagnosed at our Center according to IMWG (International Myeloma Working Group) criteria were retrospectively evaluated. Immunophenotypic characterization of marrow PC was performed by multiparametric analysis with sequential gates through the expression of CD38/CD45, CD38/CD138 antigens. FISH was performed on isolated PC with probes from MM panel. Classical cytogenetic analysis using G-banding (GTG) was also done. Morphology of BM aspirate was independently reviewed by two different hematologists. Histology of BM was reviewed to define the grade of infiltration, type of infiltration, and intensity of CD20 positivity.

Results. Among 104 evaluable pts, 23 (22,1%) were CD20+ and 81 (77.9%) CD20-: no significant differences were observed between CD20+ and CD20- pts as to the main clinical features at baseline. The main karyotypic and immunophenotypic features at diagnosis of the entire cohort and according to CD20 status are reported in the Table. CD20+ pts presented a significant high rate of t(11;;14) (43.5% vs 16.2%, p=0.006) and a trend for a lower rate of high-risk alterations (19.4% vs 37.8%, p=0.069). According to immunophenotype, CD20+ pts showed a significant higher co-expression of CD19 (22.7% vs 6.2%, p=0.020) and a trend for a lower co-expression of CD56 (52.2% vs 71.6%, p=0.080). Morphologic evaluation was done in 10 CD20+ pts, revealing a distinctive small-like lymphocyte morphology in more than 50% of PC in all 10 revised aspirates.

Conclusions. MM CD20+ pts seem to share distinctive features from classical MM. The presence of CD20 positivity, coupled with the common coexpression of CD19 and the predominant small lymphocyte–like morphologic features, suggests that neoplastic transformation could occur at a relatively more immature stage of differentiation than CD20- MM: in other words, CD20 positive MM could be considered as an intermediate phase between Waldenstrom disease and classic CD20 negative MM. Further studies are warranted to define the prognostic role of CD20 positivity and the possible utility of targeted therapies in this subset.

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Table- Main karyotypic and immunophenotypic features at diagnosis according to CD20 status

	Entire cohort (104)	CD20+ (23)	CD20- (81)	p
FISH alterations, n° evaluable (%)	98	22	76	
None	26 (26.5)	6 (27.3)	20 (26.3)	
1 alteration	14 (14.3)	4 (18.2)	10 (13.2)	0.330
2 alterations	21 (21.4)	7 (31.8)	14 (18.4)	
≥ 3 alterations	37 (37.8)	5 (22.7)	32 (42.1)	
Cytogenetic risk, n° evaluable (%)	97	23	74	
Standard risk	65 (67.0)	19 (82.6)	46 (62.2)	0.069
High risk	32 (33.0)	4 (19.4)	28 (37.8)	
Del13q, n° evaluable (%):	98	23	75	
No	68 (69.4)	13 (56.5)	55 (73.3)	0.126
Yes	30 (30.6)	10 (43.5)	20 (26.7)	
t(11;;14), n° evaluable (%):	97	23	74	
No	75 (77.3)	13 (56.5)	62 (83.8)	0.006
Yes	22 (22.7)	10 (43.5)	12 (16.2)	
Ampl-1q, n° evaluable (%):	98	23	75	
No	79 (80.6)	21 (91.3)	58 (77.3)	0.138
Yes	19 (19.4)	2 (8.7)	17 (22.7)	
Ampl-11q, n° evaluable (%):	98	23	75	
No	87 (88.8)	22 (95.7)	65 (86.7)	0.232
Yes	11 (11.2)	1 (4.3)	10 (13.3)	
Ampl-14q, n° evaluable (%):	98	23	75	
No	89 (90.8)	22 (95.7)	67 (89.3)	0.359
Yes	9 (9.2)	1 (4.3)	8 (10.7)	
CD56, n° evaluable (%):	104	23	81	
Negative	34 (32.4)	11 (47.8)	23 (28.4)	0.080
Positive	70 (67.6)	12 (52.2)	58 (71.6)	
CD117, n° evaluable (%):	103	22	81	
Negative	46 (44.7)	9 (40.9)	37 (45.7)	0.690
Positive	57 (55.3)	13 (58.1)	44 (54.3)	
CD19, n° evaluable (%):	103	22	81	
Negative	93 (90.3)	17 (77.3)	76 (93.8)	0.020
Positive	10 (9.7)	5 (22.7)	5 (6.2)	

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Myeloma and other monoclonal gammopathies

SAFETY AND RELIABILITY OF ISATUXIMAB SUBCUTANEOUS ON-BODY INJECTOR: RESULTS ACROSS THE PHASE 3 IRAKLIA, PHASE 2 IZALCO AND PHASE 1B TCD15484 TRIALS

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Background. Subcutaneous (SC) delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody for treating multiple myeloma (MM), has been investigated across clinical trials via a novel hands-free on-body injector (OBI). Isa SC OBI features a small, retractable needle, establishing the first device-enabled delivery of an oncologic treatment. The Phase 3 IRAKLIA, Phase 2 IZALCO, and Phase 1b (TCD15484) trials demonstrated similar efficacy and safety of Isa SC OBI vs Isa IV in relapsed/refractory MM (RRMM) patients (pts). Here, we present a cross-trial analysis exploring safety and reliability of Isa SC OBI in RRMM pts.

Methods. Pts with RRMM in IRAKLIA (N=263) and the Phase 1b expansion cohort (N=22) received 1400 mg Isa SC OBI plus pomalidomide and dexamethasone (d). In IZALCO, RRMM pts (N=64) received 1400 mg Isa SC OBI + carfilzomib (K)-d. Pts were monitored for 4 hrs (IRAKLIA) or 1-2 hrs (IZALCO) after first administration and for 1 hr for the following administrations to assess local tolerability. Pre-infusion medications included montelukast (cycle 1), steroids, acetaminophen and H1 antihistamines. Pts without systemic infusion-related reactions (IRRs) after 4 consecutive administrations of Isa SC OBI had pre-medication reassessed at investigator's discretion. Safety and device performance explored in this cross-trial analysis were assessed in the Isa SC OBI cohorts by the duration of injection, IRRs, local injection-site reactions (ISRs), and injection/device success, which were defined similarly across trials.

Results. Median injection duration was 13 mins (IRAKLIA), 12 mins (IZALCO), and 10 mins (TCD15484) across 6426 total injections (N=349 pts). IRRs occurred in 6/6426 (0.09%) injections and 4/349 (1.15%) pts, mostly Grade 1 (G; 3/6426, 0.05%) and 1 G3 (0.02%), none leading to discontinuation. In IRAKLIA, 80/263 (30.4%) pts did not require premedication (931/5145 injections, 18.1%); no IRRs occurred in this group. Across trials, ISRs occurred in 21/349 (6.02%) pts resulting in 35 (0.54%) ISR events. Most ISRs were G1 (33, 0.51%), the remaining were G2 (2, 0.03%) and generally occurred on the day of injection. 99.9% (6421/6426) of injections in 98.6% (344/349) pts were successful (completed without interruption) across all trials.

Conclusions. Isa SC OBI shows low, self-limiting IRRs and ISRs across trials, with 99.9% injections successfully delivered, supporting it as a novel administration option for MM pts and potential for at-home use.

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

FIGHT TRIAL: FIXED-DURATION IBRUTINIB PLUS DELAYED OBINUTUZUMAB AS FIRST-LINE THERAPY FOR *TP53*-INTACT CHRONIC LYMPHOCYTIC LEUKEMIA

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Frontline CLL therapy has moved from continuous covalent BTK inhibitor (cBTKi) therapy toward fixed-duration (FD) regimens that may allow for clinically meaningful treatment-free intervals, especially in *TP53*-intact patients (pts). Though single agent cBTKi rarely induce deep responses, ibrutinib (IBR) plus obinutuzumab (OBI) induced undetectable measurable residual disease <10-4 (uMRD4) in up to 38% of treatment-naïve (TN) high-risk pts (iLLUMINATE trial). Moreover, the IcICLLe study showed that delayed OBI after ≥1y of IBR may further deepen responses (50% bone marrow (BM) uMRD4).This is a Phase 2, national, multicenter trial that evaluated the efficacy of a 2y FD regimen of IBR + delayed OBI (added in C13–18) in TN *TP53*-intact CLL. Primary endpoint is BM uMRD4 rate at 30 days post-treatment completion (FU30D). IBR could be resumed upon progressive disease (PD).54 pts were enrolled from Dec21 to Jul25 (table 1). At data cut-off (18Feb26), 10 pts are still on therapy.After 1y of IBR, before adding OBI, 27/28 evaluable pts had a partial response (PR, 96.4%) and 1 stable disease (SD, 3.6%).At FU30D, 7/25 evaluable pts were in complete response (28%), 14 in PR (56%), yielding an ORR of 84%, while 4 (16%) had PD. Among 29 not evaluable pts, 10 had not yet reached the endpoint, 5 discontinued early (1 drop out, 1 PD, 2 for AEs, 1 for clinical decision).21/34 evaluable pts (61.8%) achieved BM uMRD4 at FU30D, 11 of them were uMRD5 (32.4%); 26/37 (70.3%) achieved PB uMRD4, 12 pts (32.4%) were uMRD5.No new safety signals emerged; there was a single grade 2 infusion-related reaction to OBI, confirming improved tolerability of the delayed schedule. 18 SAE were reported, including 2 secondary malignancies, 3 atrial fibrillation/flutter, 1 NSTEMI, 1 acute heart failure. 5 SAEs were deemed possibly related to study drugs. One pt discontinued due to treatment-emergent sensorineural hearing loss, IBR-related, not meeting SAE criteria.4 pts required dose reduction for AEs, including two grade 3 hypertension.After a median follow up of 32 months (range 2-48), 7 pts (12.9%) had PD: 1 occurred during C17 and received Venetoclax+Rituximab, 2 PD at FU30D and IBR was resumed. The remaining 4 pts had asymptomatic PD not requiring therapy (range 0-23 months). PFS and TT-NT at 30 months were 75.1% and 87.8%, respectively.In summary, 2-year FD IBR+OBI appears to achieve deep responses and allow safe treatment discontinuation in a significant proportion of TN CLL pts.

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Table 1.

Pt characteristics	Result
Sex (n=51)	22 F, 29 M
Age, median	65.4y (39.7-86.1)
Rai stage (n=50)	I: 12, 24% II: 13, 26% III: 17, 34% IV: 8, 16%
Binet stage (n=50)	A: 4, 8% B: 26, 52% C: 20, 40%
IGHV (n=47)	mutated 15, 32% unmutated 32, 68%
FISH (n=43)	normal: 6, 14% del13q: 13, 30% trisomy 12: 14, 33% del11q: 10, 23%
CIRS (n=49)	mean 3, median 2 (0-10)

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

ACALABRUTINIB MONOTHERAPY AND IMPACT OF AUTOIMMUNE CYTOPENIAS IN A SERIES OF PATIENTS AFFECTED BY CHRONIC LYMPHOCYTIC LEUKEMIA

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Background. Possible complications of chronic lymphocytic leukemia include autoimmune cytopenias (AICs), with an incidence of approximately 5-9% of affected patients. Except for a few case reports, the role of acalabrutinib, a second-generation BTK inhibitor, in the treatment of pre-existing and treatment emergent AICs, has not yet been explored.

Aims. This study aims to analyze the incidence, clinical characteristics, the management and outcomes of pre-existing AIC and the treatment-emergent AIC in patients with CLL undergoing acalabrutinib monotherapy.

Methods. This is a multicenter retrospective study collecting clinical and biological data from patients diagnosed with CLL and treated consecutively with acalabrutinib monotherapy in 13 Italian centers.

Results. In the study, 285 patients with CLL were treated with acalabrutinib monotherapy. The incidence of autoimmune cytopenias was 7,4% (21 patients), particularly 11/21 (52%) with AIHA, 9/21 (43%) with ITP, and 1/21 (5%) with PRCA. Almost all patients with pre-existing AIC (95%) received AIC-directed therapy, specifically corticosteroids (35%) as monotherapy or combined with rituximab (25%). At the start of acalabrutinib treatment, AIC were active in 38% (8/21), controlled in 38% (8/21), and resolved in 24% (5/21) of the patients. During treatment, 5 patients (1.8%) developed treatment-emergent AIC, specifically three cases of ITP and two of AIHA. Acalabrutinib therapy was maintained in 80% of these patients. Regarding management, one of the ITP patients did not require any specific intervention, one was treated with corticosteroids only, and one required sequential therapy with corticosteroids, rituximab, and intravenous immunoglobulin, with temporary discontinuation of acalabrutinib due to insufficient disease control. Of the two cases of AIHA, only one was managed with corticosteroids without discontinuation of acalabrutinib therapy. Collectively, treatment-emergent AICs resolved or were adequately controlled in 62% of cases, and no significant differences in progression-free or overall survival were observed between patients with or without AIC, including both pre-existing and treatment-emergent forms.

Conclusions. In this multicenter real-world study, pre-existing AICs were generally manageable in CLL patients treated with acalabrutinib; treatment-emergent AICs were infrequent and controllable, and overall AICs did not adversely impact clinical outcomes.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

PIRTOBRUTINIB IN RICHTER SYNDROME: OUTCOMES FROM THE NAMED PATIENT PROGRAM IN ITALY

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Richter syndrome (RS) remains a challenging event within the CLL natural history, with median overall survival (OS) rarely exceeding 12 months. Pirtobrutinib, a non-covalent BTK inhibitor, achieved an overall response rate (ORR) of 50% in patients with RS enrolled in the phase 1/2 BRUIN trial. However, real-world evidence about its efficacy and safety in RS remains scarce.We retrospectively analyzed 22 patients with RS treated with pirtobrutinib within the Italian named patient program between September 2022 and March 2026. Patients received at least one 28-day cycle of pirtobrutinib at the dose of 200 mg once daily. Median age was 69 years (range 45-90), 15 patients (68%) were male, and 6 (27%) had ECOG performance status 2-3. Elevated LDH and bulky disease (≥5 cm) were present in 17 (77%) and 12 (55%) patients, respectively. TP53 status was evaluable in 15 patients, of whom 9 (60%) carried TP53 mutations. Patients had received a median of 3.5 prior systemic lines across the CLL and RS phases; 15 (68%) had been exposed to cBTKi, 12 (55%) to venetoclax, and 11 (50%) to both. Three patients received pirtobrutinib as first-line for the RS phase.After a median follow-up of 15.8 months, 13 patients (59%) had discontinued pirtobrutinib, mainly because of disease progression. ORR was 72.7% (16/22), including complete response in 18.2% and partial response in 54.5%. Median PFS was 6.1 months and median OS was 18.2 months (Fig. 1). Responder patients were further categorized into short-lived (response lasting <4 months) and long-term responders (lasting >4 months). Short-lived responders were enriched of cBTK resistant cases (100% versus 45% among long-term responders, p=0.1186) and had a median OS comparable to that of non-responders and significantly worse than that of long-term responders (short-lived: 3.2 months; non-responders: 4.1 months; long-term responders: unreached. p<0.0001). Seven long-term responders remained progression-free beyond 6 months, with the longest ongoing response censored at 33.7 months. Grade ≥3 cytopenias occurred in 4 patients (18%), and no meaningful cardiovascular events were observed. One fatal sepsis occurred in a patient with prior allotransplant.Overall, the outcomes of RS patients in our real-life cohort confirms single agent activity of pirtobrutinib, which may reduce tumor burden in fit patients before cellular therapies, or it may serve as a definitive treatment for patients who are unfit for more intensive approaches.

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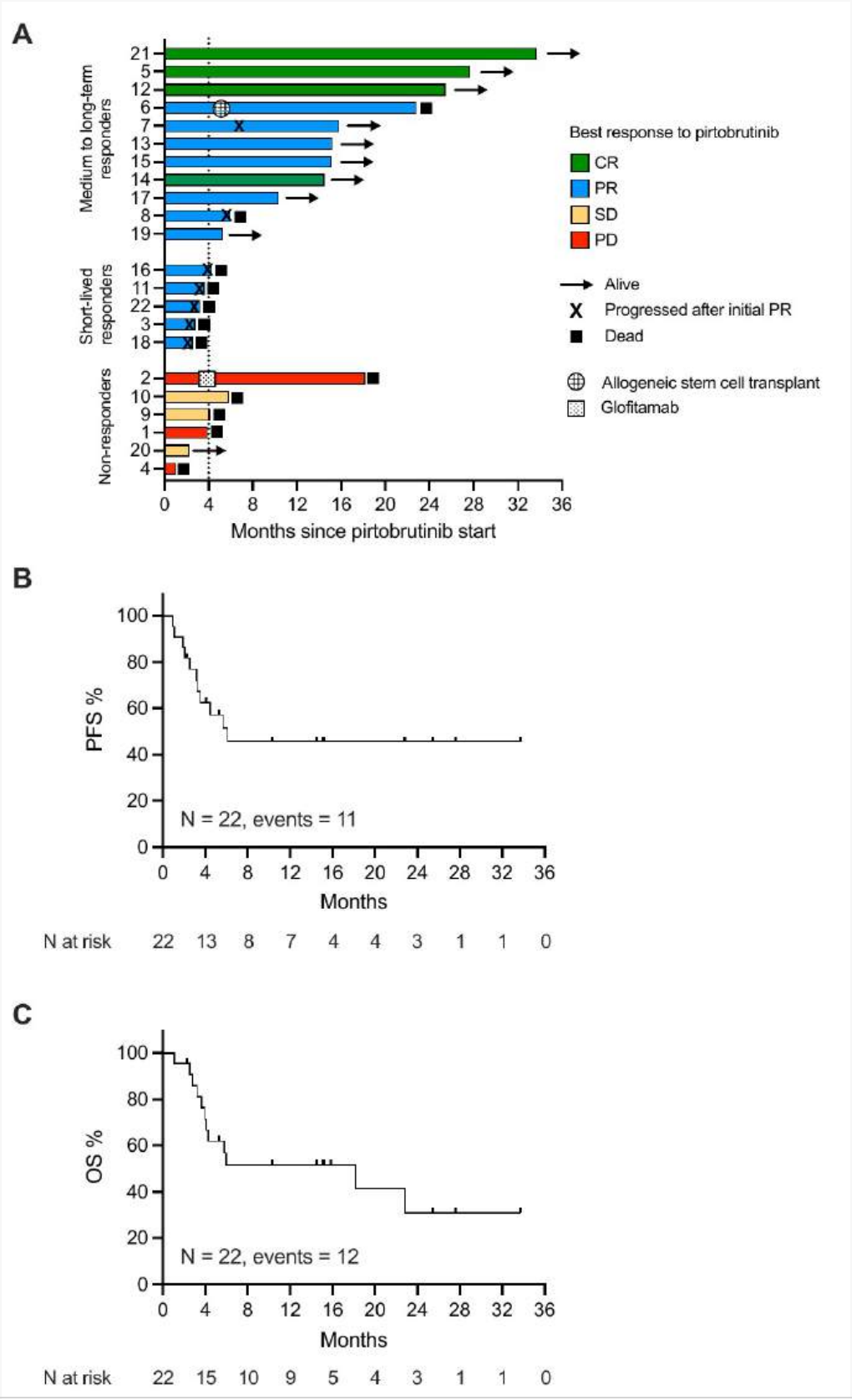

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EFFECTIVENESS AND SAFETY OF FIXED-DURATION VERSUS CONTINUOUS THERAPY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A SINGLE-TERTIARY-CENTER RETROSPECTIVE ANALYSIS

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Background. Fixed-duration therapy (FDT) and continuous therapy (CT) are approved strategies for chronic lymphocytic leukemia (CLL) in both treatment-naïve (TN) and relapsed/refractory (RR) settings. Recently, after a median follow-up of 3 years, the CLL17 trial showed non-inferiority of FDT vs CT in TN patients. In RR, randomized comparisons and real-world data remain limited.

Aim. To compare the effectiveness and safety of FDT vs CT in TN and RR CLL patients in a real-world setting.

Methods. This is a single center retrospective study. Patients were classified as TN-FDT, TN-CT, RR-FDT, or RR-CT. Baseline characteristics were compared using ANOVA for continuous variables and chi-square or Fisher's test for categorical variables. Overall survival (OS) was evaluated with Kaplan–Meier and log-rank methods. Major bleeding and cardiovascular events (CV) were assessed using Fine–Gray models, and recurrent grade ≥3 infections with an Andersen–Gill Cox model.

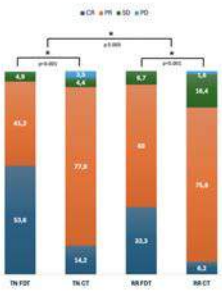
Results. 327 patients were enrolled. Baseline characteristics are reported in Table 1. TN-FDT patients were younger, while high complex karyotype (hCK, ≥5 abnormalities) and immunoglobulin replacement therapy (IgRT) were more frequent in RR patients. With a median follow-up of 53 months, complete response (CR) rates were higher in TN vs RR (p=0.003) and with FDT vs CT in both settings (p<0.001). OS did not differ between FDT and CT in TN [HR 1.24 (0.83–1.86)] or RR [HR 1.42 (0.91–2.21)]. In multivariable analysis, only hCK and CR independently predicted OS. Bleeding risk was similar in TN but higher with CT in RR [HR 12.6 (3.1–50.5)]. CV were comparable in TN and increased with CT in RR [HR 5.83 (2.08–16.8)]. Grade ≥3 infection rates were similar (8.9 vs 9.9 per 100 patient-years), with no increased risk for CT [HR 0.66 (0.36–1.23)]. Infections were mainly pneumonia (58.9%), followed by fever without microbiological documentation (22.2%). Fatal infective events, i.e. grade 5, accounted for 16.4% of cases, with no group differences (p=0.25); however, none occurred in TN-FDT. Age, but not IgRT, independently predicted a risk of infection [HR 1.07/year (1.03–1.12)].

Conclusions. In this real-world cohort, FDT and CT showed comparable survival in both TN and RR CLL. Prognosis was driven by hCK and CR, with higher CR rates observed with FDT. Infectious risk was similar between strategies. However, in RR patients, CT was associated with increased bleeding and CV, highlighting the role of safety in treatment selection.

Table 1: Baseline characteristics. uIGHV=unmutated Immunoglobulin Heavy-Chain Variable region; CK=complex karyotype; hCK=high complex karyotype; IgRT=immunoglobulin replacement therapy; ATT=anti-thrombotic therapy

	TN FDT n = 41	TN CT n = 113	RR FDT n = 45	RR CT n = 128	p value
Age (yr)	63±7,9	73±9,7	71±9,6	73±9,5	p <0,001
Sex, male	30 (73,2%)	65 (57,5%)	29 (64,4%)	67 (52,3%)	0,097
uIGHV	30 (73,2%)	59 (52,2%)	36 (80,0%)	86 (67,8%)	0,094
del(11q)	5 (12,2%)	18 (15,9%)	12 (26,7%)	29 (22,7%)	0,200
Trisomy 12	11 (26,8%)	29 (25,7%)	6 (13,3%)	20 (15,6%)	0,107
del(13q)	17 (41,5%)	57 (50,4%)	21 (46,7%)	64 (50,0%)	0,717
del(17p)	6 (14,6%)	19 (16,8%)	13 (28,9%)	34 (26,6%)	0,113
Karyotype					0,003
CK	3 (7,3%)	11 (9,7%)	13 (28,9%)	33 (25,8%)	
hCK	2 (4,9%)	13 (11,5%)	8 (17,8%)	23 (18,0%)	
CV comorbidities	23 (10,1%)	68 (60,2%)	34 (75,6%)	76 (59,4%)	0,205
IgRT	2 (4,9%)	13 (11,5%)	13 (28,9%)	40 (31,3%)	0,001
ATT	6 (14,6%)	26 (23,0%)	19 (42,2%)	36 (28,1%)	0,023
Therapy					
I	NA	58 (51,3%)	NA	72 (56,3%)	
A	NA	26 (23,0%)	NA	13 (10,2%)	
Z	NA	18 (15,9%)	NA	13 (10,2%)	
V	NA	7 (6,2%)	NA	12 (9,4%)	
VI	27 (65,9%)	NA	1 (2,2%)	NA	
VO	7 (17,1%)	NA	0 (0%)	NA	
VR	4 (9,8%)	NA	44 (97,8%)	NA	
Other	3 (7,3%)	4 (3,5%)	0 (0%)	18 (14,1%)	

Figure 1: Percentage rates of best overall response achieved in patient subgroups according to treatment strategy and line of therapy. CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease



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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD EFFECTIVENESS AND TOLERABILITY OF ACALABRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA: A MULTICENTER EXPERIENCE

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Acalabrutinib is a next-generation BTK inhibitor approved for CLL, with high efficacy and a favorable safety profile in clinical trials, but limited comprehensive real-world data on treatment durability and hematologic recovery. This retrospective, observational multicenter study evaluated the real-world effectiveness and tolerability of acalabrutinib monotherapy in 155 adult CLL patients treated across 10 Italian hematology centers, using time-to-discontinuation (TTD) as the primary endpoint and assessing overall response rate (ORR), overall survival (OS), hematologic changes, and safety. TTD was defined as time from treatment start to permanent discontinuation (≥28-day interruption, progression, Richter transformation, or death), and OS as time from initiation to death, with hematologic parameters assessed at baseline, 6, 12, and 24 months.The cohort had a median age of 74 years, was predominantly treatment-naïve, and frequently carried high-risk features, including del(17p), TP53 mutations, and unmutated IGHV. Median treatment duration was 16 months, and median TTD was not reached, with 80% of patients still on therapy and 78.7% alive at a median follow-up of 18 months. ORR reached 84.5% (32.9% complete and 51.6% partial responses) after a median of 12 months, while only 9.1% had stable or progressive disease. Responders were less often aged ≥75 years than non-responders, whereas disease biology, stage, prior lines, and comorbidities were broadly comparable between groups. Subgroup TTD analyses showed more favorable trends in younger patients and those with mutated IGHV, with no apparent differences by line of therapy or cardiovascular risk. Hematologic recovery was consistent and sustained, with progressive increases in hemoglobin and platelet counts and marked reductions in lymphocyte and leukocyte counts, while neutrophils remained stable. These improvements were more pronounced in responders ($p<0.001$ for hemoglobin/platelets at 12 months). Notably, in patients with baseline cytopenias (47%), 75% normalized by 6 months, supporting acalabrutinib's role in restoring marrow function.Acalabrutinib displayed a manageable safety profile, with limited grade 3–4 hematologic toxicity, few severe non-hematologic events, and no major cardiovascular complications even in patients with baseline cardiovascular risk; dose reductions allowed ongoing therapy in many cases, and only 20% of patients discontinued treatment, mainly due to adverse events or progression.

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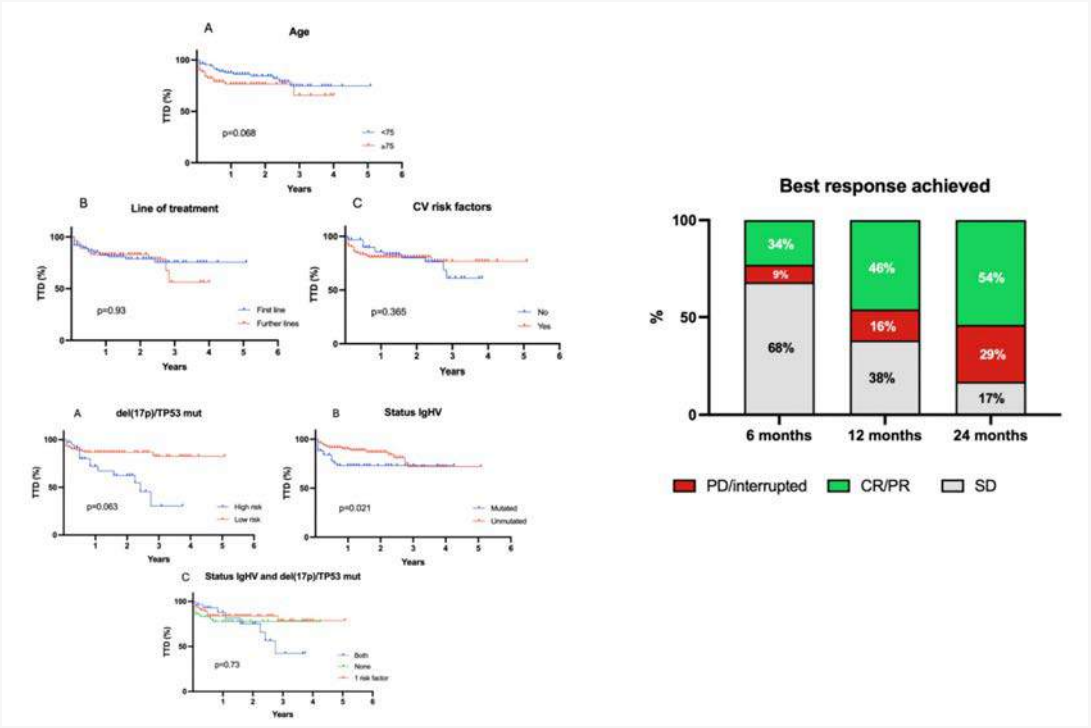
Chronic lymphocytic leukemia and other lymphoproliferative syndromes



Chronic lymphocytic leukemia and other lymphoproliferative syndromes

VENETOCLAX-BASED REGIMENS AFTER COVALENT BTKI EXPOSURE IN RELAPSED/REFRACTORY CLL: REAL WORLD OUTCOMES AND PREDICTORS OF SURVIVAL

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The treatment paradigm of chronic lymphocytic leukemia (CLL) has shifted to targeted agents, including Bruton tyrosine kinase inhibitors (BTKi) and venetoclax, creating a growing need for effective strategies in the post-BTKi setting. While venetoclax-based regimens are highly effective in BTKi-naive patients (e.g., MURANO trial), their role after BTKi exposure is not fully established.We retrospectively evaluated 59 consecutive patients with relapsed/refractory CLL previously treated with covalent BTKi who received venetoclax as monotherapy or in combination with rituximab. Median age was 71 years; 37.3% had del(17p) and/or TP53 mutations and 67.8% unmutated IGHV. Patients received a median of 2 prior lines (range: 1–5). Median duration of prior BTKi therapy was 13.5 months (range: 0-84). BTKi discontinuation occurred due to progressive disease (PD) in 61% and adverse events (AE) in 39% of patients.Venetoclax was administered as monotherapy in 45.8% and in combination in 54.2%. Treatment was prematurely discontinued in 54.2% after a median of 11.5 months, mainly due to AE (32.2%) and PD (18.6%).Overall response rate was 91.5%, including 40.7% complete responses. After a median follow-up of 2.9 years, median progression-free survival (PFS) and time to next treatment (TTNT) were not reached, while median overall survival (OS) was 4.1 years; 3-year PFS, TTNT and OS were 70.2%, 77.8% and 61.5%, respectively (Fig.1).The addition of rituximab conferred a consistent survival advantage, significantly improving PFS (p=0.0021) and OS (p=0.0229), with a trend toward longer TTNT (p=0.054).Prior BTKi discontinuation due to PD identified patients with significantly inferior OS compared to those discontinuing BTKi for AE (p=0.0031), despite comparable PFS and TTNT. In contrast, duration of prior BTKi therapy (<12 vs ≥12 months), TP53 disruption, IGHV status and number of prior lines did not impact outcomes.Eleven patients (18.6%) received subsequent therapy after venetoclax, mainly non-covalent BTKi, with limited responses.In conclusion, venetoclax-based regimens retain high efficacy after BTKi exposure, with outcomes approaching those reported in BTKi-naive populations. The addition of rituximab is associated with improved survival, while progression on prior BTKi identifies a subgroup with inferior OS despite similar disease control, suggesting intrinsically high-risk biology. These findings support a risk-adapted sequencing approach in the post-BTKi setting.

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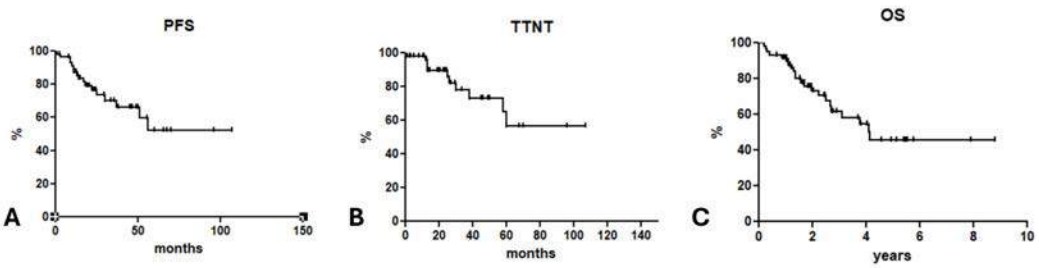

Fig. 1. A) Progression-free survival; B) Time to next treatment; C) Overall survival

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

A NEW STRATIFICATION FOR THE CARDIOLOGIC RISK IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH VENETOCLAX AND IBRUTINIB: A MULTICENTER EXPERIENCE OF THE CLL-LAZIO GROUP

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Introduction. According to guidelines,ibrutinib plus venetoclax (VI) combination is a widely used first-line treatment for Chronic Lymphociytic Leukemia (CLL).In these patients (pts), cardiovascular toxicity remains the most important adverse event. Based on our experience with continuous Bruton tyrosine kinase inhibitors (BTKi) given as single agents, we observed that the left atrial volume index (LAVI) represents in multivariable analysis a significant and independent predictor for adverse cardiovascular events.Drawing on established risk stratification approaches in amyloidosis, we categorized cardiovascular risk according to LAVI values ,applying an approximate cut-off of 32 ml/mq.

Methods. 73 untreated pts with CLL who received VI from January 2024 to December 2025 were analyzed retrospectively in a multicenter study of the CLL-Lazio Group.We focused our analysis on atrial fibrillation (AF) and we designed a predictive score, by considering LAVI, age, valvular disease and hypertension.We compared our result with the MAYO CLL AF score.

Results. The pts' median age was 64 yrs and the median-follow up was 16 months.We stratified our patients according to the Mayo risk classification and our proposed risk classification; Patients were subdivided into a high-risk (Group A) and a low-risk (Group B) group.For both groups,we calculated the positive predictive value (PPV) and negative predictive value (NPV) with their respective p-values (0.0206 vs 0.0001).According to our score, 67 pts were included in low risk and 6 pts in the high risk for AF; Mayo stratification included 61 pts in Low risk and 12 pts in High risk. 6 pts interrupted VI for AF (8%): 3 in low risk and 3 in high risk group.To note, while the overall trends were comparable, the risk model we proposed demonstrated greater statistical significance.

Conclusions. In order to improve its prognostic accuracy and cardiovascular specificity we incorporated an additional parameter, the LAVI ,in the new cardiologic risk score we proposed. By comparing data of our and the Mayo score, we found similar results. Although the small sample size of assessed patients, our score showed an increased power to discriminate significantly high from low-risk patients.AF occured also in patients who did not show risk factors. This finding suggests that a careful monitoring of patients should be considered in all patients. In Lazio this is performed using semestral 24-hour Holter monitoring during the first 12 months.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

INFECTION RATES AND IMPACT OF G-CSF PROPHYLAXIS IN CLL PATIENTS RECEIVING FRONTLINE VENETOCLAX-OBINUTUZUMAB: A REAL-WORLD STUDY BY THE CLL CAMPANIA GROUP

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Background. Venetoclax obinutuzumab (VO) is a standard first line therapy for chronic lymphocytic leukemia (CLL). However, its clinical utility is often complicated by high infection rates during and post-treatment. This study aimed to characterize real-world infection incidence in CLL patients receiving VO and to evaluate the efficacy of G-CSF prophylaxis in mitigating these complications.

Methods. This multicenter retrospective study was conducted by the "CLL Campania Group". We retrospectively analyzed data of 98 patients with CLL treated with the VO regimen outside clinical trials between June 2019 and March 2026 in 13 hematological centers in the Campania region. Treatment was administered according to current guidelines and it was administered following the approved dose and schedule. Neutrophil counts were monitored monthly, and G CSF prophylaxis was recommended for neutropenia grade >/=2.

Results. The median age at treatment start was 66 years (range 43-89), with a median observation time of 26 months (range 2-45). The patients' characteristics are shown in Figure 1. Of 98 patients enrolled, 92 were evaluable for response. The overall response rate was 98.9%, with a complete response rate of 94.5%. While 69.4% of patients completed the standard VO regimen, venetoclax was reduced in 17.3% (n=17) and suspended in 21.4% (n=21) of patients. The overall infection rate was 30.6%, comprising viral (n=16), bacterial (n=11), fungal (n=1), and unknown (n=2) etiologies. Primary G-CSF prophylaxis was administered to 47 patients (48.0%), in 53.2% of cases for grade 3-4 neutropenia. Comparative analysis revealed no statistically significant differences between patients receiving G-CSF prophylaxis and those who did not regarding infection rates (27.7% vs. 31.4%; p=0.82) or frequency of dose modifications (25.5% vs. 33.3%; p=0.50). The 2-year progression-free survival (PFS) and overall survival (OS) were 87.3% and 91.8%, respectively. Ten deaths were recorded, predominantly due to infection (n=7), followed by Richter transformation (n=1) and non-CLL related causes (n=2).

Conclusions. In this real-world cohort, the incidence of infection and the necessity for dose modifications were lower than those reported in the landmark CLL14 and CLL13 trials. Notably, an intensive G-CSF prophylactic strategy did not significantly reduce infection rates or treatment modifications. An extended follow up and a larger cohort are required to confirm these findings.

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Figure 1. Patients' characteristics.

Patients' characteristics	CLL patients (n=98)
Sex at birth	
Female	31.6% (30/98)
Male	68.4% (67/98)
Age at treatment start (median, range)	66 (43 - 89)
Rai Stage at treatment	
I	7.3% (7/96)
II	32.3% (31/96)
III	21.9% (21/96)
IV	38.5% (37/96)
Unknown	2.0% (2/98)
IGHV mutational status	
Mutated	50.0% (42/84)
Unmutated	50.0% (42/84)
Unknown	15.0% (14/98)
FISH	
del17p	3.5% (3/86)
Del13q	40.7% (35/86)
Del11q	10.5% (9/86)
Tris12	19.8% (17/86)
Unknown	12.2% (12/98)
Treatment criteria	
Progressive lymphoadenopathies	39.8% (39/98)
Symptomatic splenomegaly	28.6% (28/98)
Cytopenias	49.0% (48/98)
B symptoms	5.1% (5/98)
Lymphoadenopathy >5 cm	11.2% (11/98)
Vaccinations before therapy	
Anti-influenza	48.4% (30/62)
Anti-pneumococco	27.4% (17/62)
Anti-HZV	6.4% (4/62)
Anti-SARS-CoV2 (>3 doses)	61.3% (38/62)
Evusheld	32.3% (20/62)
None	25.8% (16/62)
Unknown	36.7% (36/98)

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

CARDIOVASCULAR TOXICITY, RISK PREDICTORS AND DOSE MODULATION IN PATIENTS WITH CLL TREATED WITH BTKI: A MULTICENTER REAL-WORLD ANALYSIS

A. Serafin[1], A. Bevilacqua[1], S. De Santo[1], R. Pasquale[2], M. Moratti[2], F. Angotzi[1], A. Cellini[1], M. D'Antiga[1], M. De Ferrari[1], N. Danesin[1], G. Leone[1], F. Martini[3], E. Albi[3], E. Sant'Antonio[3], L. Scarfò[3], P. Ghia[3], G. M. Rigolin[4], A. Cuneo[4], F. Piazza[1], L. Trentin[1], A. Visentin[1]

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Background. Bruton tyrosine kinase inhibitors (BTKi) are a cornerstone in CLL, but cardiovascular (CV) toxicity remains a major concern. Real-world comparative data on first- vs second-generation BTKi (2gBTKi), including timing, predictors of CV events and the impact of dose modulation, are limited.AimTo assess the incidence and timing of atrial fibrillation (AF), hypertension (HTN), congestive heart failure (CHF) and bleeding, identify clinical and heart ultrasound predictors, and evaluate the impact of dosing strategies.

Methods. We retrospectively analysed 410 CLL patients treated with BTKi-based regimens across three Italian centres. Cumulative incidence (CI) of CV events was estimated using competing-risk analysis. Overall survival (OS) and progression free survival (PFS) were analysed using Kaplan-Meier and multivariable (MV) Cox models, with dose reduction as a time-dependent covariate.

Results. Baseline characteristics are summarised in table 1. Median follow-up was 32 months. At 30 months, OS/PFS were 87.1%/79% for I, 87.2%/82% for 2gBTKi, and 95%/86% for I+V. In MV analyses, age>80 years (OS p=.038; PFS p<.001) and starting at reduced dose (OS p=.002; PFS p=.046) were independent predictors of inferior outcomes, considering that patients starting at reduced dose were significantly older (p<.001). Dose reduction due to AEs occurred in 61 patients, at a median of 8 months (range 1–107), and was not associated with inferior PFS (p=0.45) or OS (p=0.51).Median time-to-CV-event differed: bleeding was early (98 days, IQR 46.5-369), whereas AF and HTN occurred later (14.0 months, IQR 5.8-24.3 and 14.5 months, IQR 9.0-26.8), and CHF at 11.5 months (IQR 6.8-35.0). AF incidence was higher with I compared to 2gBTKi (24-month CI: 13.6% vs 4.4%, p=.018), while no differences were observed for HTN, bleeding or CHF. In MV analysis, AF was associated with baseline AF (p<.001), smoking (p=.002) and atrial dilatation (p=.013), whereas 2gBTKi reduced AF risk (p=.009). HTN was associated with left ventricular remodelling (p<.001), and CHF with age >80 years (p=.02).

Conclusions. 2gBTKi showed a more favourable CV profile, particularly for AF. Clinical and heart ultrasound features identify patients at higher risk of CV events, supporting tailored baseline assessment and monitoring. Inferior outcomes observed in patients starting at reduced dose may reflect baseline frailty, while dose reduction during therapy does not appear to compromise survival outcomes.

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Table 1. Main characteristics of our cohort population.

Characteristics	N (%) N=410
Therapy	
Ibrutinib monotherapy	211 (51)
Ibrutinib + venetoclax	60 (15)
Second generation BTKi	139 (34)
- Acalabrutinib	79 (19)
- Zanubrutinib	60 (15)
Age	72 years (range 65-93)
Sex F/M	157 (38)/253 (62)
Treatment naïve	262 (64)
Relapsed/refractory	148 (36)
Low dose of drug at baseline	55 (13)
IGHV um	237 (70)
Unknown	72 (17)
TP53 mut	124 (32)
Unknown	25 (6)
Del(17p)	85 (21)
Unknown	7 (1)
Complex Karyotype	84 (20)
Unknown	110 (27)
Echocardiography available at baseline	344 (84)
Baseline CV comorbidities	272 (66)
- Hypertension	216 (53)
- Atrial fibrillation	42 (10)
- Other arrythmias	21 (5,1)
- Valvular heart diseases	62 (15)
- Tobacco smoking	53 (13)
- Dyslipidaemia	110 (27)
- Diabetes	59 (14)
- Atrial dilatation	125 (36)
- Left ventricular remodelling	116 (34)
- Antiplatelets therapy	55 (13)
- Anticoagulants	54 (13)

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

DAYBREAK CLL-201: A STUDY OF BEXOBRUTIDEG (NX-5948), A BTK DEGRADER, IN PATIENTS WITH CLL/SLL PREVIOUSLY TREATED WITH A COVALENT BTK INHIBITOR, A NON-COVALENT BTK INHIBITOR AND A BCL2 INHIBITOR

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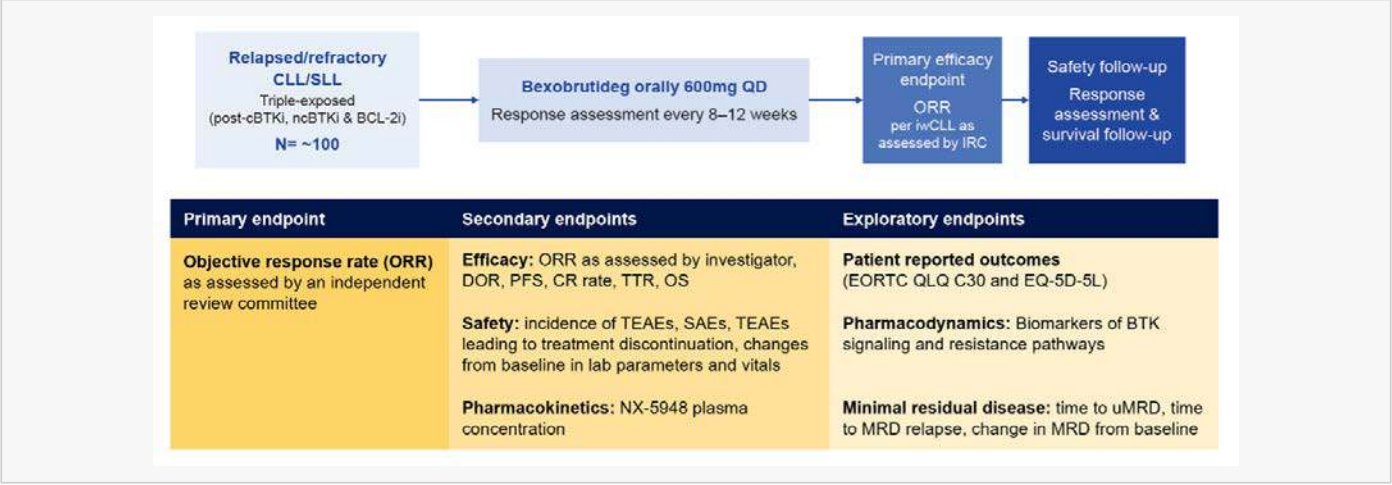
Background. BTK inhibition has proven to be a successful treatment modality in chronic lymphocytic leukemia (CLL); however, the emergence of BTK inhibitor (BTKi) resistance mutations and kinase-independent signaling underscore the need for alternative approaches to target BTK protein functions. Bexobrutideg (NX-5948) is a novel, highly selective, orally administered small molecule protein degrader that induces the removal of wild-type and mutant forms of BTK through ubiquitination by the cereblon E3 ligase complex and subsequent proteasomal degradation. In a previous Phase 1 trial in relapsed/refractory (R/R) B-cell malignancies including CLL (NX-5948-301; NCT05131022), bexobrutideg was well tolerated and showed rapid and durable responses, and a recommended Phase 2 dose of 600 mg once daily was identified.

Methods. NX-5948-201 (DAYBreak CLL-201; NCT07221500) is a single-arm, open-label Phase 2 study to evaluate the efficacy and safety of bexobrutideg in adult patients with R/R CLL or small lymphocytic lymphoma (SLL) previously exposed to a covalent BTKi, a non-covalent BTKi and a B-cell lymphoma-2 inhibitor (BCL2i). Key eligibility criteria include: histologically confirmed R/R CLL/SLL per the International Workshop on Chronic Lymphocytic Leukemia (iwCLL; Hallek 2018); ECOG PS 0–2; prior exposure to a covalent BTKi, a non-covalent BTKi and a BCL2i (separate lines or in combination); measurable disease by radiographic assessment per iwCLL; adequate organ and bone-marrow function. Exclusion criteria include: known or suspected prolymphocytic leukemia or Richter's transformation; previous treatment with a BTK degrader; active second malignancy; and known central nervous system lymphoma or leukemia. Bexobrutideg 600 mg is given orally once daily, with response assessment every 8–12 weeks. The primary endpoint is the objective response rate (ORR) without partial response with lymphocytosis (PR-L), per 2018 iwCLL criteria (as assessed by an independent review committee [IRC]). Secondary endpoints include: ORR with PR-L (by IRC); ORR with/without PR-L (by investigator); duration of response (IRC and investigator); progression-free survival (IRC and investigator); complete response rate (IRC and investigator); time to response (IRC and investigator); and overall survival. Safety, pharmacokinetics and health-related quality of life will also be evaluated. Enrollment is underway and the study is expected to recruit ~100 patients globally.



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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

ACALABRUTINIB DEMONSTRATES SUPERIOR CARDIOVASCULAR SAFETY COMPARED WITH ZANUBRUTINIB AND COMPARABLE SAFETY TO PIRTOBRUTINIB: RESULTS FROM A NETWORK META-ANALYSIS

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Background. Second-generation covalent BTK inhibitors (BTKis) (acalabrutinib [ELEVATE-R/R] and zanubrutinib [ALPINE]) and the noncovalent BTK inhibitor pirtobrutinib (BRUIN-CLL-314;) demonstrated improved cardiovascular (CV) safety relative to ibrutinib in head-to-head randomized controlled trials (RCTs) for BTKi-naïve relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). However, comparative safety profiles across these agents remain incompletely characterized.

Methods. We performed a Bayesian network meta-analysis (NMA) across ELEVATE-R/R, BRUIN-CLL-314, and ALPINE. Analyses focused on safety endpoints—discontinuation due to adverse events (AEs), grade ≥3 infections, and CV events—because heterogeneity across patient cohorts precluded reliable efficacy comparisons. Specifically, 11q deletions were more prevalent in ELEVATE-R/R than in ALPINE ($p < 0.01$) or BRUIN-CLL-314 ($p < 0.01$). Similarly, TP53 aberrations/17p deletions and complex karyotype were lowest in ALPINE compared with either BRUIN-CLL-314 ($p < 0.0001$) or ELEVATE-R/R ($p < 0.0001$).

Results. Acalabrutinib (OR 1.34, 95% CrI 0.68–2.66) and zanubrutinib (OR 1.34, 95% CrI 0.71–2.55) showed discontinuation rates due to AEs comparable to pirtobrutinib. Grade ≥3 infection rates were similar across pirtobrutinib and acalabrutinib (OR 0.99, 95% CrI 0.57–1.72) or zanubrutinib (OR 1.12, 95% CrI 0.57–1.72). Between second-generation covalent BTK inhibitors, acalabrutinib and zanubrutinib exhibited no differences in AE discontinuations (OR 1.00, 95% CrI 0.55–1.83) or grade ≥3 infections (OR 1.13, 95% CrI 0.65–1.92).Acalabrutinib demonstrated fewer CV events than zanubrutinib (OR 0.48, 95% CrI 0.29–0.80). Pirtobrutinib surpassed zanubrutinib in CV safety (OR 0.52, 95% CrI 0.31–0.88) but was comparable to acalabrutinib (OR 1.09, 95% CrI 0.62–1.92). SUCRA rankings for CV safety placed acalabrutinib first (87%), followed by pirtobrutinib (79%) and zanubrutinib (33%).

Conclusions. This NMA indicates a superior CV safety of acalabrutinib relative to zanubrutinib and noninferiority relative to pirtobrutinib. SUCRA rankings place acalabrutinib as the best-ranked agent, consistent with these findings. Limitations include immature pirtobrutinib follow-up, cross-trial heterogeneity, and absence of individual-patient-level data; head-to-head RCTs are warranted.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

LANGERHANS CELL HISTIOCYTOSIS AND OTHER HISTIOCYTOSES: A SINGLE-CENTER EXPERIENCE

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Histiocytosis is a heterogeneous group of rare disorders characterized by a wide variety of clinical manifestations and disease spread. We retrospectively reviewed the medical records of 33 pts to evaluate clinical presentation, organ involvement, and therapeutic choice. M/F ratio was 0.94, with a median age of 50 yo (range 17-85). Histopathologic subtypes were as follows: 21 pts with Langerhans cell histiocytosis (LCH), 4 with Erdheim-Chester Disease (ECD), 3 with Rosai-Dorfman Disease (RDD) and 5 with Histiocytic sarcoma (HS). Nine pts with LCH had a unifocal unisystemic disease with bone involvement: 4 were treated with indomethacin w/o surgical removal, while 5 underwent surgery only. All 9 pts achieved disease remission. Two LCH pts had unisystemic disease localized to the lungs and vocal folds, respectively: they were treated with a course of steroids, obtaining complete remission (CR). Ten LCH pts were diagnosed with multisystemic disease or unisystemic disease involving visceral and/or at-risk organs: 5 were treated with vinblastine (VBL) plus steroids, all obtaining CR except one who underwent 6 courses of cladribine (CDA), for partial response. Among others, one was previously treated with indomethacin with progression of disease, one with steroids only for prevalent bone involvement, and one was unable to underwent chemotherapy for concomitant late stage hepatic disease; 2 pts are still completing diagnostic work-up. Two pts with ECD were treated with CDA with no response and one of them eventually died; 2 were treated with VBL plus steroids for CNS involvement: one obtained a CR while the other started interferon(IFN)-α maintenance, which is still ongoing. Three pts with RDD were treated with surgery for isolate nodular lesion, IFN-α for lymph node involvement and elderly age, and VBL plus steroids for multisystemic and CNS involvement, respectively. Five pts with HS were treated with chemotherapy, except one who underwent CDA; all died from progressive disease. Overall, 3 pts with LCH and 1 with ECD were diagnosed with another malignant neoplasm (breast, lung, melanoma, and thyroid), while 2 pts with LCH and 1 with ECD were diagnosed with benign neoplasms. Prognosis for patients with histiocytosis largely varies, depending mostly on histological subtypes and involved sites that guide clinicians in the choice of the proper treatment. Prognosis is particularly poor for HS and claims for an improvement in biological knowledge and targeted therapy

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Table 1. Characteristics of involved sites

	LCH (*21*)		ECD (*4*)	RDD (*4*)	HS (*5*)
	unisystemic	multisystemic			
bone	9	4	2	2	
lung	1	3			
thyroid	1			1	
SNC	1	3	3	1	1
vocal folds	1				
lymph nodes	1	3	1	3	2
skin		1		1	
liver		1			
pararenal			2		
cardiac			2		
intra-abdominal					2

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

TRANSLATING CLINICAL TRIAL EVIDENCE INTO PRACTICE: FIRST RESULTS FROM THE RETE EMATOLOGICA PUGLIESE AS REAL-WORLD EXPERIENCE WITH FIXED-DURATION IBRUTINIB+VENETOCLAX IN TREATMENT-NAÏVE CLL (REBELLION-CLL)

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Background. The combination of IBRUTINIB and VENETOCLAX (I+V) the first all-oral, fixed-duration chemotherapy-free regimen (FDT), has emerged as a promising 1st-line strategy for patients with CLL. As a result of pivotal CAPTIVATE and GLOW studies, patients obtained durable response with improvement of PFS and treatment-free remissions, but there is still a lack of real-world (RW) data. This REP multicenter analysis was designed to provide the real-life data on I+V FDT in Apulia.AIMTo describe the patient characteristics, response rates and toxicity profile using the I+V FDT approach in RW setting.

Methods. REBELLION-CLL is a multicenter, ambispective, observational study of treatment-naïve CLL patients who initiated I+V after its approval by AIFA on Feb 2, 2024 in a routine practice, conducted in REP. This is the first analysis of the retrospective part of REBELLION-CLL study from 10 REP centers.

Results. At cut-off date (20/04/2026), 78 patients (pts) were included, from them 21/27% are still in therapy. Median age was 57 (range: 35-77) years (6.4% aged ≥70 years). Time from diagnosis to treatment initiation 35.4 months (range 0-180). The majority were male 55/64% and 41/53% had a Rai stage 0–II. All pts had an ECOG of 0–1. CIRS score 0, 1-6 and 7-10 had 33/42%, 42/54% and 3/4% of pts, respectively. CLL-IPI: low 5/6%, intermediate 38/49% and high 35/45%. IGHV unmut, del(17p) pos and TP53 mut had 47%, 6.7% and 0%, respectively. Data about vaccination before I+V initiation was available in 44/56% pts: COVID-19 – 59%, seasonal flu – 81%, HZV – 77%, pneumococcus – 61%Temporary suspension of therapy due to toxicity was documented in 11/14% pts for I and 7/9% for V (Table 1). While dose reduction occurred in 24/31% pts for I and 28/36% for V. G-CSF prophylaxis received 21/27% pts from them the majority 5/24% started at 5th cycle.At 6 months, 56/72 % pts were evaluated for response. CR and PR obtained 25/44.6% and 30/53.5%, respectively. One PD was registered for Richter. EOT response assessment was available in 35/45% CR had 28/80% pts, PR – 5/14%, SD – 2/6%. Cardiological toxicity was observed in 4/5% pts during first 3 months of therapy and 7/9% after 3rd months. FA occurred in 3/4% pts.

Conclusions. Our results support effectiveness and safety of I+V in clinical practice as a FDT for CLL pts and confirmed the outcomes of pivotal trials. Long-term follow-up will help to dive deeper in a long-term safety and effectiveness profile in the RW setting

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Table 1. Main patients' characteristics and treatment toxicities.

Patients' characteristics	N pts (n=78)
Sex	
Male	64% (50/78)
Age at diagnosis (median, range)	57 (35-77)
Comorbidities at diagnosis	
Hypertension	23% (18/78)
Dyslipidemia	14% (11/78)
Diabetes	10% (8/78)
Atrial fibrillation	4% (3/78)
Ischemic cardiac disease	1% (1/78)
Rai Stage	
0-II	53% (41/78)
IGHV	
Unmutated	56% (37/66)
TP53	
mutated	0% (0/74)
Del 17	
Positive	6.7% (5/75)
Bulky >5 cm	31% (24/77)
IgG before treatment	
<500 mg/dL	16% (12/75)
Treatment toxicities*	
Hematological	***26% (20/78)***
- *Neutropenia*	*19% (15/78)*
- *Thrombocytopenia*	*6.7% (5/78)*
- *Cytopenia*	*1% (1/78)*
Cardiological	***10% (8/78)***
- *Atrial fibrillation*	*4% (3/78)*
- *Hypertension*	*6.4% (5/78)*
Gastrointestinal	***12% (9/78)***
- *Nausea*	*1% (1/78)*
- *Hypertransaminasemia*	*5% (4/78)*
- *Diarrhea*	*4% (4/78)*
Mucocutaneous	***12% (9/78)***
- *Mucosal bleedings*	*3.8% (3/78)*
- *Mouth ulcers*	*3.8% (3/78)*
- *Itching*	*1% (1/78)*
- *Different cutaneous lesions*	*2.5% (2/78)*

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

SYNERGISTIC VALUE OF CLASSICAL CYTOGENETICS AND FISH IN THE PROGNOSTIC STRATIFICATION OF CLL: A STUDY ON 70 PATIENTS

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The role of chromosomal analysis (CBA) in the diagnostic workup of chronic lymphocytic leukemia (CLL) has been significantly reevaluated in recent years. Prognostic stratification using FISH for the most common abnormalities in CLL [del(11q), +12, del(13q), del(17p)] is not sufficient on its own for an accurate assessment of patients' genetic profiles. In particular, the complex karyotype (CK), especially when highly complex (High-CK, ≥5 abnormalities), should be considered a key indicator for better stratification of patients in terms of survival, response to treatment, and risk of transformation into Richter syndrome. In this study, we evaluated the clinical impact of integrating CBA+FISH into the routine diagnostic workup of 70 patients with CLL. CBA analysis identified an abnormal karyotype in 69% of cases (48/70), of which 27% had CK (19/70) and 20% had High-CK (14/70). The FISH analysis was abnormal in 79% of cases (55/70); specifically, a microdeletion of the DLEU1 gene (13q) was detected in 54% of patients (12/22) with a normal karyotype. The combination of the two methods increases the ability to detect at least one cytogenetic abnormality, rising from 79% with FISH alone to 86% when CBA and FISH are combined. However, the most significant finding concerns risk stratification. Based on FISH results alone, 46% of patients (42/70) would have been classified as having a favorable prognosis, but the addition of karyotyping reclassified 36% of them (15/42) into an unfavorable or intermediate category because they had abnormalities not detectable by the probes. On the other hand, 100% of patients with FISH-positive results for abnormalities associated with an unfavorable prognosis also had a pathological karyotype (CK), high-CK, or isolated del(11q). In our study, 21% of patients (15/70) would have been incorrectly classified as "low-risk" based on the standard FISH panel, while actually harboring greater genomic complexity. Analysis of our data clearly demonstrated that CBA remains an indispensable tool for visualizing genomic instability and for accurately stratifying patients.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

ASSESSMENT OF THE MINIMAL EFFECTIVE DOSE OF AVATROMBOPAG IN IMMUNE THROMBOCYTOPENIA: A SINGLE-CENTER REAL-WORLD STUDY

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Background and Aims. Avatrombopag, a 2nd-generation TPO-RA, is an effective treatment for chronic immune thrombocytopenia (ITP). In clinical practice, its use is increasingly embedded in a personalized strategy, with dosing progressively adjusted to optimize platelet count while minimizing adverse events and toxicity. In this context, defining the minimal effective dose is crucial. The aim of this study was to evaluate the minimal maintenance dose of avatrombopag required to sustain platelet count >50,000/µL, also analyzing clinical characteristics, treatment response, and safety profile.

Methods. We retrospectively analyzed 37 pts treated at our center with avatrombopag (26 F, 11 M), either on therapy or previously exposed. Median age was 47 yrs (range 19–86). At diagnosis, median platelet count was 10,000/µL, with bleeding in 56% of pts. Pts had received a median of 3 prior lines; all were treated with corticosteroids and 78.4% with IVIG. Twenty-seven pts had received a prior TPO-RA, and 24 directly switched to avatrombopag. Reasons for switching included lack/loss of response (62.5%), platelet fluctuations (8.3%), AEs (8.3%), and patient preference. We assessed time to response, number of dose adjustments, minimal effective maintenance dose and safety.

Results. During follow-up, a median of 3 dose adjustments was required to reach a stable dose maintaining platelets >50,000/µL. In 5 pts (13.5%), temporary interruption due to thrombocytosis during tapering was required, with subsequent reintroduction. The median stable maintenance dose was 50 mg/week, with median platelet count of 151,000/µL. At analysis, 25 pts (67.6%) remained on treatment, while 12 (32.4%) discontinued. Among these, median dose at discontinuation was 210 mg/week, with platelets 21,500/µL. Reasons included lack/loss of response (50%), fluctuations (33.3%), one major AE (NSTEMI, 8.3%), and sustained off-treatment response (SROT, 8.3%). AEs occurred in 37.8%: thrombocytosis (13.5%), thrombotic events (2.7%), fluctuations (10.8%), hepatotoxicity (8.1%), bleeding (5.4%), asthenia (2.7%).

Conclusions. In our real-world experience, avatrombopag confirms its effectiveness as a rapid-acting treatment for chronic ITP. Variability in maintenance dose highlights the need for a highly individualized approach, where minimal effective maintenance dose is often lower than the starting regimen. Dose tapering is a key step to optimize efficacy and safety on a pt-specific basis.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

RESPONSE AND CARDIOVASCULAR SAFETY OF FOSTAMATINIB IN CHRONIC IMMUNE THROMBOCYTOPENIA: A REAL WORLD ANALYSIS

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Background and Aims. Real-world evidence on fostamatinib (FST) in immune thrombocytopenia (ITP) has expanded substantially in recent years, with multicentre national experiences from Spain and Italy confirming its effectiveness and safety in routine clinical practice. Additional cohort analyses remain clinically relevant to better define treatment patterns and outcomes in pts with complex biological and clinical features, including autoimmune diathesis and cardiovascular/thrombotic risk. We therefore aimed to describe the characteristics of a real-world cohort of chronic ITP treated with FST, and to assess response rate, time to response, treatment exposure, and cardiovascular safety, while also exploring whether earlier response was associated with longer treatment exposure.

Methods. We retrospectively evaluated 29 patients with chronic ITP treated with FST, data cut-off April 12, 2026. Outcomes of interest included ORR, time to response, treatment exposure, and cardiovascular safety. We also explored whether earlier response was associated with longer treatment exposure. Baseline pts and treatment characteristics are reported in Table 1.

Results. The cohort showed a median TH2 score of 1, with only 4/29 pts (13.8%) displaying a hemorrhagic-risk profile, while the remainder had a prothrombotic profile; moreover, 18/29 pts (62.1%) had at least one cardiovascular risk factor.ORR was 75.9% (22/29), including 15 CR and 7 PR, while 7 pts were non-responders.Among responders, median time to response was 15.5 days (IQR 10–42.5; range 3–409), with a median platelet count at response of 160.000. In heavily pretreated patients, overall response rate was 62.5% (5/8). At cut-off, 16 pts were still on treatment, with a median platelet count of 170.000 (range 65000–328000); response was maintained in all but 2 pts who shifted from complete to PR. No significant association was observed between shorter time to response and longer treatment exposure (Spearman rho=0.37, p=0.091). No new cardiovascular events were observed.

Conclusions. In this chronic ITP cohort, fst showed high response rates and rapid activity, including in heavily pretreated patients. Outcomes were consistent with published real-world evidence. While early response did not predict longer treatment exposure, fst delivered meaningful and sustained benefit across this real-world group. Particularly reassuring was the absence of new cardiovascular events in a population enriched for cardiovascular risk factors.

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Table 1. Baseline population characteristics

Characteristic	Value
Patients, n	29
Female sex, n (%)	21 (72.4)
Male sex, n (%)	8 (27.6)
Median age at diagnosis, years (range)	49 (11–84)
Median prior treatment lines, n	3
Heavily pretreated patients*, n (%)	8 (27.6)
Splenectomized patients, n (%)	7 (24.1)
Autoimmune profile	
Autoimmune diathesis, n (%)	14 (48.3)
Antiphospholipid antibodies positivity, n (%)	5 (17.2)
Cardiovascular/thrombotic profile	
Prior cardiovascular/thrombotic history, n (%)	5 (17.2)
– Ischemic heart disease, n (%)	2 (6.9)
– Deep vein thrombosis, n (%)	2 (6.9)
– Transient ischemic attack, n (%)	1 (3.4)
≥1 cardiovascular risk factor/comorbidity, n (%)	18 (62.1)
– Arterial hypertension, n (%)	11 (37.9)
– Hypercholesterolemia, n (%)	8 (27.6)
– Diabetes mellitus, n (%)	6 (20.7)
– Obesity, n (%)	5 (17.2)
– Smoking, n (%)	3 (10.3)
– Metabolic syndrome, n (%)	1 (3.4)
– Chronic heart failure, n (%)	1 (3.4)
– Chronic venous insufficiency, n (%)	1 (3.4)
– Abdominal aortic ectasia, n (%)	1 (3.4)
– Atrial fibrillation, n (%)	1 (3.4)
– Dilated cardiomyopathy, n (%)	1 (3.4)
TH2 score analysis	
Median TH2 score	1
Hemorrhagic-risk TH2 profile, n (%)	4 (13.8)
Prothrombotic TH2 profile, n (%)	25 (86.2)
Treatment characteristics	
Fostamatinib started for non-response, n (%)	21 (72.4)
Fostamatinib started for platelet count oscillation, n (%)	5 (17.2)
Fostamatinib started for adverse events to prior therapies, n (%)	3 (10.3)
Bridging treatment, n (%)	16 (55.2)

*Heavily pretreated defined as ≥4 prior treatment lines.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

USE OF THROMBOPOIETIN RECEPTOR AGONISTS IN PERSISTENT THROMBOCYTOPENIA FOLLOWING CAR-T THERAPY AND ALLOGENEIC HSCT: REAL-LIFE EXPERIENCE

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Severe thrombocytopenia is a critical complication of CAR-T therapy and allogeneic HSCT with an increased risk of bleeding and dependence on blood transfusions. TPO-RAs (thrombopoietin receptor agonists) promote platelet count recovery; however, literature data on the efficacy of these drugs in these two clinical contexts remain limited.We evaluate the efficacy of treatment with Avatrombopag and Eltrombopag in patients with persistent thrombocytopenia following allogeneic HSCT and CAR-T therapy, by comparing the two TPO-RAs in clinical practice.The treatment goal was to achieve a platelet count of 50,000/mm^3 or higher, confirmed by at least two blood tests.This is a single-center retrospective study conducted at the Transplant Unit of the “La Maddalena” in Palermo between 2022 and 2025. A total of 25 patients were analyzed: 12 after CAR-T therapy and 13 after HSCT.Patient data included baseline diagnosis, platelet nadir, post-TPO-RA recovery kinetics, and duration of TPO-RA therapy. With the prior approval of the local ethics committee, all patients provided their consent.Twelve patients developed persistent post-CAR-T thrombocytopenia; ten received eltrombopag and two received avatrombopag. Treatment began a median of 21 days after infusion. The primary endpoint was achieved in 80% of cases treated with Eltrombopag and in 100% with Avatrombopag. Avatrombopag showed a significantly shorter median time to response (19.5 vs 70 days), suggesting faster platelet recovery. The mean platelet peak was 88×10^9/L in the Eltrombopag group and 90×10^9/L in the Avatrombopag group, with an increase from the nadir of 61×10^9/L and 78×10^9/L, respectively.8/13 patients with persistent severe thrombocytopenia following allogeneic HSCT were treated with eltrombopag, five with avatrombopag. A clinical response was observed in 75% and 60% of cases, respectively (p=0.63). No statistically significant differences were found between the two drugs in terms of mean peak platelet count (68×10^9/L in the Eltrombopag group and 56×10^9/L in the Avatrombopag group, p=0.62), increase from nadir (63×10^9/L and 52×10^9/L, p = 0.55) or duration of treatment (95 vs 74 days; p=0.41).The results confirm the efficacy of TPO-RAs in promoting platelet recovery. Although Avatrombopag appears to be associated with a more rapid response in the CAR-T setting, both drugs have proven to be effective therapeutic options.

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ANTICOAGULATION MANAGEMENT IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A SINGLE-CENTER REAL-WORLD EXPERIENCE

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Background. Paroxysmal nocturnal hemoglobinuria (PNH) is associated with a high risk of life-threatening thrombosis. Although complement inhibitors (CIs) have substantially reduced thrombotic complications, the optimal indication, intensity, and duration of anticoagulation remain uncertain.

Aims. To describe real-world anticoagulation strategies in patients with PNH.

Methods. We retrospectively reviewed clinical data from PNH patients treated at our center between 2015 and 2026, focusing on complement inhibition, thrombotic history, anticoagulation strategies, bleeding complications, and thrombotic recurrence.

Results. Ten patients with PNH were evaluated: seven with hemolytic PNH and three with aplastic anemia/PNH. Four patients had a history of thrombosis, all involving the portal/mesenteric venous district, whereas six had no previous thrombotic events. All patients received CI therapy: eculizumab(N=2), ravulizumab(N=6), iptacopan (N=1), and ravulizumab plus danicopan (N=1). Seven patients were managed without long-term anticoagulation,in one case due to severe thrombocytopenia. Three patients continued indefinite anticoagulation for secondary prophylaxis. Anticoagulant strategies included switch from warfarin to rivaroxaban after eight years, switch from long-term fondaparinux to reduced-dose apixaban because of mild thrombocytopenia, and intermediate-dose low-molecular-weight heparin (LMWH). One patient with portal vein thrombosis and filter placement received LMWH during the acute phase followed by apixaban for three months, later discontinued because of severe thrombocytopenia. For primary prophylaxis, LMWH was used before CI initiation, during breakthrough hemolysis, and in high-risk conditions such as infection or surgery, with dose adjustment according to platelet count. Two patients did not receive prophylaxis because of severe thrombocytopenia or treatment refusal. No thrombotic recurrences or bleeding events were observed.

Conclusions. CI therapy may allow anticoagulation discontinuation in selected patients with PNH, particularly in the absence of recurrent thrombosis and with careful clinical monitoring. However, anticoagulation management remains highly individualized, with platelet count representing a key determinant of treatment intensity and safety. In this cohort, DOACs appeared feasible and safe during prolonged follow-up and may represent a practical option for selected PNH patients requiring secondary thromboprophylaxis.

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Table 1. Clinical characteristics, treatment and thrombotic events

Patients	10
Haemolytic PNH	7
Aplastic anemia-PNH	3
Sex (M/F)	6/4
Mean age, years	49.5 (22-67)
Comorbidity	
Hypertension	3
Polycystic ovary syndrome	1
Benign prostatic hyperplasia	1
Depression	1
Obesity	1
History of TE	4
DVT/PE	0
Portal/mesenteric vein thrombosis	4
CI therapy	10
Eculizumab	2
Ravulizumab	6
Iptacopan	1
Ravulizumab and Danicopan	1
Mean time from diagnosis (moths)	48 (2.8-207)
Types of anticoagulants used	
Fondaparinux	1
LMWH	2
Warfarin	1
Apixaban	2
Rivaroxaban	1

Abbreviations CI= complement inhibition; LMWH = Low Molecular Weight Heparin

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

BEYOND POSITIVITY: THE HIERARCHICAL ROLE OF IMMUNOASSAYS IN HIT

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Background and Aim. HIT is an immune mediated disorder induced by the exposure to heparin with subsequent production of antibodies against heparin-platelet factor 4 (H-PF4) complexes. The diagnosis of HIT is based on a combination of 4T pre-test probability score (4Tscore) and detection of antibodies bound to H-PF4 complexes by immunoassays and, if available, a functional assay. Immunoassays are characterised by ease of performance and wide availability. Functional assays are the gold standard for HIT diagnosis but these methods are complex and completely manual. This analysis aims to investigate the hierarchical role of immunoassays and their integration with the 4Ts score for ruling out HIT.

Methods. We conducted a retrospective analysis, from 2020 to 2026, of 103 patients from Azienda Ospedaliera Molinette with suspected HIT. For each case, the pre-test clinical probability was assessed using the 4Ts score. Laboratory evaluation included immunoassays (ELISA, CLIA, and LIA) and a functional assay (HIPA), used as the reference standard.

Results. 33 patients out of 103 (32%) were positive to immunoassays. HIPA was performed on only 9 patients; for the remaining 24 patients, it was not possible to carry out HIPA due to a lack of sufficient samples. In the group of 24 patients, clinical management was based solely on the immunoassays results. In the group of 9 patients, the distribution of 4Ts scores showed a predominance of intermediate-risk cases (7), with some patients classified as high probability (2). In the same group Immunoassays demonstrated a higher rate of positivity compared to the functional assay (ELISA 100%, CLIA 78%, LIA 89%), with HIPA positive in approximately half of the cases (67%). Concordance with HIPA was highest for CLIA (88.9%), followed by ELISA and LIA (both 66.7%). CLIA showed a high Positive predictive value (PPV) (85,7%) and a negative predictive value (NPV) 100%, indicating strong rule-out capability. In contrast, ELISA and LIA showed lower reliability in excluding HIT, with NPV values of 0%.

Conclusions. The results suggest a hierarchical role among immunoassays in HIT diagnosis. The integration of immunoassays with an intermediate-to-high 4Ts score may support exclusion of HIT, potentially reducing the need for functional testing. However, functional assays remain essential in cases with discordant or uncertain results.

Comparison	Simple Accordance	Cohen's kappa (k)	Result
ELISA vs HIPA	66,70%	0	absence of variance in the ELISA
CLIA vs HIPA	88,90%	0,73	a real and strong agreement
LIA vs HIPA	66,70%	-0,12	systematic disagreement

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

RETICULATED PLATELETS IN ITP: BETWEEN IMMUNE CONTROL AND THROMBOPOIETIC DRIVE

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Introduction. Reticulated platelets (RP), the youngest circulating plt fraction still containing residual RNA, reflect megakaryopoietic activity and plt turnover. In immune thrombocytopenia (ITP), elevated RP levels are biologically consistent with enhanced peripheral destruction coupled with compensatory thrombopoiesis, rather than with a primary production defect. Despite this strong pathophysiological rationale, their potential predictive and prognostic value has not been established.

Methods. We performed a retrospective multicentric analysis of ITP patients (pts) with available RP measurements.Pts were stratified according to data availability at each disease phase: group 1 newly diagnosed (n=11), group 2 chronic untreated (n = 12), and group 3 chronic treated (n = 30) further classified as IMD group (treated with PDN, PDN+IG, RTX, FST) or TPO-Ras group (ELT, AVA, ROM).Because RP assessment was not routinely available across centers, the numbers of evaluable pts were 11, 12, and 19, respectively. For each pts, one evaluable therapeutic timepoint per treatment category was considered; when available, baseline and 3month values were compared.Continuous variables were summarized as median (IQR) and categorical variables as n (%).Analyses were primarily descriptive and exploratory.

Results. 53 pts were included (median age 56y; 31F/22M).The main findings are summarized in Table 1.Overall, RP tended to decrease after 1st line and IMD treatment, whereas they stay higher during TPO-RA exposure.From a clinical standpoint, these findings suggest that RP may help contextualize plt recovery, distinguishing pts in whom plt improvement is associated with immune control from those in whom production remains actively stimulated under TPO-RA.In chronic untreated pts, RP values were markedly heterogeneous, with a subset showing clearly elevated levels despite the absence of therapy, suggesting that this parameter may capture inter-individual differences in baseline disease biology beyond treatment effect alone.

Conclusion. RP may represent a biologically informative marker across different ITP phases and treatment settings.Their reduction appears to accompany immune-modulating approaches, whereas persistently higher values under TPO-RAs may reflect ongoing thrombopoietic stimulation.A major study limitation is the non-routine use of this test, which limited datas; however, a prospective design with systematic assessment may better clarify its predictive and clinical value.

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Results

Table 1. Key reticulated platelet findings across the 3 study groups

Variable	Group 1: newly diagnosed ITP	Group 2: chronic untreated ITP	Group 3: chronic treated ITP
Evaluable patients	11	12	19
Clinical setting	From first-line treatment	No treatment	≥3rd-line treated patients
Main treatment exposure	PDN in all; PDN+IVIG in 3/11	None	IMD: 11 pts; TPO-RA: 8 pts
Platelet count	Diagnosis: 9 (IQR 4–24); 3 months: 129.5 (67.2–154.2)*	Concurrent: 68.5 (63.0–103.8)	Used as response surrogate at 3 months
Reticulated platelets	Diagnosis: 22.0 (18.4–33.2); 3 months: 11.8 (6.8–41.4)**	Concurrent: 11.2 (7.0–20.2); range 4.6–35.2	3 months: 6.9 (5.0–18.2) in IMD vs 14.8 (12.4–24.7) in TPO-RA
Paired baseline → 3-month RP data	IMD: 26.0 → 10.7; TPO-RA exposure: on-treatment RP 45.0 (39.0–48.0), range 30.8–57.5	Not applicable	IMD (9/11): 21.4 → 10.0; TPO-RA (7/8): 24.0 → 14.3
Main message	RP decreased overall after first-line therapy; lower values with IMD, persistently higher values with TPO-RA exposure	RP values were heterogeneous, with some untreated patients showing high levels	RP tended to normalize with IMD and remained higher with TPO-RA; RP reduction was not robustly associated with response

** Platelet count available in 10/11 patients at 3 months.*

*** Reticulated platelets available in 8/11 patients at 3 months.*

Abbreviations: RP, reticulated platelets; PDN, prednisone; IVIG, intravenous immunoglobulins; IMD, immunomodulatory treatment; TPO-RA, thrombopoietin receptor agonist.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

A DIGITAL NETWORK FOR THE REMOTE MANAGEMENT OF ACQUIRED HEMOPHILIA A: A REGIONAL MODEL OF INTEGRATED CARE

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Background. Acquired hemophilia A (AHA) is a rare, life-threatening autoimmune bleeding disorder caused by factor VIII-neutralizing autoantibodies. It mainly affects older adults and is often underrecognized, causing diagnostic delay and fragmented care, with preventable bleeding, increased mortality, and higher costs. Despite available haemostatic and immunosuppressive treatments, management remains challenging outside expert centers.AimsTo implement a regional digital care pathway connecting peripheral hospitals with a Hemophilia Reference Center, to accelerate diagnosis, guide treatment, and improve follow-up.

Methods. A secure platform was developed to connect emergency departments, hematology units, laboratories, community pharmacies, and general practitioners with the Regional Hemophilia Reference Center of Palermo. It enables rapid teleconsultation for suspected AHA, centralized interpretation of coagulation tests, and shared decisions on haemostatic and immunosuppressive treatment. Clinical data, bleeding events, therapies, and lab results can be updated in real time, allowing timely treatment adjustments. A patient area supports follow-up communication. Access is role-based and compliant with data protection regulations.

Results. Platform development started on 6 December 2023 and regional implementation was completed in February 2025. Four physicians from four community hospitals were enrolled: two from emergency departments and two from hematology units. Twelve expert consultations were requested for suspected AHA. Two confirmed patients were managed through the shared pathway, one identified in the emergency setting and one in hematology. Follow-up was maintained through clinical and laboratory updates entered by general practitioners and reviewed by the reference center. In both cases, treatment was tailored remotely and complete remission was achieved. In one patient, follow-up also led to a cancer diagnosis, highlighting a potential role in oncological surveillance, given the association between AHA and malignancy. During the first six months, the platform improved communication, strengthened care continuity, and helped avoid inappropriate interventions.

Conclusions. A digitally integrated care network can improve access to expertise in AHA, supporting earlier diagnosis, coordinated treatment, and follow-up. This model may be extended to other rare diseases, promoting equitable access to specialized care and real-world data collection.

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FOSTAMATINIB IN CHRONIC IMMUNE THROMBOCYTOPENIA: A REAL-WORLD MONOCENTRIC EXPERIENCE

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Aims. Our analysis aims to evaluate fostamatinib efficacy and safety in chronic ITP (cITP).

Methods. We retrospectively analyzed 43 consecutive adult patients (> 18 years) with cITP treated with fostamatinib in our center. Efficacy was evaluated as time to treatment failure (TTF); data were censored for patients who did not relapse until the last follow-up or who discontinued treatment for reasons other than loss of efficacy. Clinical response was categorized according to the international consensus criteria by Rodeghiero et al. (2009). Safety was assessed by monitoring treatment-emergent adverse events. Infections were defined severe if they required hospitalization. Patients were stratified by therapy line in Group 1 (1-2 prior treatment lines) and Group 2 (≥ 3 prior treatment lines). Time-to-event analysis was performed using Kaplan-Meier curves. Statistical significance was set at $p < 0.05$.

Results. Thirty patients were female, 13 male. Prior to fostamatinib, patients had received a median of 4 therapy lines (range 2-12). All patients had been previously treated with corticosteroids (100%), while 21 (48.8%) received eltrombopag, 15 (34.9%) rituximab, 13 (30.2%) romiplostim, 8 (18.6%) avatrombopag, 6 (14.0%) splenectomy, 5 (11.6%) azathioprine and 1 (2.3%) cyclosporine A. Twenty-three patients (53.4%) had a concomitant autoimmune diathesis. Seven patients (16.3%) had previous thrombosis. Median age at fostamatinib start was 55 years (range 25-80). The median duration of fostamatinib treatment was 282 days (range 26-1319). The overall response rate (ORR) was 90.7%, with a complete response rate (CR) of 67.4%. Thirty-five patients (81.4%) received concomitant ITP treatments (15 corticosteroids, 12 TPO-RAs+corticosteroids, 6 TPO-RAs, 2 rituximab+corticosteroids). Twelve patients (27.9%) discontinued fostamatinib due to non-response or loss of response and two patients (4.7%) due to diarrhea; one patient (2.3%) tapered and discontinued fostamatinib maintaining a response of therapy. No patients discontinued treatment due to arterial hypertension. No thrombotic events were reported. Severe infections occurred in 2 patients (4.7%), none of which led to permanent drug discontinuation. Kaplan-Meier analysis showed that therapy line is a significant predictor of response durability. Patients in Group 1 achieved a significantly longer median TTF compared to Group 2 (not reached vs. 112 days) (Log-Rank p=0.026) (Figure 1).

Conclusion. Fostamatinib proved to be safe and effective in our monocentric experience with a median follow up of about 10 months (16/43 patients with a drug exposure more than a year). The use of fostamatinib as second/third line of treatment led to a significantly more durable response, supporting its early use in the ITP treatment algorithm.

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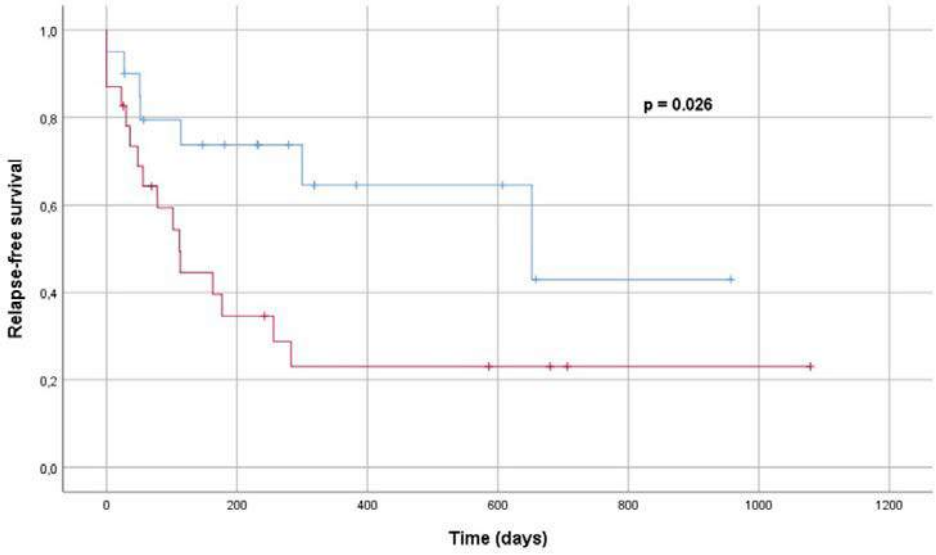
Figure 1. Time to Treatment Failure (TTF) according to line of therapy.



Time (Days)	0	200	400	600	800	1000	1200
Group 1	20	11	4	3	1	0	0
Group 2	23	7	4	3	1	1	0

Patients of *Group 1* (1-2 prior treatment lines) showed a significantly longer median TTF compared to patients of *Group 2* (≥ 3 prior treatment lines) (not reached vs. 112 days; Log-Rank p=0.026). Censure was applied for patients who did not relapse until the last follow-up or who discontinued treatment. for reasons other than loss of efficacy.

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

ROMIPLOSTIM FOR CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA IN ADVANCED SOLID TUMORS: A SINGLE-CENTER EXPERIENCE

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Background and Aims. Chemotherapy-induced thrombocytopenia (CIT) is a common hematologic toxicity in cancer patients receiving cytotoxic agents, particularly platinum derivatives, taxanes, and antimetabolites. It may lead to dose reductions and treatment delays, potentially affecting outcomes. TPO mimetics, such as romiplostim, stimulate platelet production and, although approved for ITP, have been used off-label in CIT. This study conducted in our centre aimed to assess the appropriateness and effectiveness of romiplostim in patients with advanced solid tumors.

Methods. We retrospectively analyzed 7 patients (4 females, 3 males) with CIT referred to our centre between 2024 and 2026. All at referral had stage IV tumors; median age at cancer diagnosis was 57 years (37-77) and 5 patients (72%) had received ≥3 prior chemotherapy lines. Median platelet count at CIT onset was 78×10^9/L (23-113), without bleeding manifestations.Bone marrow evaluation was performed in all cases. Romiplostim was finally administered just to 3 patients based on clinical judgement, initially with a median dose of 1 µg/kg (range 0.5-2), and platelet response was assessed at 7, 14, and 21 days. Adverse events were recorded.

Results. Bone marrow findings varied: 2 patients had preserved hematopoiesis, 1 patient partially preserved hematopoiesis, the others showed diffuse tumor infiltration.Among the 3 treated patients with Romiplostim, 2 (67%) achieved a significant increase in platelet counts, allowing continuation of oncologic treatment. The non-responder had an extensive marrow involvement and a rapid disease progression. Median platelet count increased from 73 ×10^9/L (31-101) at baseline to >100 ×10^9/L at day 14 (14-127) and during follow-up.Dosing schedules varied from weekly to every 3 weeks. About complications 1 patient experienced pulmonary embolism after trauma. Median follow-up was 2 months overall (1-12), and 5 months (1-12) in patients treated with TPO mimetics. In this subgroup, 2 patients died due to disease progression, both with marrow infiltration, while 1 patient remains on treatment for both CIT and the underlying malignancy.

Conclusions. In our experience, Romiplostim appeared to be an effective option for managing CIT in patients with preserved bone marrow reserve; efficacy was limited in cases of extensive marrow infiltration. Complications need to be monitored, and careful assessment of thrombotic risk is essential.

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OVERALL POPULATION	7 (100%)
DEMOGRAPHIC	
Female	4 (57%)
Male	3 (43%)
Median age at cancer diagnosis (years old)	57 (37-77)
Type of cancer	
Breast	2 (29%)
Prostatic	2 (29%)
Pulmonary	1 (14%)
Bowel	1 (14%)
Neuroendocrin	1 (14%)
Lines of therapy	
1	1 (14%)
2	1 (14%)
≥3	5 (72%)
Median age at diagnosis of CIT	62 (39-76)
Deceased patients	6 (96%)
Mendian months of follow-up	2 (1-12)
LABORATORISTIC VALUES	
Median plt count at CIT	78×10⁹/L (23-113)
BM involvement	
No	2 (29%)
Partial tumor infiltration	1 (14%)
Diffuse tumor infiltration	4 (58%)
TREATED PATIENTS	3 (100%)
Inital Romiplostim dose (mcg/kg)	1 (0,5-2)
Plt count at day 7	77 (17-115)
Plt count at day 14	102 (14-127)
Romiplostim administration	
Once weekly	1 (33%)
Once every 3 weeks	1 (33%)
On demand	1 (33%)
Median months of therapy/follow-up	5 (1-12)
Deceased patients	2 (67%)

COMBINATION STRATEGIES WITH FOSTAMATINIB IN SECONDARY IMMUNE THROMBOCYTOPENIA: A SINGLE-CENTER REAL-WORLD EXPERIENCE

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UOC Ematologia - ARNAS Garibaldi

Introduction. Secondary immune thrombocytopenia (ITP) is a complex condition often associated with autoimmune diseases, requiring a dual therapeutic approach targeting both thrombocytopenia and the underlying disorder. Fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, is effective in chronic ITP, but data on combination strategies in secondary forms remain limited, particularly in patients with antiphospholipid antibodies (aPLAs), who are at increased thrombotic risk.Patients and aim: We retrospectively evaluated efficacy and safety of fostamatinib-based combination therapies in a monocentric cohort. Among 11 patients with secondary ITP, 8 received combination regimens and were included. The cohort included 6 females and 2 males, with a median age of 59.2 years (range 36–67.4) and a median baseline platelet count of 21×10⁹/L (range 3–39). Underlying diseases were mixed connective tissue disease (n=1), rheumatoid arthritis (n=1), and systemic lupus erythematosus (SLE; n=5). Combinations included hydroxychloroquine (n=2), methotrexate (n=1), mycophenolate mofetil (n=2), belimumab (n=1), or steroids (n=1) with fostamatinib. aPLAs were present in 6/8 patients (75%), including 3 triple-positive cases, all with prior thromboembolic events (Tab. 1).

Results. All patients achieved a platelet response, with rapid and sustained increases across regimens, irrespective of the underlying disease. Patients with aPLAs showed particularly favorable outcomes, with high complete response rates. No thromboembolic events occurred during treatment despite the high-risk profile. Combinations were well tolerated, with no discontinuations due to toxicity and no new safety signals. Adverse events included diarrhea (grade ≤2) in 3/8 patients (37.5%) and non-febrile neutropenia (grade ≤3) in 4/8 patients (50%), both manageable and reversible.

Conclusions. In this real-world experience, fostamatinib-based combinations demonstrated high efficacy and excellent tolerability in secondary ITP. These findings support its use in complex autoimmune-associated thrombocytopenia, including high-risk aPLA-positive patients. Larger prospective studies are warranted to confirm these results and optimize treatment strategies.

Characteristic	Value
Patients, n	8
Female, n (%)	6 (75%)
Male, n (%)	2 (25%)
Age, median (range), years	59.2 (36–67.4)
Platelet count at baseline, median (range), ×10⁹/L	21 (3–39)
Underlying disease	
– SLE, n (%)	5 (62.5%)
– Mixed connective tissue disease, n (%)	1 (12.5%)
– Rheumatoid arthritis, n (%)	1 (12.5%)
aPL positivity, n (%)	6 (75%)
Triple aPL positivity, n (%)	3 (37.5%)
Prior thromboembolic events, n (%)	3 (37.5%)

Table 1. Baseline demographic and clinical characteristics of patients with secondary immune thrombocytopenia (sITP) treated with fostamatinib-based combination regimens. Data are reported as absolute numbers (percentages) or medians (ranges).

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

FROM TREATMENT TO DISCONTINUATION: ACHIEVING SROT IN ITP PATIENTS TREATED WITH TPO-RAS IN A SINGLE-CENTER EXPERIENCE

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Background and Aims. The introduction of thrombopoietin receptor agonists (TPO-RAs) has significantly improved response rates in patients with immune thrombocytopenia (ITP). In a subset of patients, a sustained response can be achieved despite progressive dose reduction and even after treatment discontinuation, defined as sustained response off treatment (SROT). We analyzed patients from our center who achieved SROT, evaluating response duration, tapering strategies, and relapse rates, with the aim of contributing to process standardization.

Methods. Seventeen patients (9 males, 8 females) were included, with a median age at diagnosis of 63 years (range 21–73). Before TPO-RA initiation, 12/17 patients (70.6%) had received one prior treatment line, 3/17 (17.6%) two lines, and 2/17 (11.8%) ≥3 lines. TPO-RAs were started within 3 months from diagnosis in 2/17 patients, during the persistent phase in 5/17, and in the chronic phase in 10/17. Six patients received eltrombopag, ten romiplostim, and one avatrombopag.

Results. Median duration of TPO-RA therapy was 24 months (range 3–79), with a median peak platelet count of 308×10^9/L. Tapering was performed over a median of 12 months; median platelet count at tapering initiation was 223.5×10^9/L, with a nadir of 119×10^9/L during dose reduction. In 2/17 patients, treatment was discontinued without tapering due to adverse events; both maintained SROT for more than 10 years. Median dose at discontinuation was 25 mg/week for eltrombopag, 0.065 mL/week for romiplostim, and 10 mg/week for avatrombopag. Median platelet count at discontinuation was 139×10^9/L. Median follow-up after discontinuation was 53 months. Relapse occurred in 4/17 patients: two were successfully treated with corticosteroids, while two resumed TPO-RA therapy; one of these regained SROT after a second tapering attempt, while the other remains on treatment.

Conclusions. SROT is an achievable goal in a subset of ITP patients treated with TPO-RAs, with relevant clinical and psychological impact, although relapse may occur in a minority of cases. Our monocentric experience is consistent with available literature and supports the need for standardized tapering strategies. Data on avatrombopag remain limited, and further studies are warranted to identify predictive factors for SROT

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Hodgkin's Lymphoma

PROGNOSTIC ROLE OF THE SIMPLIFIED GERIATRIC ASSESSMENT IN OLDER PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA

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Background. Older adults (≥60 years) with classical Hodgkin lymphoma (cHL) have inferior outcomes compared with younger patients due to comorbidity burden, functional impairment, lack of standardized treatment approaches, and treatment-related toxicity. Simplified geriatric assessment (sGA), including baseline evaluation of Activities of Daily Living (ADL), Instrumental ADL (IADL), and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), may support treatment stratification by identifying patients suitable for curative-intent chemotherapy and those requiring less intensive, adapted approaches.

Aims To evaluate the feasibility and the prognostic impact of the sGA in older patients newly diagnosed with cHL treated with ABVD/ABVD-like regimens.

Methods. We conducted a retrospective multicenter study including 103 consecutive patients aged ≥ 60 years with newly diagnosed cHL treated with ABVD/ABVD-like regimens between 2010 and 2023 at three hematology centers in Italy. Patients were classified according to sGA as FIT, UNFIT, or FRAIL and the prognostic impact of this stratification was analysed. Survival outcomes were analysed using Kaplan–Meier and Cox regression models.

Results. According to sGA, 85.6% of patients were classified as FIT, 8.7% as UNFIT, and 5.8% as FRAIL. Reduced-dose regimens were more frequently administered to UNFIT (55.6%) and FRAIL (66.7%) patients compared with FIT individuals (24.7%). Complete remission rates were similar across groups. However, sGA showed a significant prognostic impact on survival. In univariate analysis, UNFIT status was associated with inferior progression-free survival (PFS) both in the overall cohort (HR 3.28, p=0.015) and among patients receiving full-dose ABVD (HR 3.85, p=0.028), while FRAIL status showed a borderline association (HR 2.87, p=0.049). FRAIL status (HR 6.67, p=0.004) and functional impairment (ADL p<0.001; IADL p=0.033) strongly predicted worse overall survival.

Summary/Conclusions. The sGA is a feasible and clinically relevant tool for risk stratification in older patients with cHL. FRAIL status and functional impairment emerged as strong determinants of survival despite similar response rates, supporting integration of sGA into treatment decision-making in this population. Further prospective studies are needed to confirm these findings.

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Non-Hodgkin's Lymphoma

EARLY ACCESS TO INNOVATIVE THERAPIES IN RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMAS: A MONOCENTRIC RETROSPECTIVE ANALYSIS AND IMPACT ON SURVIVAL OUTCOMES

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Patients with relapsed/refractory peripheral T-cell lymphomas (R/R PTCL) have poor prognosis, with durable remissions typically achievable only through salvage therapy followed by allogeneic stem cell transplantation (allo-SCT). Early access to clinical trials (CTs) represents a crucial opportunity, especially as a bridge to transplant. Between 2020 and 2026, 56 R/R PTCL patients were treated at our center with novel therapies (NTs), including valemetostat (27%), duvelisib (29%), linperlisib (20%), PRT2527 (11%), nanatinostat plus valganciclovir (7%), anti-CDK9 (2%), and an anti-CD94 antibody (5%). Median age at NT initiation was 53 years (range 21–80), with 98% presenting Ann Arbor stage III/IV disease. Patients had received a median of two prior therapy lines (range 1–6), with 80% refractory to the last treatment and 23% having previously undergone autologous transplantation. The most common histology was PTCL-not otherwise specified (36%), followed by follicular helper T-cell lymphoma (18%), angioimmunoblastic T-cell lymphoma (17%), ALK− anaplastic large cell lymphoma (9%), ALK+ anaplastic large cell lymphoma (4%), hepatosplenic T-cell lymphoma (4%) and monomorphic epitheliotropic intestinal T-cell lymphoma (4%). Among the 41 patients for whom an evaluation was available, the overall response rate (ORR) was 63% (26 patients). At a median follow-up of 35.7 months, median overall survival (OS) and progression-free survival (PFS) were 11.3 and 4.4 months, respectively. Patients treated within the first two lines of therapy had longer median OS (17.3 vs 2.4 months, p=0.2479) and significantly longer PFS (6.9 vs 2.4 months, p=0.0266) than those treated later. Eighteen patients received subsequent therapies after CTs, with a median of one additional line (range 1–3) and a median time to next treatment (TTNT) of 4.5 months. Sixteen patients proceeded to allo-SCT, achieving continuous complete metabolic remission at last follow-up, although two transplant-related deaths occurred; median OS and PFS were not reached. These findings suggest that early enrollment of patients with R/R PTCL in clinical trials appears to offer the best potentially curative strategy, enabling disease control with achievement of a response that can be consolidated with allo-SCT and ultimately improving patient outcomes.

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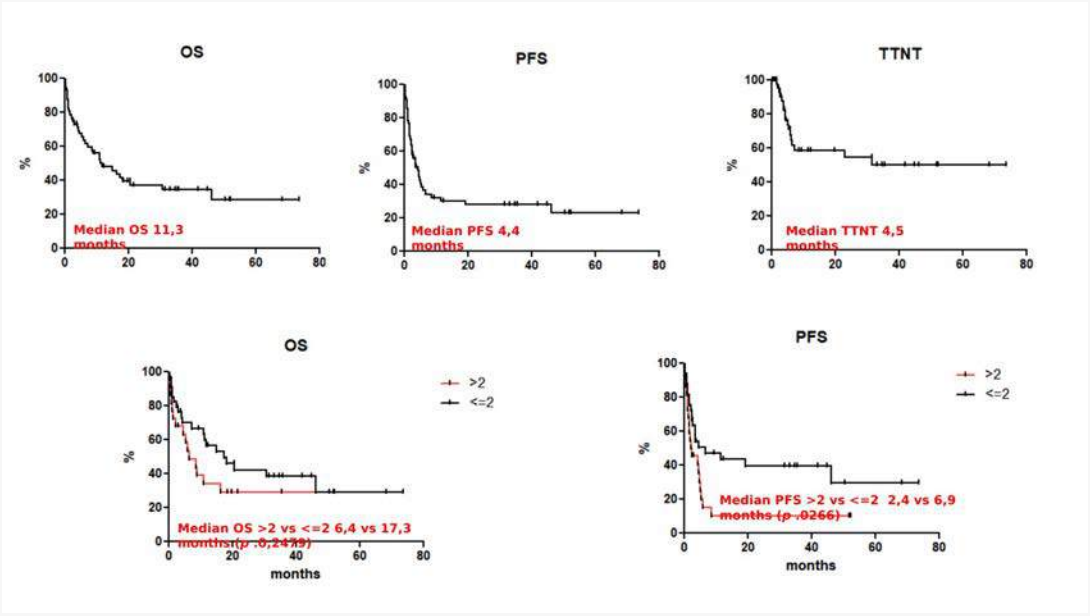
Non-Hodgkin's Lymphoma



Non-Hodgkin's Lymphoma

HIGH INCIDENCE AND DISMAL PROGNOSIS OF INVASIVE FUNGAL INFECTIONS IN T-CELL NON-HODGKING LYMPHOMA PATIENTS: RESULTS OF A 11-YEAR RETROSPECTIVE STUDY

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Intrinsic immunological disfunction, as well as intensive treatments, could predispose T-cell non-Hodgkin lymphoma (T-NHL) patients (pts) to an increased susceptibility to invasive fungal infections (IFI). However, epidemiological data about this topic are scanty.To better define the incidence, predisposing factors, and outcome of IFI, we retrospectively evaluated a large series of T-NHL pts diagnosed at our Institution.Between 2015 and 2025, all the patients affected by T-NHL were recorded. Data concerning probable/proven IFI (diagnosed according to ECIL 2019 definitions) were extracted and correlated to age, gender, type of T-NHL, treatment received, hematologic response and outcome.One hundred and eighty-three pts were recorded. Male/female ratio was 117/66 and median age 66y (range 18-90). Ten pts did not receive any specific treatment and rapidly died and were excluded from the analysis; 173 received at least 1 line of treatment and 106 experienced relapsed/progressive disease. A 2nd line was offered to 62 pts, of which 11 received also a 3rd line. Overall, 21/173 (12.1%) pts developed an IFI (2 candidemia, 16 pulmonary aspergillosis and 2 pulmonary+cerebral aspergillosis). Incidence was significantly higher at 2nd or further line of treatment (11/73, 15.1%) as compared to 1st (10/173, 5.8%) (p=0.024). After a median follow up of 13 months (range 1-108), 77 (44.5%) pts deceased. In 8/21 (38.1%) cases, IFI was considered a contributing cause of death together with lymphoma. Death was associated with age≥65y (53/92, 57.6% vs 24/81, 29.6%, p<0.0001), relapsing/refractory disease (49/100, 49% vs 20/73, 27.4%, p=0.0001), IFI event (17/21, 80.9% vs 60/152, 39.5%, p=0.014) and advanced stages (18/145, 12% vs 2/29, 7%, p=0.045), whereas both autologous (12/57, 21% vs 65/116, 56%, p=0.0001) and allogeneic stem cell transplantation (3/15, 20% vs 74/158, 46.7%, p=0.014) were protective. Median overall survival was only 13 mo (CI 11-15) in patients developing IFI, as compared to 80 mo (CI 11-148) in patients without, p=0.004 (figure 1).IFI incidence was high in T-NHL, particularly in advanced diseases. IFI occurrence was not associated with advanced age, probably because of an intrinsic immunodeficiency, typical of this lymphoma histotype. Early diagnostic and treatment strategy should be implemented in T-NHL, as IFI events could have a negative impact on the choice of hematologic intensive treatments and are associated with a dismal prognosis.

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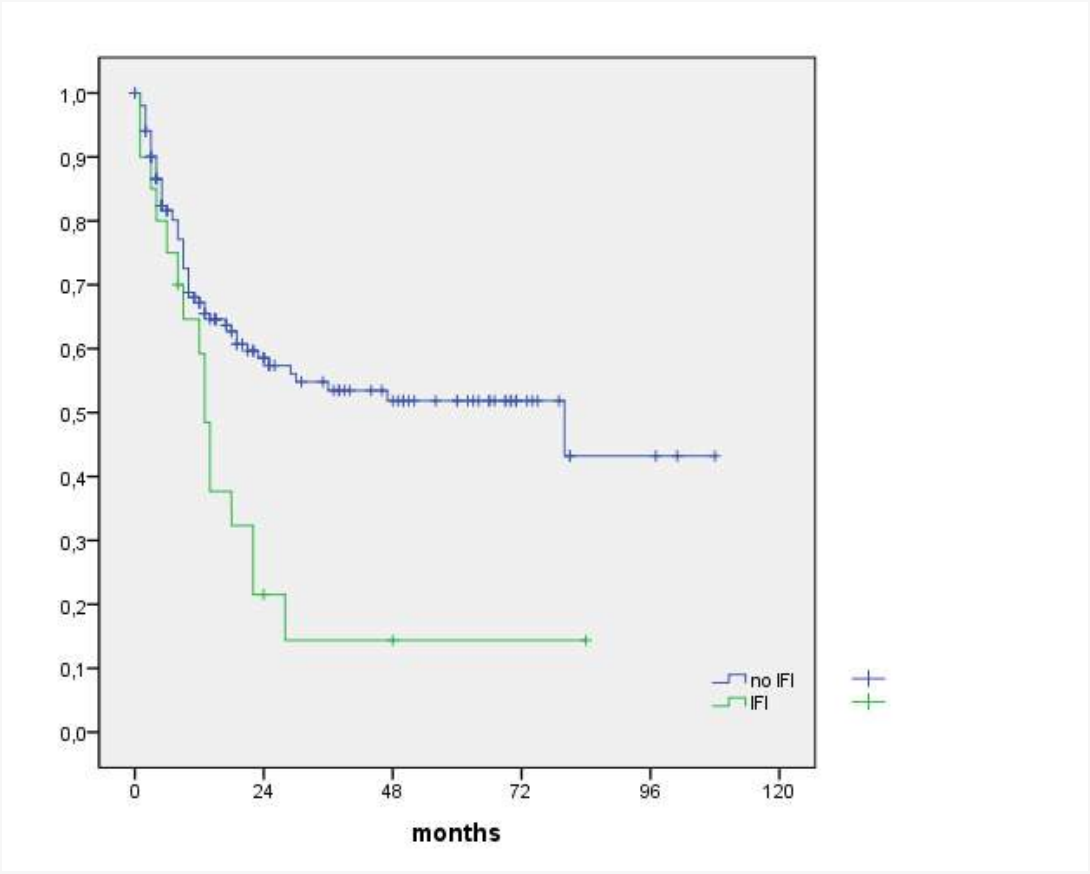
Non-Hodgkin's Lymphoma



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Non-Hodgkin's Lymphoma

BIOIMPEDANCE DERIVED SARCOPENIA AND PHASE-ANGLE PREDICT TOXICITY AND SURVIVAL AFTER CART CELL THERAPY

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Background. CAR-T are highly effective for hematologic malignancies but remain limited by relapse and acute toxicities (CRS and ICANS). Early predictors of response and toxicity are needed.Bioelectrical impedance analysis (BIA) is a simple, non-invasive tool for assessing body composition, including sarcopenia. Phase angle (PhA), a BIA-derived parameter, reflects cellular integrity and systemic inflammation. We investigate whether baseline BIA parameters and serial PhA measurements are associated with outcome and with CRS/ICANS onset.

Methods. Patients (pts) aged ≥18 years treated since July 2023 with anti-CD19 CAR-T were prospectively included. BIA was performed before lymphodepletion, at infusion, twice weekly until discharge, and at CRS/ICANS onset. BIA parameters included PhA, fat mass, total muscle mass, and appendicular skeletal muscle mass (ASMM). Sarcopenia was defined by European criteria (ASMM <20/15 kg or ASMM/height^2 <7/5.7 kg/m^2 for males/females). Associations with toxicity, progression free survival (PFS) and overall survival (OS) were analyzed.

Results. Forty pts were included: 25 (62.5%) had large B-cell lymphoma (LBCL), 9 follicular lymphoma, 4 mantle cell lymphoma, and 2 acute lymphoblastic leukemia. CAR-T products were axi-cel (n=25), tisa-cel (n=9), and brexu-cel (n=6). Median age was 61 years. Thirty-three pts (83%) developed CRS and/or ICANS (severe 10%).Among LBCL, 8/25 (32%) were sarcopenic, with no baseline differences compared with non-sarcopenic pts. Sarcopenia was associated with significant inferior PFS (12-month: 16.7% vs 62.5%; p=0.04; Fig1) and worse OS (2-year: 60% vs 82%).Lower PhA at CAR-T infusion was associated with ICANS (Median PhA of 4.7° [IQR 4.3–4.9] vs. 5.3° [IQR 5.0–5.9]; p=0.03, Fig1).A significant PhA decline occurred at CRS onset (–1.0° [IQR –1.4 to –0.6]), whereas pts without toxicity showed no reduction (+0.15° [IQR 0.1–1.25]; p<0.001, Fig.1). PhA recovered after CRS resolution. Among CRS pts, those who developed ICANS showed persistently low PhA, whereas others recovered more rapidly, suggesting that PhA dynamics may predict subsequent ICANS (Fig.1).PhA dynamics was independent of CAR-T product and baseline characteristics.

Conclusions. Bioimpedance-derived metrics enable simple, non-invasive risk stratification and real-time monitoring in CAR-T recipients. Sarcopenia predicts inferior PFS, while dynamic PhA changes act as an early biomarker of CRS and ICANS. Prospective validation is warranted.

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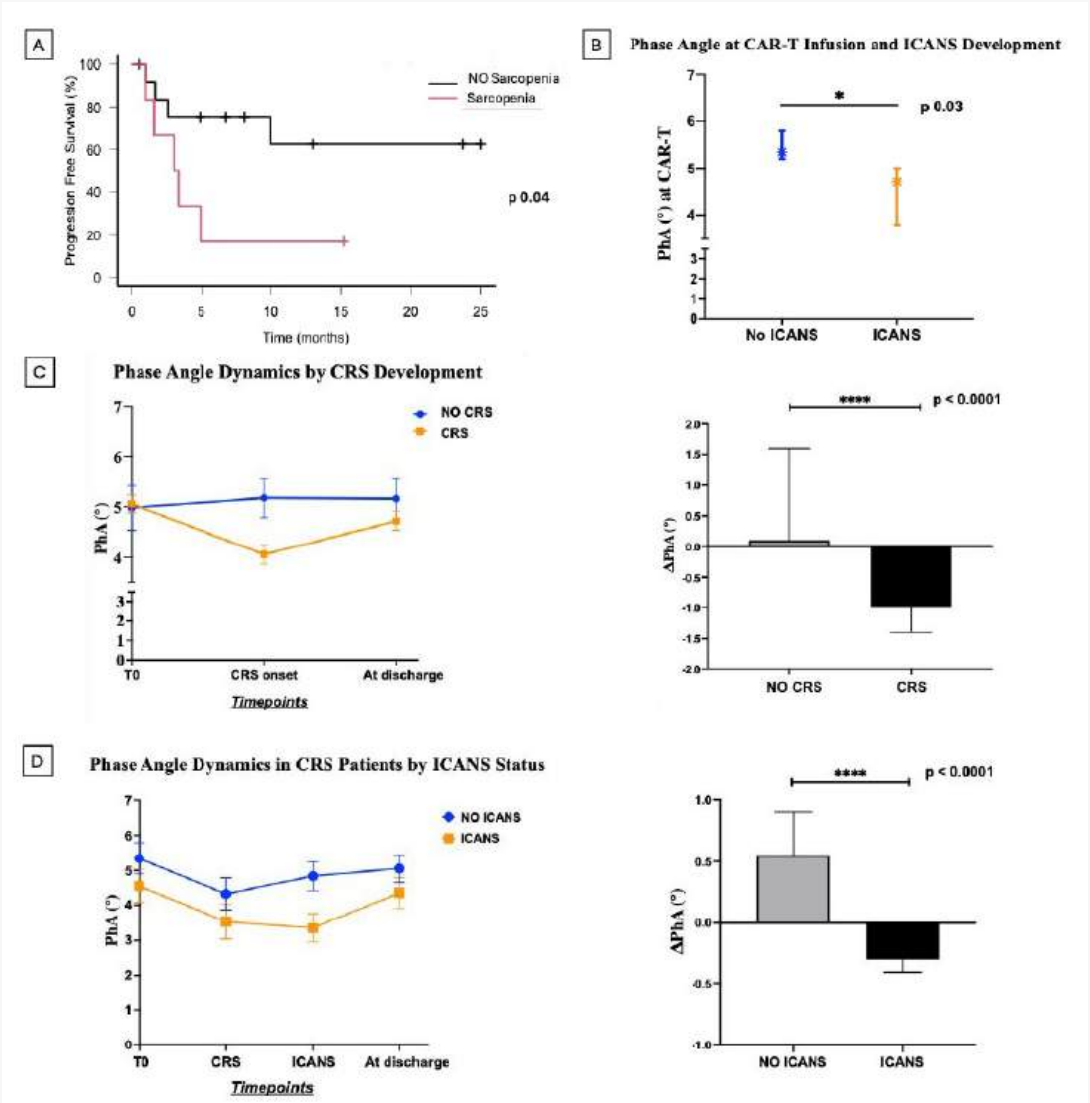

Figure 1 Sarcopenia, phase angle (PhA), and CAR-T–related toxicities.
(A) PFS stratified by sarcopenia. (B) Baseline PhA at CAR-T infusion predicts ICANS development. (C) PhA dynamics in patients with and without CRS, with corresponding ΔPhA (right), showing a significant reduction at CRS onset ($p < 0.0001$). (D) PhA dynamics in CRS patients according to ICANS development, with corresponding ΔPhA (right), showing a greater decline in patients who developed ICANS ($p < 0.0001$).

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Non-Hodgkin's Lymphoma

BENDAMUSTINE, GEMCITABINE AND VINORELBINE IN RELAPSED OR REFRACTORY PERIPHERAL T CELL LYMPHOMAS: A RETROSPECTIVE MULTICENTER STUDY ON BEHALF OF FONDAZIONE ITALIANA LINFOMI

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In relapsed/refractory (R/R) peripheral T cell lymphomas (PTCL), prognosis remains poor, with a median overall survival (OS) and progression free survival (PFS) of 5.5 and 3.1 months, respectively. Targeted agents as monotherapy show limited activity, with overall response rates (ORR) of 22–31%, whereas bendamustine and gemcitabine achieve higher efficacy (ORR 50% and 55%, respectively). The bendamustine, gemcitabine and vinorelbine (BEGEV) regimen is increasingly used in Fondazione Italiana Linfomi (FIL)–affiliated centers. This study evaluated the efficacy, tolerability, and bridging potential of BEGEV to autologous (ASCT) or allogeneic stem cell transplantation (allo SCT).Patients with R/R PTCL treated with BEGEV as second or third line salvage chemotherapy were included. Response was assessed after 2 and/or 4 cycles by PET and/or CT according to Lugano criteria. Primary endpoints were ORR and complete remission (CR); secondary endpoints included transplantation rate (TR) and OS.Thirty three patients were included (median age 59 years; range 28–75). Histological subtypes were PTCL NOS (n=13), angioimmunoblastic T cell lymphoma (AITL/TFH; n=8), gamma-delta PTCL (n=1), ALCL ALK (n=9), ALCL ALK+ (n=1), and hepatosplenic T cell lymphoma (n=1). Advanced stage disease was present in 88% of patients and 36% were refractory to frontline therapy. B symptoms and bulky disease were observed in 55% and 21%, respectively. Median time from diagnosis to relapse was 8.1 months (range 1–82), and from end of prior chemotherapy was 3 months (range 0–94). All but one patient received anthracycline based frontline therapy.Overall, 30 patients received BEGEV as second or third line treatment. The ORR was 63%, with a CR rate of 23%. TR was 58% (7 ASCT and 12 allo SCT). When BEGEV was used as second line therapy (n=20), ORR was 61% with a CR rate of 21%. As third line therapy (n=10), ORR was 43% with a CR rate of 29%. After BEGEV, the TR was 42%. One year OS was 54% (Fig.1) and was significantly higher in patients receiving allo SCT (100% vs 24%, p=0.015).After a median follow up of 12 months from BEGEV, 48% of patients were alive. Deaths were due to disease progression (n=9) and treatment related toxicity (n=7; 1 after BEGEV and 6 after allo SCT). Despite the retrospective design, small sample size and limited follow up, BEGEV demonstrated substantial activity and represents a feasible bridging strategy to transplantation in R/R PTCL.

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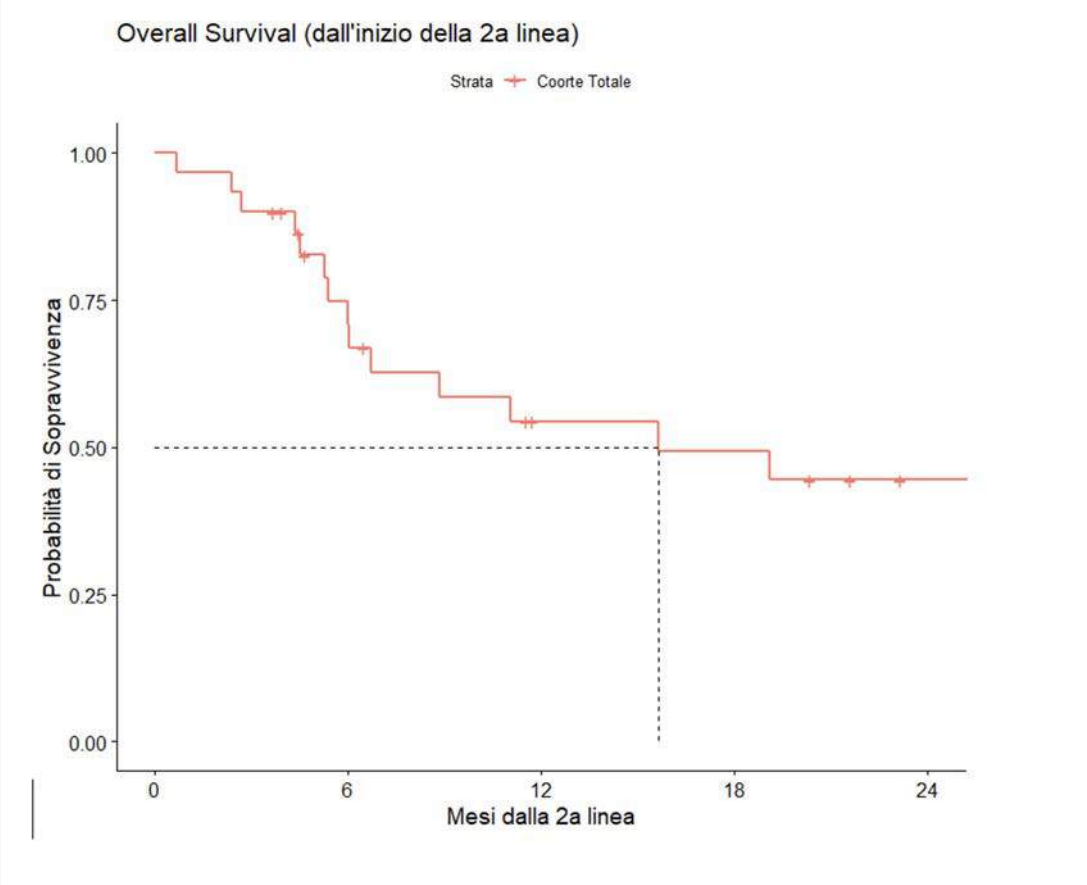
Non-Hodgkin's Lymphoma



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Non-Hodgkin's Lymphoma

EARLY IMMUNE SIGNATURE FEATURES, INCLUDING TLR2 AND TLR4 EXPRESSION, ARE ASSOCIATED WITH COMPLETE REMISSION AFTER CD19 CAR-T CELL THERAPY

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Background/Objectives. CD19-directed CAR-T therapy induces a profound immune remodeling involving innate and adaptive compartments. However, reliable early biomarkers capable of predicting complete remission (CR) remain incompletely defined. In this study, we longitudinally characterized cytokine dynamics, immune-cell subset modulation, and Toll-like receptor (TLR) expression following CAR-T infusion to identify early immunological features associated with clinical response.

Methods. A longitudinal immune-monitoring approach was applied to 18 patients with non-Hodgkin lymphoma, including 14 individuals with relapsed or refractory diffuse large B-cell lymphoma treated with anti-CD19 CAR-T cells. Peripheral blood samples were collected at baseline and on days 7, 14, 21, 28, and 60 after infusion. Multiparameter flow cytometry assays quantified lymphoid and myeloid populations and evaluated TLR2 and TLR4 expression and circulating cytokine levels. Finally, an exploratory machine-learning–based feature-selection strategy was performed to explore candidate biomarkers associated with treatment response.

Results. Longitudinal analysis revealed a biphasic inflammatory response following CAR-T administration. The first wave was characterized by increased levels of IL-6, IL-10, IFN-α, IFN-γ, and TNF-α, accompanied by expansion of $CD4^+$ T cells and activation of HLA-DRhigh classical and non-classical monocytes. A second inflammatory phase was associated with elevated IL-5, IL-6, IL-12, IFN-γ, and GM-CSF, together with broader immune-cell expansion including $CD4^+$ and $CD8^+$ T cells, regulatory T cells, NK-T cells, and non-classical monocytes. TLR2 expression was significantly upregulated at day 7 across multiple immune subsets, including T cells and classical and intermediate monocytes, whereas TLR4 modulation was less pronounced. Exploratory feature-selection analysis identified baseline and early post-infusion expression of TLR2 and TLR4, early IFN-γ levels, and monocyte subset frequencies among the variables associated with CR.

Conclusions. These findings demonstrate that CD19 CAR-T therapy induced temporally coordinated waves of cytokine release and immune-cell activation. Early modulation of innate immune pathways, particularly TLR2-related signaling across lymphoid and myeloid compartments, emerged as a candidate CR correlate, supporting its evaluation as a biomarker for response stratification pending validation in larger cohorts.

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Non-Hodgkin's Lymphoma

GLOBAL BREXUCABTAGENE AUTOLEUCEL MANUFACTURING EXPERIENCE FOR ADULT PATIENTS WITH RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA OR MANTLE CELL LYMPHOMA

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Brexu-cel is an autologous CD19-directed CAR T-cell therapy approved in many countries for adults with R/R ALL or MCL. Two recent studies showed that a shorter vein-to-vein time (V2Vt) was associated with improved clinical outcomes in patients with R/R LBCL. In a realworld analysis, disease progression was the most common reason R/R MCL patients did not receive brexu-cel. Rapid and reliable manufacturing is a key component of reducing V2Vt and optimizing outcomes. Here, we report global manufacturing metrics for brexu-cel in adults with R/R ALL or MCL who underwent leukapheresis for brexu-cel from Jul 2021-Jun 2024. Manufacturing success rate (MSR) is the percentage of brexu-cel lots manufactured within specification or released for clinical review/total lots dispositioned. First-pass MSR (FP-MSR) is the percentage of lots manufactured within specification on first manufacturing attempt/total first-pass lots dispositioned (excluding those terminated for patients who withdrew). Delivery success rate (DSR) is the percentage of lots successfully shipped to treatment centers across all manufacturing attempts/total number of patients who underwent leukapheresis (excluding lots in process or withdrawn). Turnaround time (TAT) is the time from leukapheresis to the quality release of final brexu-cel product. Descriptive statistics were used to analyze metrics for patients whose product was manufactured from Jul 2021-Jun 2023 (early process) and Jul 2023-Jun 2024 (recent process). A total of 3277 patients were analyzed (R/R ALL, 1120; R/R MCL, 2157). Among patients with R/R ALL, MSR improved from 92.7% (509/549) to 97.6% (571/585) from the early to recent process, and FP-MSR increased from 89.4% (463/518) to 94.8% (541/571), respectively. Similar improvements were observed in patients with R/R MCL (MSR: 92.5% [1263/1366] to 96.3% [837/869]; FP-MSR: 88.4% [1134/1283] to 93.6% [787/841], respectively). DSRs remained >97% for patients with R/R ALL (97.6% [489/501] to 98.7% [531/538]) and MCL (97.6% [1203/1233] to 99.6% [782/785]). Median TAT was consistent across early and recent processes for patients with R/R ALL (15 days for both) and MCL (15 vs 16 days, respectively). Rapid and reliable manufacturing aids in shortening V2Vt, providing timely CAR T therapy to patients with R/R ALL or MCL. Over time, the brexu-cel manufacturing process has shown improved and reliable manufacturing and delivery metrics demonstrating robust manufacturing capabilities.

Table: Global brexu-cel manufacturing metrics for patients with R/R ALL or MCL[a]

Time Period	Manufacturing Metric	R/R ALL (N=1120)	R/R MCL (N=2157)
Early process: July 2021–June 2023	MSR, % (n/n)	92.7 (509/549)	92.5 (1263/1366)
	FP-MSR, % (n/n)	89.4 (463/518)	88.4 (1134/1283)
	DSR, % (n/n)	97.6 (489/501)	97.6 (1203/1233)
	mTAT, days	15	15
Recent process: July 2023–June 2024	MSR, % (n/n)	97.6 (571/585)	96.3 (837/869)
	FP-MSR, % (n/n)	94.8 (541/571)	93.6 (787/841)
	DSR, % (n/n)	98.7 (531/538)	99.6 (782/785)
	mTAT, days	15	16

[a] Data were based on indications as entered into Kite Konnect® by the healthcare provider.

ALL, acute lymphoblastic leukemia; brexu-cel, brexucabtagene autoleucel; DSR, delivery success rate; FP-MSR, first pass manufacturing success rate; MCL, mantle cell lymphoma; MSR, manufacturing success rate; mTAT, median turnaround time; R/R relapsed or refractory.

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Non-Hodgkin's Lymphoma

SELINEXOR PLUS IFOSFAMIDE, ETOPOSIDE, AND DEXAMETHASONE DID NOT IMPROVE OVERALL RESPONSE RATE IN RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMAS: FINAL RESULTS OF PHASE II S-IDE STUDY

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Background. Relapsed/refractory peripheral T-cell lymphomas (R/R PTCLs) [PTCL-NOS, angioimmunoblastic T cell (AITL), anaplastic ALK negative (ALK neg), T follicular helper (TFH)] have a poor prognosis with standard therapies. Selinexor showed promising overall (complete, CR plus partial, PR) response rate (ORR 91%), when combined with ifosfamide-based regimen (Tang 2021).

Methods. The PTCL S-IDE, EudraCT 2021-006229-23, was a non-profit multicenter phase II study aimed to detect an ORR increase from 50% (null) to 80% (alternative hypothesis) at the end of 4 courses of 21-day S-IDE (selinexor 40 mg on day 3, 5 and 7; ifosfamide 5g/mq on day 2; etoposide 100 mg/mq on days 1-3; dexamethasone 20 mg/day on days 3-7) in R/R PTCLs. The planned sample size was 30 patients aged 18-75 years, who would receive 4 cycles of S-IDE; patients achieving CR proceeded to allo-SCT or auto-SCT based on donor availability, prior SCT, age and comorbidities; patients ineligible for SCT could receive selinexor maintenance (60 mg weekly) until progression or unacceptable toxicity.

Results. From 2022 to 2025, 30 patients were enrolled in 9 Italian centers, and were evaluable for response. Median age was 66 years (IQR 60;71); 83% (25) had stage III-IV; 47% (14) were PTCL-NOS, 27% (8) ALK neg, 10% (3) AITL and 16% (5) TFH. All patients received one prior line of therapy, 30% (9) had failed prior auto-SCT, and 46% (14) were primary refractory. After induction, ORR was 43% (13), with CR 33% (10). Among the 10 patients in CR, 6 underwent allo-SCT consolidation; 1 elderly patient started selinexor maintenance and remains on therapy at cycle 22; 3 did not proceed to transplant (donor unavailability, n=1; comorbidities, n=2). At the time of analysis, all transplanted patients were alive and in ongoing CR. At a median follow-up of 13 months (IQR: 6.81, 16.61), the median PFS was 4.13 months, with 12-months PFS 30.3% (95% CI: 16.9%-54.3%) and the median OS was 7.27 months, with 12-months OS 41.8% (95% CI: 26.4%-66.1%). The most frequent toxicities were hematological, in 57% (17) of the patients. Treatment related mortality was 10% (3) patients: one due to West Nile infection not related to the treatment, and 2 due to pneumonia.

Conclusions. In this pilot phase II study S-IDE, the primary end-point was not met, with ORR of 43% at the end of induction. Overall, S-IDE did not improve outcomes in R/R PTCLs compared with currently available salvage approaches.

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Non-Hodgkin's Lymphoma

LORLATINIB IN ALK-POSITIVE LYMPHOMA PATIENTS REFRACTORY AND PREVIOUSLY EXPOSED TO OTHER TYROSINE KINASE INHIBITORS

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Background. Anaplastic lymphoma kinase (ALK) rearrangements drive several malignancies, including ALK-positive anaplastic large-cell lymphoma (ALK+ ALCL), ALK-positive large B-cell lymphoma (ALK+ LBCL), and ALK-positive histiocytosis. Despite initial chemosensitivity, over half of patients relapse. Among these, 50–70% achieve durable remission with crizotinib, a first-generation ALK tyrosine kinase inhibitor (TKI), but outcomes after TKI failure remain poor. Lorlatinib, a third-generation ALK/ROS1 TKI, retains activity against resistance mutations to earlier agents. We evaluated lorlatinib in relapsed/refractory (R/R) ALK-positive lymphomas after prior ALK TKI failure.

Methods. In this phase 2, open-label study (NCT03505554), patients with histologically confirmed R/R ALK-positive lymphoma who had received at least one prior ALK inhibitor were treated with lorlatinib 100 mg once daily until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR), assessed by 18F-FDG PET using the 5-point Deauville Score and Lugano criteria; complete (CMR) and partial metabolic responses (PMR) were considered responses. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Minimal residual disease was assessed by RT-PCR for ALK-rearranged transcripts.

Results. Between January 2019 and December 2025, nine patients were enrolled (median age, 21 years; range, 18–57). Histologies included ALK+ LBCL (n=4), ALK+ ALCL (n=4), and ALK+ histiocytosis (n=1). At a median follow-up of 25 months (range, 1–75), ORR was 100%. Four patients (44%) achieved CMR at 1 month, all with RT-PCR negativity. Five (56%) achieved PMR; three converted to CMR by month 3, while two progressed and died. Five patients underwent allogeneic hematopoietic stem cell transplantation, including two in CMR. In the lymphoma setting, median PFS and OS were not reached; 18-month PFS and OS rates were 75% and 88%, respectively. Early CMR (at 1 month) and negative RT-PCR correlated with durable response and prolonged survival (Figure 1; p=0.04). Lorlatinib was well tolerated, with mainly grade 1–2 adverse events and one grade 3 hypercholesterolemia.

Conclusions. Lorlatinib induced high and durable response rates with favorable tolerability in R/R ALK-positive lymphomas. Early combined 18F-FDG PET and RT-PCR assessment may identify patients likely to achieve sustained remission versus those requiring early treatment consolidation.

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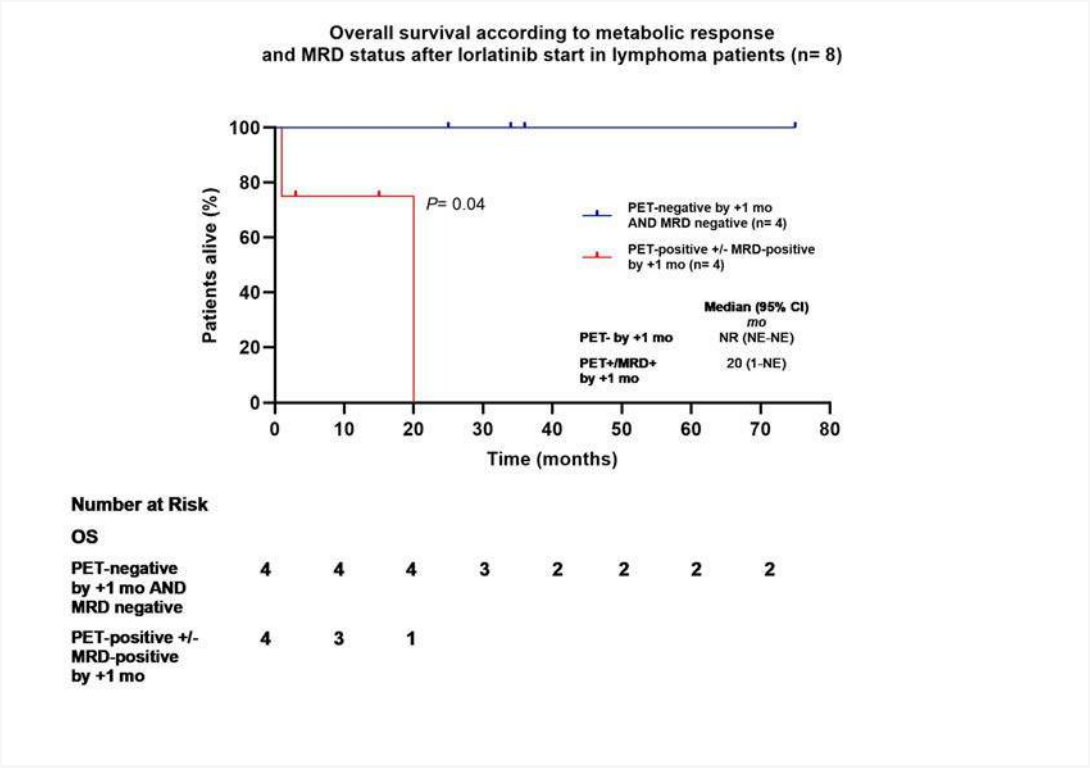
Overall survival according to metabolic response
and MRD status after lorlatinib start in lymphoma patients (n= 8)
Patients alive (%)
100
80
60
40
20
0
P= 0.04
PET-negative by +1 mo
AND MRD negative (n= 4)
PET-positive +/- MRD-positive
by +1 mo (n= 4)
Median (95% CI)
mo
PET- by +1 mo
NR (NE-NE)
PET+/MRD+
by +1 mo
20 (1-NE)
0 10 20 30 40 50 60 70 80
Time (months)
Number at Risk
OS
PET-negative by +1 mo AND MRD negative
4 4 4 3 2 2 2 2
PET-positive +/- MRD-positive by +1 mo
4 3 1

Non-Hodgkin's Lymphoma

FIRST-LINE ODRONEXTAMAB PLUS CHEMOTHERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA: OLYMPIA-3 PART 1B RESULTS

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Background. In Part 1A (dose escalation) of the Phase 3 OLYMPIA-3 study (NCT06091865), Odro-CHOP demonstrated generally manageable safety (the most common TEAEs were neutropenia [82%] and CRS [55%]) and encouraging preliminary efficacy in previously untreated DLBCL, with a CR rate of 100% on PET/CT (160 mg dose, selected for Part 1B dose optimization). Here, we report Part 1B results.
Methods. Part 1B included adults with untreated CD20+ DLBCL with ≥1 high-risk feature. Odro-CHOP was administered in 6×21-day cycles, with Odro 0.7/4/20 mg step-up dosing from Cycle 1 Day 8. Patients (pts) were randomized 1:1 to receive Odro 160 mg QW/320 mg Q2W (Regimen [R] 1) or Odro 160 mg QW/160 mg Q3W (R2) with CHOP. Primary endpoint: safety. Secondary endpoints: investigator-assessed ORR and CR rate per 2014 Lugano criteria.
Results. At data cut-off (Aug 19, 2025), 40 pts were enrolled in Part 1B (20 per R). Median age was 67.5 years, 60% of pts were male, and 75% had an IPI score of 3–5. Median duration of treatment exposure: 18.1 weeks (R1) and 16.6 weeks (R2); 68% of pts completed 6 cycles. Median relative dose intensity: 90–100% for Odro; 93–100% for CHOP. The safety profile of Odro-CHOP was similar across regimens. TEAEs led to dose interruption/delay in 70% (R1) vs 50% of pts (R2) and led to treatment discontinuation in 1 pt (Grade [Gr] 4 neutropenic sepsis, R2). TEAEs led to CHOP dose reduction in 10% vs 5% of pts with R1 vs R2, respectively. Most common TEAEs: neutropenia (58%), CRS (55%; Gr 1: 43%; Gr 2: 13%; no Gr ≥3), and anaemia (43%). ICANS occurred in 3 pts (all Gr 1) and resolved completely. Efficacy was analysed as ITT, including 3 pts who discontinued treatment prior to efficacy assessment. With a median follow-up of 2.3 months in both regimens, ORRs were 95% (R1) and 90% (R2); CR rates were 85% (R1 and R2).
Conclusions. In Part 1B of OLYMPIA-3, the safety profile of Odro-CHOP was generally manageable with no new safety signals, and preliminary efficacy was encouraging with no meaningful differences between regimens. Combination with Odro did not impact the delivery of CHOP. The less frequent Odro regimen (R2) with CHOP was selected as the recommended Phase 3 dose for Part 2 (randomized controlled trial). Biomarker data will be presented.© 2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting. All rights reserved

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Non-Hodgkin's Lymphoma

FLOW CYTOMETRIC ASSESSMENT AND QUANTIFICATION OF SURFACE ANTIGENS IN DIFFUSE LARGE B CELL LYMPHOMA IN TARGET THERAPY ERA ON LYMPH NODE BIOPSIES

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New target therapies as antibodies and CAR-T have been implemented for Diffuse Large B cell Lymphoma (DLBCL). Our study aimed to evaluate flow cytometry (FC) for quantifying target antigens in DLBCL. We analyzed 100 lymph node (L-N) biopsies with DLBCL histology (68 diagnosis, 32 relapse) and a control group of 12 benign reactive LN hyperplasia (BRH) between May 2020 and November 2024. Cell suspensions were obtained with GentleMACS (Miltenyi) and stained with antibodies against CD19 CD10 CD20 CD45 CD79b Kappa Lambda CD5 ROR1 and with 7-AAD. Data were acquired with DxFLEX (Beckman Coulter). Each antigen was quantified as percentage of expression and median fluorescence intensity (MFI) on pathological B cells. CD5+ CD19- T cells were used as negative control.At diagnosis CD20 was highly expressed (median 99% IQR 99-99). It was heterogeneous (< 70%) in 3/68 (4.4%) patients (pts). At relapse, it was <20% in 2/32 (6.2%) and negative in 3/32 (9.3%) pts after rituximab or bispecific antibodies. No difference was seen for its expression between DLBCL and BRH.At diagnosis median CD19 expression was 99% (IQR 99-99) and only 1/68 pt (1.4%) had CD19 <1%. At relapse, 3/32 (9.3%) pts were negative after CAR-T, while 1/32 (3%) pt had low CD19 (25%) despite no previous anti-CD19 therapy. CD19MFI was lower in DLBCL compared to BRH (median 6.3x104 IQR 3.3x104-9.3x104 vs 15x104 IQR 12x104-16x104, p<0.0001), even considering only DLBCL at diagnosis vs BRH (p<0.0001).Median CD79b expression was 72.5% (IQR 3.6-98) in the entire group. It was high (>70%) in 58/100 (58%), partial (20-69%) in 9/100 (9%), weak (1-19%) in 13/100 (13%) and negative (<1%) in 18/100 (18%) pts. A positive correlation was seen between CD79bMFI and clonal light-chainMFI (R=0.55 p 0.0001) suggesting a co-regulation of these BCR components. CD79b was lower in DLBCL compared to BRH (median 87% IQR 3.6-98 vs 96% IQR 94-98, p<0.01), even considering only DLBCL at diagnosis vs BRH (p 0.01). At relapse, it was negative in 2/5 pts previously treated with Polatuzumab.ROR1, an new target with selective expression on malignant cells, was analyzed in 23 DLBCL and 16 mantle cell lymphoma (MCL). Its expression was very low in DLBCL (0.5% IQR 0.2-3.8) compared with MCL (96% IQR 0.7-99) (p 0.005).Our data show heterogeneous target antigen expression in DLBCL at diagnosis and relapse. FC is a rapid and accurate method to quantify these antigens and may support treatment selection and clinical decision-making in DLBCL.

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Non-Hodgkin's Lymphoma

VALEMETOSTAT AS A BRIDGE TO ALLOGENEIC STEM CELL TRANSPLANTATION IN RELAPSED/REFRACTORY PERIPHERAL T-CELL LYMPHOMAS: A SINGLE-CENTER EXPERIENCE

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Peripheral T cell lymphomas (PTCL) are rare and aggressive disease with poor outcomes, particularly in relapsed/refractory (r/r) setting, where therapeutic options are limited and participation in clinical trials is strongly recommended. Durable disease control is primarily achieved through salvage therapy followed by consolidation with allogeneic stem cell transplantation (allo HSCT). Valemetostat tosylate, a dual EZH1/2 inhibitor with epigenetic activity, is approved in Japan for r/r adult T cell leukemia/lymphoma based on a 48% objective response rate (ORR) in phase 2 studies, with comparable activity also reported in r/r PTCL.We report a retrospective, single-center experience with valemetostat used as a bridging therapy to allo-HSCT in patients with r/r PTCL. The drug was provided through the AIFA 5% fund access program and administered orally at 200 mg once daily. From January to November 2025, 7 patients were treated: median age 49 years (32-66), all with advanced stage disease and 43% with extranodal involvement. Median number of prior lines of treatment was 2 (1-5); all patients were primary refractory. Histological subtypes included nodal T-helper follicular lymphoma (n=5), angioimmunoblastic T-cell lymphoma (n=1) and PTCL-NOS (n=1). Patients received a median of 8 cycles (range 4-12). The ORR was 100% (2 complete responses [CR] and 5 partial responses [PR]), with a median time to best response of 96 days, achieved between the 2nd and 4th cycles. Median duration of response was 3 months (range 1.8-9.0). Only one patient achieving CR proceeded to allo-HSCT and remains in CR at two months post-transplant. Among the six patients who did not proceed to transplant consolidation, reasons included donor unavailability (n=2), patient refusal (n=1), infectious complication (n=1), and transplant ineligibility (n=2). Of these, one patient remains in CR at 12 months from treatment initiation, while five patients relapsed and were referred to salvage therapy (Figure 1). Valemetostat was generally well tolerated: three patients developed grade 4 neutropenia, and two experienced grade 3 infectious requiring hospitalization. In conclusion, valemetostat is a promising option in r/r PTCL, achieving disease control in all treated patients. However, based on this pilot experience, transplant consolidation should be pursued promptly upon best response, even in PR, as this may represent the critical therapeutic window to avoid losing the transplant opportunity

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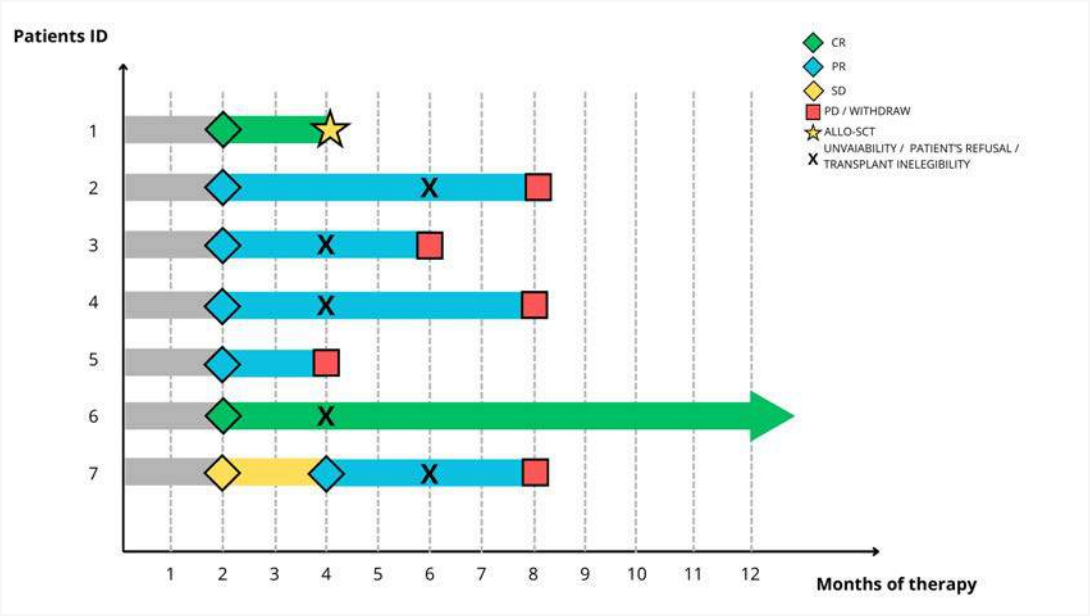
Non-Hodgkin's Lymphoma



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Fitness, palliation, quality of life and pharmacoeconomics

HEALTH-RELATED QUALITY OF LIFE PROFILE OF NEWLY DIAGNOSED PATIENTS WITH PH+ ALL: A COMPARISON WITH THE GENERAL POPULATION

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Introduction and aim. Very limited evidence exists on pretreatment (i.e., baseline) health-related quality of life (HRQoL) of patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL). Such evidence may be critical for identifying the most vulnerable patient groups requiring special attention from the very beginning of therapy. In this analysis we aimed to compare HRQoL profile and symptom burden of patients with newly diagnosed Ph+ ALL with those of the general population.

Methods. Data were analyzed from the GIMEMA ALL2820 trial, which enrolled adult patients (≥18 years) with newly diagnosed Ph+ ALL and included baseline EORTC QLQ-C30 assessment prior to induction therapy. Mean scores were summarized using means and standard deviations and compared with Italian normative data from the general population, adjusted for age, sex, and comorbidities. Between-group differences were assessed using t-tests, and clinically meaningful differences were defined according to established thresholds. The prevalence of clinically important symptoms was also calculated based on previously established EORTC criteria.

Results. Overall, 236 patients were enrolled; 226 completed baseline HRQoL assessment and 216 had both available clinical/laboratory and HRQoL data. At this pretreatment stage, mean age was 54.4 years, 53.2% were male, and 56.9% had at least one comorbidity. Compared with the adjusted general population, patients with Ph+ ALL reported statistically and clinically meaningful worse scores across multiple domains. Differences were observed in physical functioning (Δ =-10.4; 95% CI, -13.5 to -7.3), role functioning (Δ -=27.7; 95% CI, -31.9 to -23.4), social functioning (Δ =-15.0; 95% CI, -18.8 to -11.3) and global health status/QOL (Δ = -9.7; 95% CI, -13.1 to -6.2). Patients with Ph+ ALL reported clinically meaningful worse fatigue (Δ=15.5; 95% CI, 11.9 to 19.1), dyspnea (Δ=10.0; 95% CI, 6.1 to 13.8) and appetite loss scores (Δ= 9.7; 95% CI, 6.1 to 13.2).The top three most prevalent clinically important symptoms were dyspnea (55.8%), fatigue (46.5%), and pain (42.5%).

Conclusions. Our analysis revealed that patients with Ph+ ALL present with substantial HRQoL deficits at diagnosis compared with age- sex- and comorbidity-adjusted normative data. Recognizing this early symptom burden may help clinicians to implement timely supportive interventions and to better understand the patient's health status beyond purely clinical parameters.

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Fitness, palliation, quality of life and pharmacoeconomics

AGE-RELATED DIFFERENCES IN PALLIATIVE CARE ACCESS AND END-OF-LIFE INTENSITY IN ACUTE LEUKEMIA: A MULTICENTER STUDY USING AN EOL SCORE

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Background. Patients with acute leukemia are often managed with highly intensive treatments at the end-of-life (EOL), while the integration of palliative care (PC) remains limited. In solid tumors, several studies have reported reduced access to PC among older patients, suggesting the presence of age-related disparities in EOL care. Whether similar patterns exist in hematologic malignancies is less well defined. An EOL score, commonly used in solid tumors but less explored in this setting, may help characterize age-related differences in care intensity.

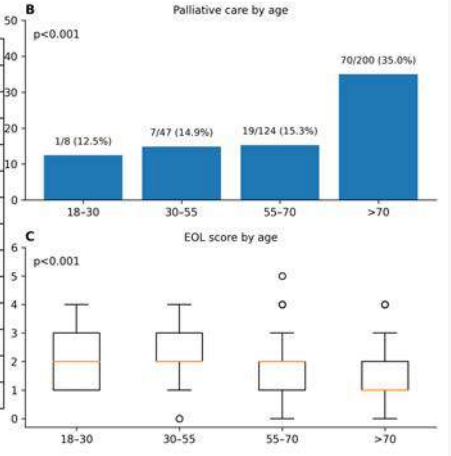
Methods. We conducted a retrospective multicenter analysis of patients with acute leukemia who died across four Italian centers. Patients were stratified by age at death (18–30, 30–55, 55–70, and >70 years). PC use was assessed across age groups. An EOL score (range 0–6) was calculated assigning one point for each of the following: therapy in the last 14 days of life, in-hospital death, emergency department (ED) visits in the last 30 days of life, intensive care unit (ICU) admissions in the last 30 days of life, >1 hospitalization in the last 30 days of life, and >14 days of hospitalization in the last 30 days of life.

Results. A total of 381 patients were included, and baseline characteristics are summarized in Figure 1A. PC use increased with age, being 1/8 (12.5%) in patients aged 18–30 years, 7/47 (14.9%) in those aged 30–55 years, 19/124 (15.3%) in those aged 55–70 years, and 70/200 (35.0%) in patients >70 years (p<0.001; Figure 1B). The EOL score ranged from 0 to 6 and differed across age groups (p<0.001; Figure 1C), being lower in patients >70 years compared to younger patients. Older patients showed lower rates of ICU admission (10.9% vs ~40% in younger groups, p<0.001) and reduced use of therapy in the last 14 days of life (18.0% vs ~40% in patients <55 years, p=0.007). In contrast, ED visits in the last 30 days of life were more frequent in older patients (57.7% in >70 years vs ~36–37% in younger groups, p<0.001).

Conclusions. Access to PC increases with age and is associated with lower EOL aggressiveness. Despite this, older patients show higher ED utilization, suggesting unmet supportive care needs and the underlying clinical fragility of older patients with acute leukemia. These findings support the use of an EOL score in hematologic malignancies and highlight the need for earlier and more integrated PC strategies, particularly in younger patients.

A

Variable	Value
Total patients	381
Diagnosis, AML	343 (90.0%)
Diagnosis, ALL	34 (8.9%)
Sex, male (%)	220 (57.7%)
Nationality, Italian (%)	358 (94.0%)
Allogeneic transplant	89 (23.4%)
Cause of death	
Disease-related	114 (29.9%)
Infection	132 (34.6%)
Hemorrhage	19 (5.0%)
Other	50 (13.1%)
Age, median (IQR)	70.7 (61.3–78.1)
Lines, median (IQR)	1 (1–2)



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Fitness, palliation, quality of life and pharmacoeconomics

A COMPREHENSIVE GERIATRIC ASSESSMENT TO EVALUATE INDIVIDUAL FRAILTY STATUS AND QUALITY OF LIFE IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA: A PROSPECTIVE ITALIAN STUDY

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As frailty and chemoimmunotherapy (CIT) ineligibility are not defined in Waldenström macroglobulinemia (WM), we aimed to assess frailty through an integrated geriatric and quality of life (QoL) approach.In this prospective, multicenter observational study, consecutive WM pts completed Practical Geriatric Assessment (PGA) and EORTC QLQ-C30 at baseline, 6, 12 and 18 months. PGA domains included physical, functional, psychological, cognitive, nutritional, social support and self-perceived comorbidities. Primary objective: frailty definition; secondary: feasibility, correlations with clinical characteristics, impact on therapy and outcomes.From November 2024 to July 2025, 198 WM patients (pts) were enrolled: 78 on active treatment (a-Tx), 62 previously treated in watch and wait (t-ww); 58 untreated in ww (u-ww). Median age was 72 y (41–92), 66% male, 14% high--IPSSWM, 17% neuropathy, 13% ECOG-PS>1. Median CIRS was 3 (0–19), with 17% ≥1 major comorbidity. MYD88L265P was present in 88%; CXCR4 in 13%. a-Tx pts were older (74 vs 69 vs 69), with higher IgM, lower hemoglobin and more concomitant medications; 73% received targeted agents, 15% CIT, 12% trials. All t-ww had prior CIT. 96% had ≥1 impaired PGA domain (median 3, 0–6), no differences among groups. Median QLQ-C30 global health status (GHS) was 67 (67, 67, 75; range 0-100 p=.628). Among pts with CIRS>6 and/or CIRS3+, 97% reported QoL impact of comorbidities; notably 90% without severe comorbidities also reported impact. At univariate, concomitant medications, ECOG-PS, respiratory, neurologic and psychiatric CIRS were associated with worse GHS, but not at multivariate. Independent PGA domains affecting GHS were functional and psychological status (p<.001) and lack of social support (p=.002). Higher number of impaired domains was associated with neuropathy (p=.052), comorbidities (p=.009), ECOG-PS≥1 (p=.001), vascular CIRS (p=.023). Prior CIT negatively affected cognitive function (p=.018). Age and concomitant medications most frequently impacted single domains. According to CIT fitness (CIRS>6 and/or CrCl<70 mL/min), unfit pts had more impaired domains (4.0 vs 3.0; p=.023) and were older (77.4 vs 65.9 years; p<.001), though a median of 3 altered domains persisted in fit pts, supporting added value of PGA. Median completion time was 20 minutes (pts) and 5 (physicians). This approach is feasible, time-efficient and may improve frailty stratification; ongoing enrollment will clarify its clinical implications.

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Fitness, palliation, quality of life and pharmacoeconomics

THE CAREGIVERS IN HEMATOLOGICAL MALIGNANCIES: WHAT THEY SAY AND WOULD DESIRE

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Advances in the treatment of hematologic malignancies have significantly improved survival, transforming conditions such as multiple myeloma, lymphomas, and myelodysplastic syndromes into long-term or chronic diseases. This progress has reshaped the cancer trajectory into a prolonged experience marked by repeated treatment decisions, clinical uncertainty, and sustained psychosocial demands. Within this evolving context, informal caregivers play a crucial role. From a gender medicine perspective, understanding whether and how caregiver gender influences the multidimensional burden of care is essential to promote equitable and personalized health strategies.This study examined the impact of caregiver gender on psychological, organizational, and economic burden using a comprehensive framework tested through Structural Equation Modeling (SEM). An ad hoc questionnaire was administered to caregivers recruited at the Hematology Unit in Pisa, Italy. The survey collected sociodemographic data and assessed three burden dimensions: psychological (emotional distress and loss of personal time), organizational (logistical demands and preference for home-based care), and economic (work impact and increased expenses). The sample included 207 caregivers, mostly female (66.2%), with a mean age of 58.4 years.Results showed high levels of worry about disease outcomes, while anger, depression, and insomnia were less frequent. Restrictions in personal time and work were limited, although many perceived a moderate life impact. Travel for medical care was a key organizational burden. Economically, moderate increases in expenses were reported, while severe financial hardship was rare. A strong preference emerged for home-based services, highlighting the importance of decentralized care models.Contrary to expectations, caregiver gender was not a significant predictor of burden. Age, instead, was positively associated with psychological and economic strain. These findings suggest that caregiving burden is more influenced by life-course and healthcare organization than by gender alone, supporting more inclusive and context-sensitive care strategies.

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Fitness, palliation, quality of life and pharmacoeconomics

PALLIATIVE CARE IN PATIENTS WITH ACUTE LEUKEMIAS IS ASSOCIATED WITH LESS AGGRESSIVE TREATMENT IN THE END-OF-LIFE: A RETROSPECTIVE STUDY

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Introduction. Patients with acute leukemia often receive high-intensity medical care near the end of life (EOL), with low rates of hospice referral and palliative care (PC) involvement and a high likelihood of in-hospital death. The goals of care (GOC) in the treatment of terminal cancer patients include low chemotherapy use, low access to the emergency room (ER) or intensive care unit (ICU), and a low rate of in-hospital deaths. However, data in hematologic malignancies, particularly acute leukemia, are limited.AIM: to evaluate EOL quality indicators in acute leukemia patients managed with or without PC.

Methods. We retrospectively analyzed a cohort of consecutive deceased acute leukemia patients followed at four Italian institutions. Indicators included the use of antineoplastic therapy at EOL, place of death, transfusions, ER and ICU access, and days of hospitalization in the last month of life.

Results. 381 patients were included: 98 (25.7%) received PC and 283 (74.3%) did not. Lines of therapy and leukemia subtypes were comparable in the two groups, whereas the patients receiving PC were older and less frequently underwent allogeneic stem cell transplantation; also the main cause of death was different. Patients receiving PC were followed for a median of 25 days (range: 1-462). Sixty-two patients received PC at home, 18 in hospice and 1 in both settings.Results are described in Table 1. We found differences in favor of the PC group for several GOC: patients receiving PC underwent less intensive treatments during the EOL across all parameters considered. Furthermore, the PC group required fewer red blood cell and platelet transfusions in the last 7 days of life. Only the ER rates were similar between groups, reflecting the frailty of these patients.Finally, 74.8% of PC patients died at home or in hospice, while 92.1% of the non-PC group died in a hospital (seven of them in the ER and 69 in the ICU).

Conclusions. most acute leukemia patients receive intensive EOL care. Our data show that PC involvement is associated with significantly less aggressive management. Earlier and improved integration of PC should be a goal in the management of patients with acute leukemia.

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	PC	no PC	All the population	p	OR (95% IC)
Palliative care	98 (25,7%)	283 (74,3%)	381		
Age, range	75,8 (29,8 – 92,4)	68,9 (19,8 – 92,6)	70,7 (19,8 – 92,6)	< 0.001	
Sex, M (%)	64 (65,3%)	156 (55,1%)	220 (57,7%)	0,101	
Nationality, Italian (%)	96 (98%)	263 (92,9%)	359 (94,2%)	0,11	
Diagnosis					
AML	90 (91,8%)	255 (90,1%)	345 (90,6%)	0,76	
ALL	7 (7,1%)	28 (9,9%)	35 (9,2%)		
ASCT	8 (8,2%)	81 (28,6%)	89 (23,4%)	< 0.001	
Death cause					
Disease progression	44 (44,9%)	70 (24,7%)	114 (29,9%)	< 0.001	
Infection	13 (13,3%)	119 (42,0%)	132 (34,6%)		
Bleeding	2 (2,0%)	17 (6,0%)	19 (5,0%)		
Other	7 (7,1%)	43 (15,2%)	50 (13,1%)		
Lines of therapy, range	1 (0-6)	1 (0-7)	1 (0-7)	0.1	
Place of Death					
Home	39 (41,1%)	22 (7,9%)	61 (16,3%)	<0.001	
Hospice	32 (33,7%)	0 (0%)	32 (8,6%)		
Hospital	24 (25,3%)	257 (92,1%)	281 (75,1%)		
ER	1 (1%)	7 (2,5%)	8 (2,1%)	0.28	
ICU	2 (2%)	69 (24,4%)	71 (18,6%)	<0.001	
Chemotherapy in the last 30 days of life	11 (11,2%)	148 (52,3%)	159 (41,7%)	<0.001	8,7 (4,4 – 16,9)

Chemotherapy in the last 14 days of life	3 (3,1%)	88 (31,1%)	91 (23,9%)	<0.001	14,3 (4,4 – 46,3)
RBC transfusion in the last 7 days of life	35 (35,7%)	197 (69,6%)	232 (60,9%)	<0.001	4,12 (2,54 – 6,69)
Platelets transfusion in the last 7 days of life	21 (21,4%)	201 (71,0%)	222 (58,3%)	<0.001	8,99 (5,20 – 15,53)
ER access in the last 30 days of life	45 (45,9%)	129 (45,6%)	174 (45,7%)	1	0,99 (0,62– 1,56)
ICU access in the last 30 days of life	3 (3,1%)	80 (28,3%)	83 (21,8%)	<0.001	12,48 (3,84 – 40,54)
Intubation	1 (1,0%)	56 (19,8%)	57 (15,0%)	<0.001	23,9 (3,27 – 175,35)
Hospitalization in the last 30 days of life	51 (52,0%)	256 (90,5%)	307 (80,6%)	<0.001	8,74 (4,99 – 15,31)
Median days of hospitalization, range	2,5 (0-30)	16 (0-30)	13 (0-30)	<0.001	
>14 days of hospitalization in the last 30 days of life	21 (21,4%)	152 (53,7%)	173 (45,4%)	<0.001	4,25 (2,49 – 7,27)
All the last month of life hospitalized	5 (5,1%)	74 (26,1%)	79 (20,7%)	<0.001	6,59 (2,58 – 16,83)

Table. Population characteristics and results. PC, Palliative Care, AML, Acute Myeloid Leukemia; ALL, Acute Lymphoid Leukemia; ASCT, Allogenic Stem Cell Transplant; ER, Emergency Department; ICU, Intensive Care Unit.

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Fitness, palliation, quality of life and pharmacoeconomics

QUALITY OF LIFE AND CARE ORGANIZATION OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA WITHIN THE LOMBARDY HEMATOLOGY NETWORK: INSIGHTS FROM SMALL CENTERS INVOLVED IN THE CML-OPERAP STUDY

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Background. Tyrosine kinase inhibitors have transformed CML into a chronic condition with near-normal life expectancy, but whether CML patients' (pts) quality of life (QoL) approaches that of the general population remains unclear. Care organization may influence QoL and patient satisfaction, and smaller centers are often perceived as disadvantaged.

Aims. The CML-OPERAP study (Outcome and PErformances Reported and Analyzed by Patients) evaluates the impact of hematology center organization on QoL of CML pts. This analysis focuses on small centers (<100 CML pts) compared with larger centers.

Methods. Cross-sectional, multicenter observational study involving 22 REL centers. Eligible pts are ≥18 with confirmed CML, followed for ≥6 months. Data includes clinical variables and patient-reported questionnaires:- Custom CML Hematology Center Questionnaire (CCHCQ): assessing satisfaction with physicians, nurses, logistics- EORTC QLQ-C30/CML24 QoL surveyCenters are categorized as:- Categories 1-2: large centers (>100 CML pts) with/without a dedicated CML clinic- Categories 3-4: small centers (<100 CML pts) with/without dedicated time slots for CML pts.

Results. Within REL, 6 centers are large and 16 small, with dedicated CML structures in 3 and 5, respectively.Pts in small centers (n=326) were older (65.2 vs 62.9 ys) and less often in treatment free remission (29.1% vs 20.6%) than those in large centers (n=700).QoL in small centers was comparable or slightly better than in large centers: Global Health Status was 73.7 vs 73.2 (p=0.31), Summary Score was 87.4 vs 85.9 (p= 0.04). Small but statistically significant differences favoring small centers were observed in cognitive functioning, nausea, sleep, appetite and constipation. Within small centers, those with dedicated time slots for CML pts showed slightly better QoL, statistically significant in emotional functioning, dyspnea, symptom burden and impact on worry/mood and daily life.Care satisfaction was slightly lower in small centers, particularly for nursing, with fewer "excellent" ratings in care information (42.0% vs 56.0%, p=0.03) and time dedicated to pts (46.3% vs 61.0%, p=0.02), while Category 3 and 4 showed similar results except for better center accessibility in Category 3.

Conclusions. Smaller center size was not associated with worse QoL. Dedicated time slots were associated with improved QoL and represent a feasible organizational strategy. The model will be further detailed at the meeting.

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PERSISTENT IMPAIRMENT OF QUALITY OF LIFE IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS ON LONG-TERM COMPLEMENT INHIBITOR THERAPY: A REAL-WORLD PATIENT-REPORTED OUTCOME STUDY

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Paroxysmal nocturnal hemoglobinuria (PNH) is associated with chronic complement-mediated hemolysis and systemic symptoms that significantly impact quality of life (QoL). Although complement inhibitors improve clinical outcomes, their impact on patients' perceived health and daily functioning in real-world settings remains uncertain.We conducted a cross-sectional study of adult PNH patients (pts) treated with a parenterally administered complement inhibitor (PACI) for ≥ 6 months at our Institution. QoL was assessed using FACIT-Fatigue and EORTC QLQ-C30 questionnaires, with additional evaluation using the disease-specific EORTC QLQ AA-PNH module. Work productivity and activity impairment were measured with WPAI-GH. Clinical data were retrieved retrospectively. Spearman correlations were computed between PRO scores and hematological parameters (Lactate Dehydrogenase [LDH], hemoglobin [Hb], reticulocytes [ret]).Ten pts were included (median age 44.7 [26.8-74.0] years, 60% female). Most pts presented with classical PNH (n=8) and were receiving Ravulizumab (n=9). Median therapy duration was 19.7 (6.1-41.0) months. At last outpatient visit, median Hb was 11.9 (8.2-14.2) g/dL, median LDH 1.6 (0.8-2.1)×ULN, median ret count 99.5 (77-443)x10^9/L. Six pts (60%) showed at least a good response as per IPIG criteria. Median FACIT-Fatigue score was 36 (12–49), with 5 pts (50%) falling below the clinically meaningful threshold of 43. Global HRQoL was markedly impaired (median EORTC QLQ-C30 global health status 50/100), with cognitive and role functioning as most affected; fatigue, insomnia, and dyspnoea were the leading symptom domains. The disease-specific EORTC QLQ AA-PNH module revealed prominent fear of progression and illness intrusiveness, with impaired emotional functioning but preserved social support. In 9 actively employed pts, overall work impairment on the WPAI-GH reached a median 41% (0–100%), driven primarily by presenteeism, with median activity impairment at 40% (10-90%). No significant correlation was found between any PRO score and hematological parameters (Table 1). Clinically significant fatigue and HRQoL impairment seemed to be prevalent in our treated PNH cohort, with substantial functional and occupational impact. The lack of correlation between PRO scores and hematological parameters suggests that laboratory monitoring alone may be insufficient to report disease burden, supporting routine integration of validated PRO tools in clinical follow-up.

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A — Patient and Clinical Characteristics (n = 10)			
Age, median (range), years			44.7 (26.8–74.0)
Female sex, n. (%)			6 (60%)
PNH subtype			
Classical, n. (%)			8 (80%)
Associated with Bone Marrow Failure disorders, n. (%)			2 (20%)
Ongoing treatment			
Ravulizumab, n. (%)			9 (90%)
Eculizumab, n. (%)			1 (10%)
Treatment duration, median (range), months			19.7 (6.1–41.0)
Response at last outpatient visit			
Hemoglobin, median (range), g/dL			11.9 (8.2–14.2)
LDH, median (range), × ULN			1.6 (0.8–2.1)
Reticulocytes, median [range] ×10³/L			99.5 [77–443]
Complete response (CR), n. (%)			2 (20%)
Major response (MR), n. (%)			1 (10%)
Good response (GR), n. (%)			3 (30%)
Partial response (PR), n. (%)			4 (40%)
B — FACIT-Fatigue (n = 10)			
Total score, median (0–52)			36 (12–49)
Spearman Correlation			
Vs LDH			ρ = +0.30, p = 0.433
Vs Hb			ρ = +0.27, p = 0.488
Vs ret count			ρ = −0.07, p = 0.865
C — EORTC QLQ-C30 (n = 10)			
Global health status / QoL, median, (0–100)			50 (33–100)
Spearman Correlation			
Vs LDH			ρ = +0.34, p = 0.374
Vs Hb			ρ = +0.60, p = 0.088
Vs ret count			ρ = −0.46, p = 0.208
Functional scales, median (0–100)			
Physical functioning	87 (47–93)	Role functioning	67 (17–100)
Emotional functioning	75 (33–100)	Cognitive functioning	50 (0–100)
Social functioning	67 (50–100)		
Symptom scales, median, (0–100)			
Fatigue	33 (11–78)	Nausea and vomiting	0 (0–33)
Pain	0 (0–50)	Dyspnoea	33 (0–67)
Insomnia	33 (0–67)	Appetite loss	0 (0–33)
Constipation	0 (0–67)	Diarrhoea	0 (0–33)
Financial difficulties	0 (0–67)		
D — EORTC QLQ AA-PNH (n = 10)			
Total raw score (54–216)			120 (56–184)
Spearman Correlation			
Vs LDH			ρ = −0.14, p = 0.715
Vs Hb			ρ = −0.29, p = 0.444
Vs ret count			ρ = +0.17, p = 0.667
Functional scales, median, (0–100)			
Body image	67 (0–100)	Emotional functioning	47 (13–100)
Cognitive functioning	67 (0–100)	Physical functioning	56 (0–100)
Role functioning	52 (14–100)	Social support	83 (67–100)
Symptom scales, median, (0–100)			
Illness intrusiveness	48 (0–78)	Infections	33 (0–100)
Other symptoms	38 (0–71)	Fear of progression	57 (0–91)
Fatigue	27 (13–93)	Stigmatization	42 (0–100)
E — WPAI-GH (n = 9)			
Activity impairment (%)			40 (0–100)
Spearman Correlation			
Vs LDH			ρ = −0.15, p = 0.696
Vs Hb			ρ = −0.24, p = 0.540
Vs ret count			ρ = +0.11, p = 0.779
Overall work impairment (%)			41 (0–100)

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Fitness, palliation, quality of life and pharmacoeconomics

THE CHRONIC LYMPHOCYTIC LEUKEMIA TREATMENTS AND THEIR SUSTAINABILITY: A NOVEL PHARMACO-ECONOMIC MODEL

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The introduction of targeted therapies in Chronic lymphocytic leukemia (CLL), including Bruton tyrosine kinase inhibitors (BTKIs) and venetoclax-based regimens, has significantly improved patient outcomes. However, these treatments are associated with substantial costs and specific adverse events.This study aimed to develop a pharmacoeconomic model comparing continuous and fixed-duration first-line therapies for CLL, integrating drug acquisition costs, adverse event management, and social costs. A cost-effectiveness model was developed to compare BTKIs (ibrutinib, acalabrutinib, zanubrutinib) and fixed-duration regimens (obinutuzumab–venetoclax, ibrutinib–venetoclax) over 3- and 5-year time horizons. Costs included drug acquisition, management of adverse events, and social costs. Effectiveness was evaluated using progression-free survival (PFS), overall survival (OS), and response rates. Incremental cost-effectiveness ratios (ICERs) were calculated using a willingness-to--pay threshold of €33,004/QALY.In the model, fixed-duration therapies showed higher upfront costs but became economically advantageous after the third year compared with continuous treatments. Adverse event management represented a minor proportion (<2%) of total costs. Continuous therapies generated progressively increasing cumulative costs, whereas fixed-duration regimens concentrated expenses within the first 1–2 years. Social costs were limited, accounting for about 3% of total costs. Among BTKIs, zanubrutinib emerged as the most cost-effective option, while ibrutinib–venetoclax represented a strong fixed-duration alternative. Scenario analyses indicated that reallocating patients toward zanubrutinib and ibrutinib–venetoclax could yield significant savings over both 3- and 5-year periods. Fixed-duration therapies require higher initial cash flow within the first 12–15 months but stabilize thereafter, unlike continuous therapies that continue to consume resources. Over 5 years, total costs are approximately 30–50% of continuous regimens; shifting 60% of patients to fixed-duration treatments could reduce overall expenditure by about 40%. Both continuous and fixed-duration therapies for CLL are clinically effective and economically sustainable. Integrating pharmacoeconomic evaluations into routine clinical practice can support more sustainable and patient-centered treatment decisions.

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Fitness, palliation, quality of life and pharmacoeconomics

COMPASSIONATE USE PROGRAMS IN HEMATOLOGY: CLINICAL, ORGANIZATIONAL, AND ECONOMIC IMPACT OF A DEDICATED MULTIDISCIPLINARY TRIAL OFFICE

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Compassionate use programs (CUPs) provide early access to innovative therapies for patients with severe hematologic diseases and no standard alternatives. Beyond their organizational and economic value, CUPs may also provide clinical benefit by enabling timely access to potentially effective therapies in settings of high unmet need. CUP management involves a heavy bureaucratic burden, often relying on extra-duty efforts by clinical staff. We evaluated the impact of a dedicated, funded multidisciplinary trial office on patient access and healthcare sustainability. We conducted a retrospective single-center analysis of all CUP requests managed between 2023 and 2025. Data were extracted from our registry, tracking therapeutic classes, dosing, and treatment duration. Cost avoidance was calculated using a hierarchical price-source strategy: national public pricing or ex-factory AIFA pricing whenever available; otherwise FDA/international pricing or official literature estimates were used. The analysis focused on the role of clinicians, regulatory affairs officers, and research nurses in managing the full CUP lifecycle.

Results. CUP activity increased from 14 requests in 2023 to 20 in 2024 and 34 in 2025. The dedicated trial office transformed CUP management into a structured process, reducing clinical workload while ensuring compliance, safety, pharmacovigilance, and timely ethics updates. This model managed high-cost agents, including bispecific antibodies and cellular therapies, generating cumulative pharmaceutical cost avoidance of €7,022,972 over 3 years (€485,601 in 2023; €3,456,189 in 2024; €3,081,183 in 2025). Particularly relevant was the impact of therapies for acute and chronic GvHD, an area of major unmet need. Programs involving belumosudil, mesenchymal cells, and fecal microbiota approaches highlighted the value of CUPs in making complex options available to fragile patients. The Ethics Committee, with a mean 2-day opinion time, was a key operational enabler.

Conclusions. CUPs are a strategic asset for clinical excellence and healthcare sustainability. Their value lies not only in cost avoidance, but also in expanding access to clinically meaningful therapies where approved options remain limited. A dedicated trial office is essential to manage the increasing complexity of these programs. Institutional recognition of these roles, together with collaborative engagement with pharmaceutical sponsors, is needed to harmonize innovation with the long-term sustainability of the National Health Service

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Fitness, palliation, quality of life and pharmacoeconomics

FRONTLINE TREATMENT AT HOME WITH DARATUMUMAB: IS A POSSIBLE NEW STANDARD OF CARE IN FRAIL PATIENTS WITH MULTIPLE MYELOMA?

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Background. Frontline treatment of Multiple Myeloma (MM) is difficult in patients (pts) due to advanced age, comorbidities, bone lesions/fractures at onset that can hinder transport, lack of an available caregiver and/or long distance from the hospital. The effective role of a Domiciliary Hematologic Care Unit (DHCU) in pts with advanced phases of MM has been already reported, but data on efficacy with frontline daratumumab (dara)-based schemes at home are still missing.

Aims. Herein, the experience with frontline treatment at home in 4 hematologic Centres with a DHCU in different geographic settings [big metropolitan town (Rome), middle-sized towns (Verona and Reggio Emilia) and wide geographic area with several small centres (Viterbo province)] is reported, as part of the Myel-Home project.

Methods. Data from 31 pts were collected from 9/2021 to 12/2025. The initial 2 dara administrations were given in hospital to prevent side effects, while subsequent administrations were done at home.

Results. Clinical features at diagnosis, main reasons for home-care activation and different dara-based protocols used are reported in the Table. Distance from DHCU to pts home was < 10 Km in 16 cases (51.6%), ≥ 10 < 30 Km in 11 (35.5%) and ≥ 30 Km in 4 (12.9%). On the whole, 311 administrations of sc-dara were performed at home by DHCU physicians/nurses, without any early adverse severe event (grade > 2). Main toxicities during home treatment were infections (6 episodes) and neuropathies (5 pts). Among 30 pts evaluable for response, 3 achieved a complete remission (stringent in 2 cases), 16 a very good partial remission and 5 a partial remission, with an overall response rate of 80.0%: 3 pts had a stable disease and 3 pts a disease progression. Among pts potentially eligible for transplant, 4 were transplanted, 1 is in evaluation for the procedure and 2 refused the procedure shifting to maintenance treatment. At the last follow-up, 23 pts are alive and 8 pts died (5 from disease progression, 2 from cardiological diseases, 1 from evolution in acute myelogenous leukemia). Three-year cumulative overall survival from the start of home management was 63.7% (95%CI 41.4 – 85.9).

Conclusions. Frontline home treatment with dara-based schemes in frail pts with MM is feasible and safe also in different geographical settings: it makes possible a curative approach also in subjects otherwise excluded by best available therapies or forced to long periods of hospitalization.

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N° of patients	31
M/F, n° (%)	**12/19 (38.7/61.3)**
Median age, years (interquartile range)	**73.8 (66.8 – 78.2)**
Patients aged > 80 years, n° (%)	**6 (19.3)**
Hb < 10g/dl, n° (%)	**12 (38.7)**
Creatinine > 2 mg/dl, n° (%)	**5 (16.1)**
Calcium > 11 mg/L, n° (%)	**5 (16.1)**
Type of MM, n° (%):	
IgG-k	**10 (32.3)**
IgG-λ	**2 (6.4)**
IgA-k	**7 (22.6)**
IgA-λ	**3 (9.7)**
Light chain k	**4 (12.9)**
Light chain λ	**3 (9.7)**
Plasma-cell leukemia	**2 (6.4)**
Main reason for home treatment, n° (%):	
Bone lesions/fractures secondary to MM	**20 (64.6)**
Long distance and/or social conditions	**5 (16.1)**
Age > 80 years	**6 (19.3)**
Treatment schedule, n° (%):	
Dara-RD	**16 (51.6)**
Dara-VTD	**8 (25.9)**
Dara-VMP	**5 (16.1)**
Dara-VD	**1 (3.2)**
Dara-VCD	**1 (3.2)**

Fitness, palliation, quality of life and pharmacoeconomics

DEVELOPMENT OF AN INTEGRATED BEHAVIORAL MODEL FOR THE TIMELY AND APPROPRIATE USE OF BLOOD TRANSFUSIONS FOR TRANSFUSION-DEPENDENT HEMATOLOGICAL PATIENTS WITHIN THE TRANSITIONAL PALLIATIVE CARE SETTING

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Background. Transfusion dependence represents a significant barrier to the effective management of hematological patients within palliative care (PC). These critical challenges stem from cultural, organizational, and economic factors.

Aims. To develop an interdisciplinary behavioral model designed to: 1) Facilitate shared literacy among professionals regarding PC needs—whether simultaneous with active treatment or for end-of-life care—for patients with AML, MDS, or other advanced-stage transfusion-dependent hematological malignancies; 2) Foster the definition of shared goals of care (GOC), with specific emphasis on blood transfusion utilization; 3) Standardize the transitional care process for PC admission.

Methods. Utilizing team coaching sessions led by facilitators, the project aims to develop a behavioral model focused on the organization of integrated services. This includes enhancing result-oriented performance, focused negotiation skills, and empathetic communication. The project consists of four 3-hour meetings centered on the discussion of three clinical cases and Recommendation No. 4 of the SIE (Italian Society of Hematology) guidelines for AML in patients >60 years. The working group comprises healthcare professionals from the Lazio Region (5 hematologists, 8 palliative care physicians, 1 general practitioner, 2 transfusion medicine specialists, 2 nurses, 1 psychologist, and 1 member of the charity AIL Roma). A pre-working questionnaire asked participants to rank the two most significant barriers (out of four) to timely PC enrollment and correct transfusion policies (patient identification for PC, multidimensional needs assessment, communication, and economic/organizational aspects).

Results. To date, the first meeting has been conducted. The pre-working survey identified the following critical barriers for PC enrollment: 1) the need for PC needs assessment using appropriate tools, and 2) communication issues (discussion of goals of care). Regarding transfusion policy, the primary barriers identified were: 1) organizational and economic aspects, and 2) the multidimensional assessment of needs and transfusion outcomes (appropriateness).

Conclusions. Team coaching can serve as an effective interdisciplinary tool to overcome cultural and methodological barriers between professionals. The final output of this process will be presented at the SIE Congress.

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Fitness, palliation, quality of life and pharmacoeconomics

FROM DISEASE-SPECIFIC ELIGIBILITY TO AUTOLOGOUS TRANSPLANTATION: A REGIONAL PATHWAY FOR GENE THERAPY ACCESS IN B-THALASSEMIA AND SICKLE CELL DISEASE

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Background. The regional implementation of exagamglogene autotemcel for transfusion-dependent β-thalassemia and severe sickle cell disease requires standardized pathways integrating disease-specific eligibility, transplant feasibility, regulatory procedures and long-term follow-up. As non-oncologic disorders, hemoglobinopathies are not routinely managed within most transplant programs. Moreover, genetically modified autologous hematopoietic stem cell infusion may be delivered in centers accredited for autologous transplantation, provided that close interaction with hemoglobinopathy experts is ensured. In Sicily, a regional decree (DA n455) established a sequential model involving the Hub of the Regional Network for Thalassemias and Hemoglobinopathies and the Transplant Center.

Aims. To describe the Sicilian pathway for access to gene therapy in β-thalassemia and sickle cell disease.

Methods. The pathway was defined after inclusion of Casgevy in the regional formulary and alignment with AIFA eligibility criteria. Disease-specific eligibility was assigned to the Hematology and Rare Diseases Unit, while transplant eligibility and procedural feasibility were assigned to the Bone Marrow Transplant Unit of AOOR Villa Sofia-Cervello. Both units participate in AIFA registry procedures. A multidisciplinary team evaluates candidate patients and coordinates access with referring centers across Sicily. The model also includes molecular confirmation, fertility preservation, biobanking for long-term safety surveillance, and reporting linked to the Innovative Drugs Fund.

Results. The decree formalized a hub-and-spoke, sequential and multidisciplinary pathway integrating hemoglobinopathy care, autologous transplantation, molecular diagnostics, fertility preservation, biobanking and regional governance. The model standardizes patient selection, regulatory validation, treatment access, inpatient and early post-discharge management, shared follow-up with referral centers, and monitoring of activity and resources (Figure 1).

Conclusions. The Sicilian model provides a reproducible framework for implementing gene therapy in hemoglobinopathies, balancing clinical appropriateness, regulatory compliance, equity of access and sustainability. By integrating autologous transplantation with disease-specific expertise, it may support safe delivery of current and future advanced therapies within regional hematology networks.

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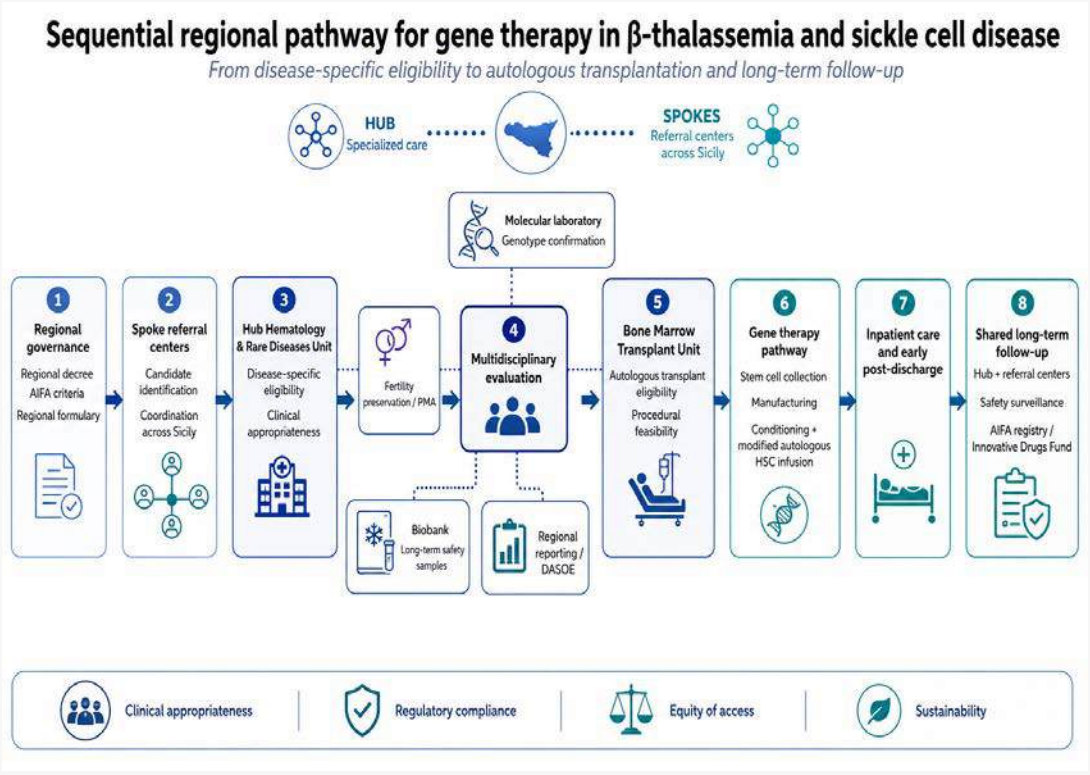
Fitness, palliation, quality of life and pharmacoeconomics



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Acute lymphocytic leukemia

BLINATUMOMAB AND INOTUZUMAB OZOGAMICIN IN OLDER ADULTS WITH RELAPSED/REFRACTORY PHILADELPHIA NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA: A CAMPUS ALL REAL-LIFE STUDY

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Introduction. Since their approval, bispecific anti-CD19 T--cell engager Blinatumomab (BLINA) and anti-CD22 Inotuzumab Ozogamicin (INO) have become cornerstones of treatment for relapsed/refractory (R/R) and minimal residual disease-positive (MRD+) acute lymphoblastic leukemia (ALL). However, their impact in older adults remained poorly explored.

Aims. To analyze efficacy and tolerability of BLINA and INO in older (≥55 years) R/Ror MRD+ ALL.

Patients and Methods. data from 154 patients (median age 64.8 years, range 55-82; 48% >65 years) treated in 33 Campus ALL Centers were collected. According to EGIL, 43 (28%), 90 (58%) and 21 (13%) cases were BI, BII and BIII, respectively. Median ECOG was 1 (0-3) and median number of comorbidities was 2 (0-7). First-line treatment was LAL1913 in 69(45%), LAL1104 in 22(14%), NILG10/07 in 10(6.5%), HyperCVAD in 9(5.5%) patients. BLINA was administered to 74(48%) patients, INO to 42(27%), and 38(25%) received both. First immunotherapy was BLINA (BLINA-F) in 101(66%) and INO (INO-F) in 53(34%) cases. BLINA-F and INO-F patients differed significantly in age, bone marrow blast count, *KMT2A* rearrangements, prior LAL1913 treatment (p<0.05) and indication for immunotherapy (MRD+/Rel/Ref: 47/41/12% vs 21/57/22%; p=0.001).

Results. median number of immunotherapy cycles was 2(1-5). After 1 cycle, 132 patients (85%) achieved CHR; CHR MRD-negative was more frequent with BLINA-F than INO-F (49% vs 28%; p=0.024). Grade 3/4 adverse events occurred in 27(26%) BLINA-F and 15(28%) INO-F patients (p=NS). Observed toxicities during cycle 1 were in line with previous studies (ICANS and CRS more frequent in BLINA-F, thrombocytopenia more frequent with INO-F; p<0.001). CRS was more common in patients ≤65 years (p=0.05), while infections more frequent in those>65 years (p=0.002). Median OS was 23.25 months and median EFS 11 months. OS was longer in BLINA-F patients than INO-F (48.6 vs 13.7 months; p=0.0169). However, in multivariate analysis, *KMT2A* and extramedullary disease were independently associated with inferior OS, and only MRD-negativity after cycle 1 was associated with improved OS (HR=0.45,

p=0.03). For EFS, *KMT2A*, extramedullary disease and elevated LDH were significant (p<0.05) adverse factors.
Conclusions. This large real-life experience confirms efficacy and acceptable tolerability of BLINA and INO in older adults with ALL. Early MRD clearance emerged as favorable prognostic factor, while adverse biology retained a negative impact.

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Acute myeloid leukemia

EVOLUTION OF TREATMENT ALGORITHMS IN UNFIT ACUTE MYELOID LEUKEMIA: REAL-WORLD EVIDENCE ACROSS TREATMENT ERAS AND PATIENT SELECTION

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We conducted a retrospective analysis of 707 AML pts from twelve institutions, treated with hypomethylating agent alone (HMA) before or after venetoclax (VEN) approval: PreVEN, 2010-2019 and PostVEN, >2020. These groups were compared with pts treated with HMA+VEN in terms of response and overall survival (OS).A total of 270 pts were included in the HMA group (149 PreVEN, 121 in PostVEN), and 437 in HMA+VEN group, respectively. Median age of the whole series was 75 years, with no difference between HMA (76 years) and HMA+VEN (74 years) pts. HMA pts more frequently had an ECOG ≥2 (62.2% vs 47.5%) and were more often unfit according to Ferrara criteria, including those frail (16.7% vs 3.2%). HMA+VEN pts had more frequently a better ECOG status, many of them being also fit to intensive chemotherapy (11.0% vs 6.3%). Comorbidity burden according to Charlson index was comparable. Response rates differed significantly across groups, with CR/CRi achieved in 65.0% of pts treated with HMA+VEN compared to 33.7% in the HMA group. At a median follow up of 19.3 months, median OS was 12 months in pts receiving HMA+VEN, and 8.5 months in those treated with HMA [Fig. 1A] ($p<0.001$). Within the HMA cohort, PostVEN vs PreVEN pts had a higher rate of ECOG ≥2 (66.9% vs 58.4%) and frailty l (33.1% vs 3.4%). Accordingly, survival was significantly inferior in PostVEN compared to PreVEN pts (median OS of 6.4 vs 13.1 months, respectively; [Fig. 1B] $p<0.001$). On the other hand, in pts receiving HMA+VEN we observed a constant improvement in OS over the time (median OS of 14.4 months vs 10 months for pts treated after vs before 2023; [Fig. 1C] $p=0.042$).In conclusion, HMA+VEN was associated with a superior survival of unfit AML pts. In addition, the progressively improving outcomes over the time of HMA+VEN-treated pts suggests a physicians' learning curve characterized by increasing clinical confidence and optimization in the use of VEN-based regimens. The inferior outcome observed in HMA-treated pts in the VEN era likely reflects the selection of a more fragile population, for whom the Italian physicians believed HMA alone represented the most valid option.

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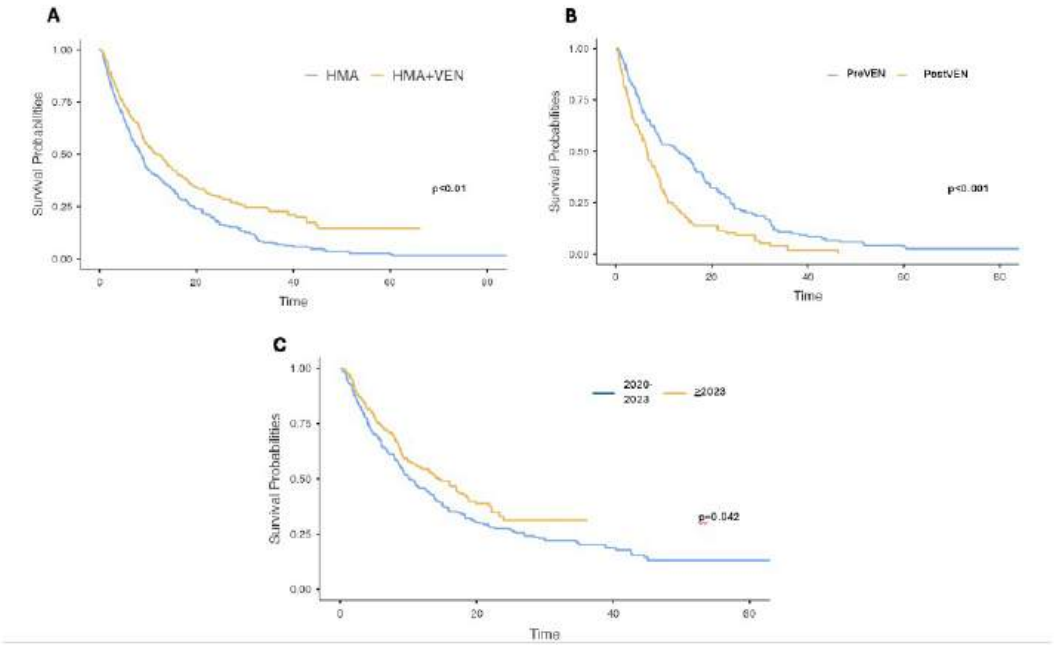
Figure 1. Overall survival according to treatment strategy and therapeutic era comparing HMA and HMA+VEN (A), HMA by treatment era (PreVEN vs PostVEN) (B), and HMA+VEN according to treatment period (before vs after 2023) (C)



Acute myeloid leukemia

FIRST INTERIM ANALYSIS OF VENETOCLAX REAL-WORLD OBSERVATIONAL STUDY ON NEWLY-DIAGNOSED AML PATIENTS IN ITALY

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Introduction. Venetoclax+Azacitidine(Ven/Aza) is approved as standard of care in Italy for Newly Diagnosed(ND) acute myeloid leukemia(AML) adult patients(pts) ineligible for intensive chemotherapy(IC). The VERO study collects prospective real-world data on Ven/Aza management, effectiveness, safety and quality of life(QoL).

Methods. 25 Italian clinical sites enrolled 151pts. Inclusion criteria: ND IC-ineligible AML; independent investigator's treatment choice according to local label. This interim analysis(IA) was conducted after 50% of pts had ≥3months(mos) of follow-up on 27Jan25, reporting baseline features/QoL data(EORTC QLQ C-30/EQ-5D-5L), Ven/Aza treatment management, Tumor Lysis Syndrome(TLS) risk assessment and early effectiveness/safety data.

Results. In 75 analyzed pts mean age was 76.2(±6) years; 24% >80 years, 48% 75-80 years; 70.7% of pts had de novo AML and 29.3% a secondary AML.Molecular tests reported mutations for NPM1-TP53-IDH1/2-FLT3. ELN2022 risk classification: intermediate 16pts(21%), adverse 41(55%), missing 18.Mean baseline QoL scores showed moderate global health, higher cognitive / lower physical functioning.Median Ven treatment duration was 28 days(dd) with median doses 100-200 mg/d (Tab1). Antifungal prophylaxis was used in 51/75pts(68%,Tab2), and G-CSF in 27/47(55%).Overall Response Rate(ORR): 58.7%(44/75pts). Composite Complete Remission(cCR:CR+Cri+CR and Cri MRD-)53.8%(25/65pts). Median time to best response: 0.95mos (IQR:0.7- 1.9); 65pts (86.7%) had at least 1 response assessment post C1.Measurable residual disease(MRD) was tested on <50% of pts(Tab2).Transfusion independence (>56dd): mo 1=77.8%, mo 2=42.6%, mo 3=58.8%. 3pts underwent bone marrow transplant. 3-Months OS estimate(95% CI):0.73(0.61, 0.82,-Fig1).AEs of interest: cytopenia: 51.7%(31/60) [mostly febrile neutropenia(48.4%), neutropenia(51.6%)], overall infection rate: 66.7%(57 pts) 81.6% bacterial, 5.3% fungal]. Study discontinuation: 26.7%(20pts)-mainly for infections(55%)-cytopenia(15%). 26 reported deaths: mainly for progression(8), septic shock(6).

Conclusions. The IA describes the first 50% of pts with AML from the VERO study, mainly elderly. Despite the short follow-up and limited sample size, data show Ven/Aza effectiveness in the real-world setting. Median time to response was <1mo, showing timely response assessment in real life. No new safety signals were reported. Our findings, though only descriptive, align with published real-world and clinical trial data1-2.

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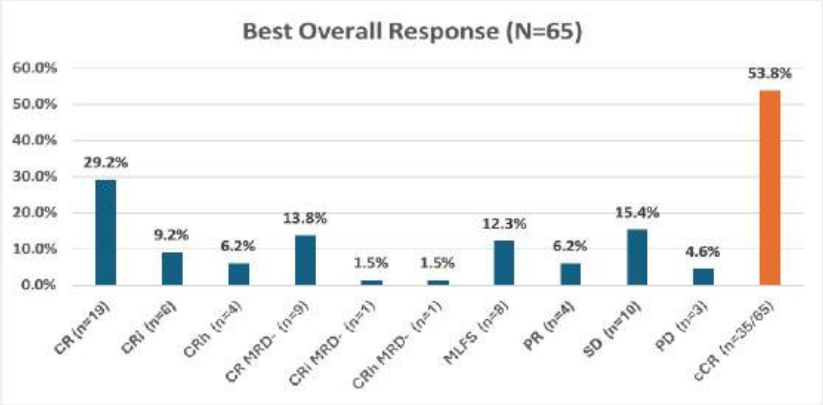
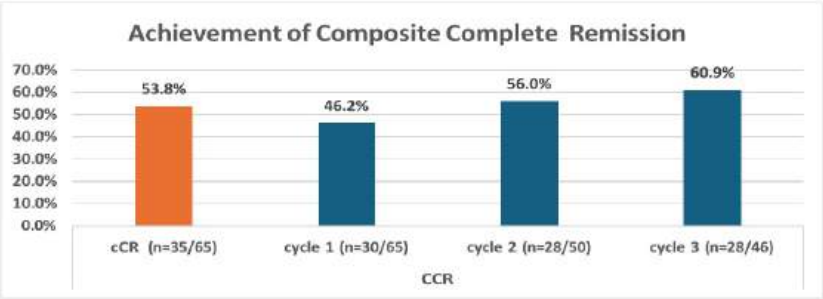
Figure 1: A) Best Overall Response; B) Composite Complete Remission;

A



Best Overall Response Rate: frequency of patients achieving CR without MRD (CRMRD-), CRh without MRD (CRhMRD-), CRi without MRD (CRiMRD-), Complete Remission (CR), Complete Remission with partial hematologic recovery (CRh), Complete Remission with incomplete hematological recovery (CRi) and Partial Remission (PR) up to the cut-off date

B



n=number of patients reaching cCR/number of patients with a cycle response assessment completed

Table 2. Patient management: Venetoclax dose and duration of treatment-MRD evaluation

	Cycle 1	Cycle 2	Cycle 3
Patients performing visit	73	50	45
Median **Ven** dose (mg/d)	133.3	100	200
IQR	100-225	100-233	100-400
Median **duration of cycle** (dd)	28	28	28
IQR	21-28	22-28	21-28
MRD performed	31 (42.5%)	14 (28%)	10 (22.2%)
MRD-	8/31 (25.8%)	4/14(28.6%)	3/10 (30%)

Ven: Venetoclax; Measurable residual disease (MRD, mainly performed by flow cytometry)

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Table 1		N 75
Age at study entry (years), Mean (SD)		76.2 (6.0)
Median		78
Sex, Female/ Male, n (%)		28 (37.3%)/47 (62.7%)
BMI (Kg/m2), Mean (SD)		25.3 (4.4)
AMLsubtype, n (%)		
De novo		53 (70.7%)
Secondary		22 (29.3%)
	prior Myelodysplastic syndromes(MDS), Aza-pretreated	10 (45.5%)
	Myeloproliferative neoplasms (MPN)	5 (22.7%)
	therapy related-AML(t-AML)	4 (18.2%)
	Chronic myelomonicitie leukemia (CMML)	2 (9%)
	previous other malignancies	1 (4.5%)
AMLcharacterization		
Mutated NPM1		11/69 (16%)
Mutated TP53		6/43 (14%)
Mutated IDH1/2		14/61 (23%)
Mutated FLT3		14/68 (20.6%)
Mutated NPM1 w/o FLT3-ITD		7/56 (12.5%)
Mutated NPM1 with FLT3-ITD		6/54 (11.1%)
Wild-type NPM1 with FLT3-ITD		5/53 (9.4%)
Assigned Risk- ELN2022, n (%)		
	Intermediate	16 (21.3%)
	Adverse	41 (54.7%)
	Missing	18 (24%)
2022 WHO classification, n (%)		
AMLwith defining genetic abnormalities, n:		44
	AML, myelodysplasia-related	25 (37.9%)
	Not evaluated/Not evaluable	22 (33.3%)
	AMLdefined by differentiation, n:	32
	Not evaluated/Not evaluable	34 (51.5%)
Cytogenetic and molecular abnormalities defining AML, Myelodysplasia-Related, n (%):		
	Complexkaryotype (>=3 abnormalities)	12 (18.2%)
	Not evaluated/Not evaluable	45 (68.2%)
Reasons for ineligibility to intensive chemotherapy, n (%):		66
An age older than 75 years		39 (59%)
Any other comorbidity that the physician judges to be incompatible with IC		23 (35%)
pulmonary disease with DLCO or FEV≤65%		6 (9%)
Tumor Lysis Syndrome (TLS) risk assessment, n(%)		
Renal impairment		10/75 (13.3%)
	CKD*1-3	7 (70%)
	Unknown	3 (30%)
Elevated tumor burden		17/75 (22.7%)
Prophylactic measures		62/75 (82.7%)
Measures type:	Antihyperuricemic treatments	41
	Blood chemistry monitoring	41
	Intravenous hydration	35
	Cytoreduction	25
EORTC QLQ-C30, n		75
Global health status, n		71
Mean (SD)		50.8 (23.7)
Functional Scales, Mean (SD)	Physical functioning, n 72	67.5 (25.9)
	Cognitive functioning, n 71	80.5 (22.9)
Symptom scales / items, Mean (SD)	Fatigue, n 72	43.1 (27.8)
	Dyspnoea, n 72	25.5 (27.1)
	Insomnia, n 72	26.4 (27.4)
	Appetite loss, n 72	27.8 (27.4)
EQ-5D-5L, n		75
no or little problems in, %	Mobility	72%
	Self-care	77.30%
	Usual Activities	65.30%
	Pain/discomfort	77.30%
	Anxiety/depression	73.40%
VAS, mean (SD)		55.8 (19.9)
Proportion of patients receiving antifungal prophylaxis, n (%)		51/75 (68%)
Treatment duration of antifungal prophylaxis (days)	n	28
	Mean (SD)	33.9 (23.7)
Type of antifungal prophylaxis, n (%)		
	Posaconazole	46 (61.3%)
	Isavuconazole	1 (1.3%)
	Voriconazole	2 (2.7%)

Acute myeloid leukemia

MOLECULAR CHARACTERISTICS OF TP53-MUTATED ACUTE MYELOID LEUKEAMIA: ANALYSIS OF A SINGLE-CENTER RETROSPECTIVE COHORT

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TP53-mutated acute myeloid leukaemia (AML) represents a distinct subgroup of myeloid neoplasms characterized by marked biological heterogeneity and a unique landscape of co-mutations and gene expression profiles. We analyzed 54 TP53 mutations (mut) identified in 50 AML patients (pts) diagnosed between 2018 and 2025 at a single institution. TP53 mut were detected by next-generation sequencing (NGS) in 52% of cases (n=26) and by Sanger sequencing in the remaining 24. Overall, 41 mut (76%) were missense, 5 (9%) frameshift, 3 affected splice-site, 3 (5.5%) nonsense, and 2 (4%) were an in-frame insertion. The majority of mut (48/54; 89%,) occurred within the DNA-binding domain, including 38 missense variants. Multiple hotspot mut were observed, most frequently R273H/S (n=5), R248Q/W (n=4), G245S (n=3), and R282W (n=3). Only 4 pts (8%) had >1 TP53 mut detected (2 mut). The median variant allele frequency (VAF) of TP53 mut was 50% (range: 3.9-95). Most pts (49/50; 98%) exhibited a complex karyotype, 38 pts (76%) with deletion of 5q, 29 (58%) with deletion of 7q, and 26 (52%) showed abnormalities of 17p or loss of 17. Applying ICC criteria to our cases, only one pt was classified as mono-hit TP53 mutated AML. Median bone marrow blasts was 32% (range: 10-94). Concurrent mut were identified in 18 out of 26 (69%) pts analyzed by NGS. The most frequent co-mut, i.e. detected in at least 3 pts, were detected in TET2, DNMT3A, ASXL1, JAK2, IDH1/2 and SF3B1 (ranging from 27% to 11.5%). Considering the co-mutational status, we identified three subgroups: 8/26 pts had TP53 mut alone, 12/26 pts had DNMT3A and TET2 mut (CHmut) and 15/26 had other mut affecting spliceosome, AML defining genes, JAK2, chromatin gene modifiers etc. Of note only 3/26 pts were exclusively CHmut. No differences among the three groups were observed regarding baseline characteristics. Forty-one pts received chemotherapy or Hypomethylating Agents. In this cohort overall survival and disease-free survival were 9.9 and 6.6 months, respectively, without differences according to presence of 17p abnormalities, co-mutation in NGS or according to TP53 VAF (<10%, 10%<-VAF<50%, >50% respectively). In our small series we confirmed that TP53 mut in AML are heterogenous and there are no specific hotspots. Concurrent mut are mainly those affecting CH genes, IDH1/2 and spliceosome genes. However, co-occurring mutations or VAF neither mitigated nor worsened the dismal prognosis associated with TP53 mut in AML pts.

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Acute myeloid leukemia

CLINICAL IMPACT OF *NPM1* AND *IDH1/2* AS MEASURABLE RESIDUAL DISEASE MARKERS IN ACUTE MYELOID LEUKEMIA TREATED WITH LESS-INTENSIVE VENETOCLAX-BASED REGIMENS: A SINGLE-CENTER EXPERIENCE

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Background. Venetoclax plus hypomethylating agents (HMAs) has become a standard-of-care for AML patients inelegible for intensive chemotherapy. In this setting, the prognostic role of molecular MRD based on *NPM1* and *IDH1/2* mutations remains incompletely defined.
Aim. To assess the role of *NPM1* and *IDH1/2* mutations as MRD markers during therapy and after its discontinuation in AML patients receiving venetoclax+HMAs.
Materials and Methods. Sixty-nine AML patients were profiled at diagnosis using a 51 gene NGS panel.Among them, 19 patients harboring *NPM1* and/or *IDH1/2* mutations underwent MRD monitoring: 9 with *IDH1/2* mutated, 5 with isolated *NPM1* mutated and 5 with *NPM1–IDH1/2* co-mutation. *IDH1/2* variants were assessed on DNA by digital droplet PCR (ddPCR), while *NPM1* transcripts were quantified on RNA by RT-qPCR. MRD was assessed longitudinally retrospectively and prospectively during therapy and after its discontinuation.
Results. Patients with *NPM1* and/or *IDH1/2* mutations achieved high complete remission (CR) rate (83% and 89%) in line with the favorable outcomes associated with these mutations. Five out of 14 patients evaluable after cycle 4 achieved MRD negativity, while 9/14 remained MRD positive. Overall, 10 /19 patients achieved MRD negativity at any timepoint, whereas 9/19 remained persistently MRD positive. MRD negativity either by the end of cycle 4 or at any time point was associated with improved overall survival (OS) and event free survival (EFS) evaluated at 12 months from therapy start (OS 100% vs 67%, p=0.0024; EFS 100 % vs 33%, p=0.0003,fig.1). Nine patients discontinued therapy in CR (4 due to toxicity, 1 patient decision and 4 other): 1 relapsed, 8 are in ongoing clinical remission, including 7 who were MRD negative at discontinuation, with follow-up exceeding 50 months in one case. In 1 co-mutated patient *NPM1* and *IDH2* p.R140Q, the achievement of *NPM1* MRD negativity despite persistent *IDH2* high positivity was associated with a sustained clinical remission, supporting the hypothesis that persistent *IDH2* positivity may reflect clonal hematopoiesis rather than active leukemia.
Conclusions. MRD negativity associates with improved outcomes in *NPM1* or *IDH1/2* mutated AML patients treated with venetoclax + HMAs. A sustained CR, among MRD-negative patients supports the need for prospective studies to evaluate the feasibility and safety of MRD-guided treatment discontinuation. In co-mutated cases, *NPM1* represent a more reliable MRD marker than *IDH1/2*

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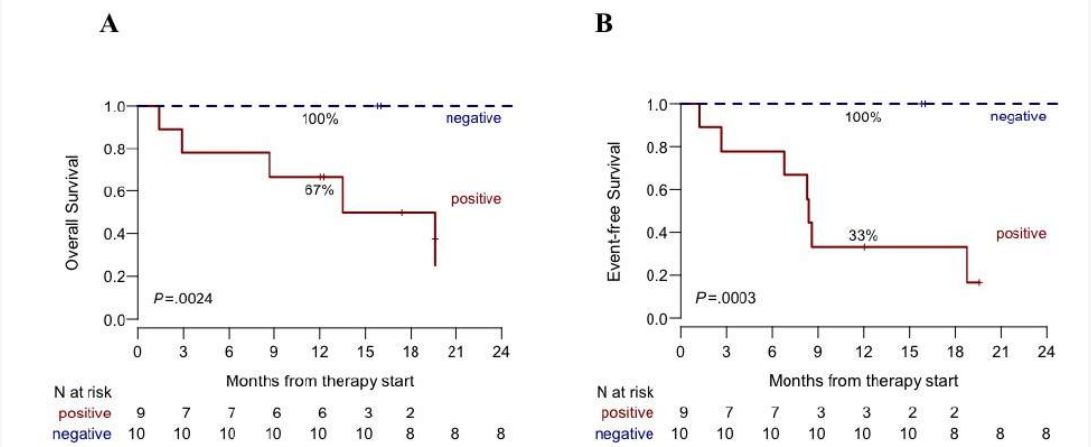
ACUTE MYELOID LEUKEMIA

Figure 1: Outcomes by MRD status



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Acute myeloid leukemia

ONE ASSAY, INTEGRATED INSIGHT: A DNA-BASED NGS APPROACH FOR MOLECULAR AND CYTOGENETIC PROFILING IN ACUTE MYELOID LEUKEMIA

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According to the World Health Organization (WHO) and the International Consensus Classification (ICC), comprehensive genetic characterization of Acute Myeloid Leukemia (AML) is essential for accurate diagnosis, risk stratification, and therapy. This requires integration of molecular assays for single nucleotide variants (SNVs) and copy number variations (CNVs) with cytogenetic analyses to detect chromosomal abnormalities. However, multiple complementary tests may increase workload and prolong turnaround time (TAT).The scope is to evaluate a Next-Generation Sequencing (NGS)-based approach for comprehensive genomic profiling in a single assay, enabling simultaneous detection of SNVs and prediction of chromosomal abnormalities, optimizing resources and TAT.A total of 29 samples (1 reference, 28 AML patients with known genetic profiles) were analyzed. DNA was extracted from bone marrow or peripheral blood using Maxwell CSC 48. Sequencing was performed with the SOPHiA DDM™ Community Myeloid Solution v2 on Illumina NextSeq 550. The assay uses UMI-based adapters to achieve high sensitivity, and detects SNVs, CNVs, internal/-partial tandem duplications, and fusions exclusively from DNA (Fig. 1A). It also infers chromosomal aberrations by clustering gene-level losses and gains (Fig. 1B). Pathogenic variants were assessed using ClinVar, COSMIC and Franklin databases.Four sequencing runs, including selected replicates for reproducibility and repeatability assessment, generated high-quality data (29–44 million reads/run; >99% mapping) and uniform coverage. All expected variants in the reference sample were detected achieving 100% sensitivity. Previously identified SNVs were confirmed with 100% concordance and no false negatives. Known CNVs were validated and additional CNVs detected, in agreement with cytogenetic approach, including Del5q, Del7q, trisomy 8, Del17p, monosomy 18, although some regions were not fully covered (Fig. 1C). DNA-based fusion detection showed lower sensitivity than RNA-based assays.These preliminary results show how this NGS panel integrates both molecular and cytogenetic data for AML characterization. Larger cohort studies are actually ongoing. While fusion detection remains limited and should be complemented by RNA analysis, CNV profiling shows strong concordance with cytogenetics. This approach complements karyotyping, which remains essential for genome-wide assessment, and together refine diagnostic and biological interpretation in AML.

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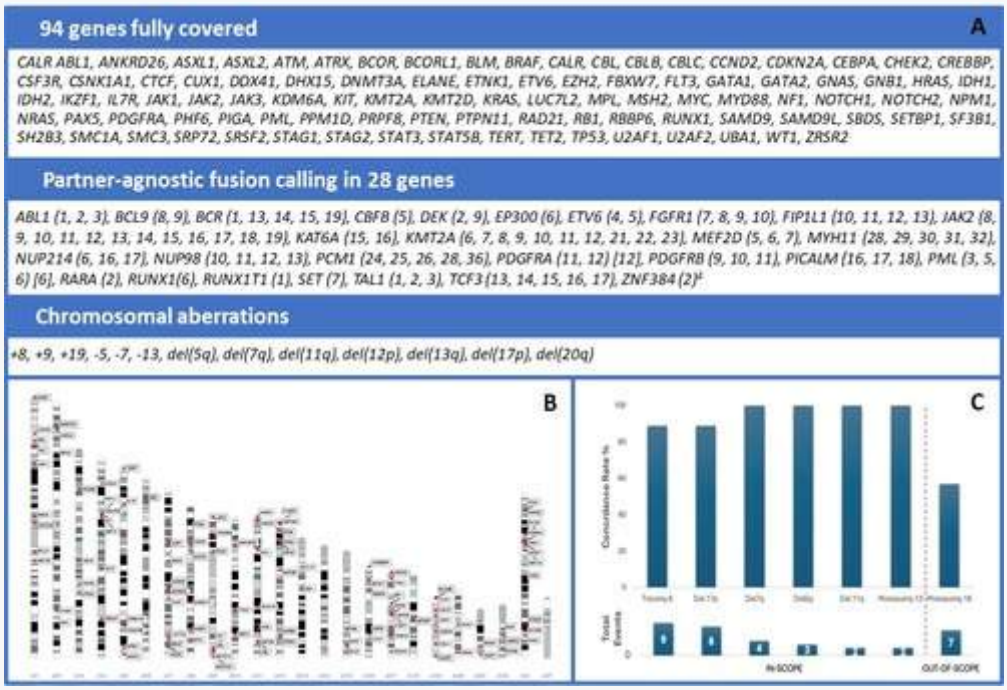
Acute myeloid leukemia



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Myelodysplastic syndromes

MYELODYSPLASTIC SYNDROME WITH MODERATE-SEVERE FIBROSIS: COMPARISON BETWEEN PRIMARY AND THERAPY-RELATED CASES OF A SINGLE-CENTRE COHORT

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Myelodysplasia with fibrosis (MDS-f) was first recognised as a nosographic entity in the WHO 5th classification of myeloid neoplasms [Khoury J.D. et al, Leukemia, 2022]: given the limited treatment options and poor prognosis, we analysed retrospectively all the cases of myelodysplastic neoplasm (MN) with moderate-severe fibrosis diagnosed at our centre.All consecutive cases of primary (P-) or therapy-related (T-) MN diagnosed from 1 January 2022 to 31 December 2025 with bone marrow histology available were included. The diagnosis complied with the WHO 5th criteria, the prognosis with IPSS-R in all cases and IPSS-M if possible; the histological assessment of fibrosis was carried out according to the international guidelines [Thiele J. et al, Haematologica, 2005] by two independent operators.Among the 127 MN cases: 55 (43%) showed no medullary fibrosis (MF-0), 42 (33.6%) had mild fibrosis (MF-1) and 30 (23.6%) had moderate-severe fibrosis (MF-2/3). Of these: 21 (70%) cases were P-MN-f and 9 (30%) T-MN-f (6 previous cases of haematological malignancies and 3 cases of cancer). Table 1 compares the clinical baseline characteristics of our cases with a recently published series of P-MN-f cases [Xu G et al, Hematol Oncol 2025]. Twenty-five (83%) were transfusion dependent (TD) and 21 (66.6%) presented a bone marrow blast count (BM BL) of ≥5%. Our cohort has higher: median BM BL (8% vs 4.5%), prevalence of MN with blast excess (70% vs 44.6%) and proportion of high- and very high-risk IPSS-R cases (79.9% vs 48.5%). The number of patients who developed leukaemic evolution after a median of 3 months was 7 (23%). After a median follow-up of 8 months (1–47): 16 patients died because of disease progression (8, 26.6%) or complications of cytopenia (8, 26.6%), mainly due to infection (7/8, 87.5%). Ten out of 14 surviving patients were treated with erythropoietin (2), azacitidine (4) +/- allogeneic bone marrow transplantation (6, median age 58.5, 46-71). In the whole cohort, P-MN-f and T-MN-f the median outcome data were respectively: a) OS: 11 (1-47), 21 (1-42) and 9 (1-47) months (p: NS); b) PFS: 11 (1-47), 11 (1-42) and 5 (1-47) months (p: NS).This study confirms the clinical characteristics and the unfavourable prognosis of MN-f as defined by the WHO 5th edition. It also suggests a possible additional prognostic effect of a therapy-related nature in MN with MF-2/3 compared with primary forms; this finding requires confirmation on a large scale.

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Table. Baseline characteristics of newly diagnosed MN with moderate-severe marrow fibrosis (MF-2/3)

	Brescia (N=30)	Xu et al, 2025 (N=65)
Sex – no. (%)		
Male	10 (33.3)	22 (33.8)
Female	20 (66.6)	43 (66.2)
Median age – years (range)	73.5 (46-88)	N/A
Age group – no. (%)		
< 60 years	9 (30)	25 (38.5)
≥ 60 years	21 (70)	40 (61.5)
Laboratory parameters – median (range)		
WBC (x10^9/L)	2.88 (1.49–12.3)	2.89 (2–4.2)
ANC (x10^9/L)	1.28 (0.3–9.4)	1.3 (0.8–2.15)
MO (x10^9/L)	0.3 (0.07–3.45)	N/A
HGB (g/L)	8.6 (6.0–13.2)	6.9 (N/A)
PLT (x10^9/L)	61.5 (4.0–388)	48 (N/A)
LDH (U/L)	236 (73–1712)	314 (136–1424)
Poikilocytosis/leukoerythroblastosis – no. (%)	17 (56.6)	N/A
Splenomegaly – no. (%)	2 (6.67)	N/A
BM BL – median % (range)	8 (1–15)	4.5 (0–19)
BM BL group – no. (%)		
≥ 5%	21 (70)	29 (44.6)
< 5%	9 (30)	36 (55.4)
IPSS-R risk groups – no. (%)		
Very low	2 (6.6)	1 (1.6)
Low	1 (3.3)	11 (17.2)
Intermediate	3 (10)	21 (32.8)
High	13 (43.3)	12 (18.8)
Very high	11 (36.6)	19 (29.7)
IPSS-M risk groups – no. (%)	10 (33.3)	65 (100)
Very low	1 (10)	1 (1.5)
Low	1 (10)	8 (12.3)
Moderate low	1 (10)	3 (4.6)
Moderate high	1 (10)	14 (21.5)
High	3 (33.3)	10 (15.4)
Very high	3 (33.3)	29 (44.6)

Abbreviations: ANC, absolute neutrophil count; BM BL, bone marrow blasts; HBG, haemoglobine; IPSS-M, international prognostic scoring systems-molecular; IPSS-R, revised international prognostic scoring system; LDH, lactate dehydrogenase; MF, marrow fibrosis; MN, myelodysplastic neoplasms; MO, monocites; N/A, not assessed; PLT, platelet count; WBC, white blood cell count.

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Acute myeloid leukemia

AML-FIT65: IMPACT OF A SIMPLIFIED GERIATRIC ASSESSMENT ON SURVIVAL AND TREATMENT ALLOCATION IN ELDERLY PATIENTS WITH ACUTE MYELOID LEUKEMIA: A REAL-WORLD STUDY

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Background. Acute myeloid leukemia (AML) predominantly affects older adults and is associated with poor outcomes. Elderly patients represent a heterogeneous population in terms of comorbidities, functional status, and treatment tolerance. Chronological age alone is insufficient to guide therapeutic decisions, and geriatric assessment may improve prognostic stratification.

Methods. We conducted a retrospective single-center real-world study including consecutive patients aged ≥65 years with newly diagnosed AML between 2018 and 2022, excluding acute promyelocytic leukemia. Baseline data included clinical characteristics, ECOG performance status, and geriatric assessment using ADL, IADL, and CIRS-G. Patients were classified as fit, unfit, or frail according to a simplified geriatric assessment (sGA) score (Merli et al 2021) results were comparated with Ferrara Criteria (Ferrara et al 2013). Treatment strategies were categorized as intensive chemotherapy, low-intensity therapy, or best supportive care. The primary endpoint was overall survival (OS), analyzed using Kaplan–Meier and Cox regression models.

Results. A total of 84 patients were included (median age 76 years, range 65–99; 51.2% male). According to geriatric assessment, 38.1% were fit, 17.9% unfit, and 40.5% frail. Treatment allocation included intensive chemotherapy (n=20), low-intensity therapy (n=27), and best supportive care (n=31). Complete remission was achieved in 9 patients. The sGA classification showed high concordance with Ferrara criteria (91%). Median OS was 18.3 months. Survival differed across fitness categories: 18 months in fit, 13 months in unfit, and 4 months in frail patients, reflecting progressive functional impairment. In multivariable analysis, geriatric fitness status remained an independent prognostic factor for OS.

Conclusions. sGA allows us to identify subgroups of elderly patients with AML with different expected benefits from therapeutic intensity. The high concordance with the Ferrara criteria and consistency with treatment allocation suggest that sGA may contribute to patient assessment, helping to reduce the risk of over- and undertreatment. These real-world data support sGA use as a decision-making tool in clinical practice and justify its prospective validation.

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Acute myeloid leukemia

WT1-GUIDED VENETOCLAX DOSING IN UNFIT AML: A REAL-WORLD STRATEGY TO BALANCE EFFICACY AND TOXICITY

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Background/Objectives. Minimal residual disease (MRD) negativity is associated with improved outcomes in patients with acute myeloid leukemia (AML). However, to date, there are no standardized guidelines for MRD monitoring in patients unfit for intensive induction regimens. In this retrospective observational real-life case series study, we investigated the efficacy and safety of venetoclax dose adjustments in unfit AML patients and the role of WT1 expression levels as a surrogate marker for MRD monitoring.

Methods. A total of 24 consecutive unfit AML patients treated with azacitidine and venetoclax were enrolled in this study, and MRD monitoring was performed by flow cytometry according to per international guidelines and by WT1 expression levels assessed by RT-qPCR at diagnosis and after each treatment cycle. Venetoclax dose adjustments were guided by MRD status and the occurrence of grade > 2 neutropenia.

Results. The overall response rate was 87.5%, with 16 patients (66.7%) achieving a response at the first re-evaluation. Venetoclax dose was reduced in half of the patients already after the first re-evaluation, and in 9 of them (75%) the dose was further adjusted at a median of the fourth cycle. No statistically significant differences were observed between patients receiving the standard dose and those undergoing venetoclax dose adjustment in terms of overall survival (19.6 months vs. 30.1 months; p = 0.9428) and progression-free survival (not reached vs. 22.1 months, respectively; p = 0.3865). However, a numerical trend toward lower relapse rates was observed in patients with late (33.3%) or both early and late dose reduction (37.5%) compared to those who had dose adjustment only at the first re-evaluation (75%) (p = 0.3014). The toxicity rate was 33.3% in patients with both early and late dose adjustments, lower than that observed with early adjustment only (58.3%) and compared to that reported in the VIALE-A study (84%). These differences were not statistically significant, likely due to the small sample size (p = 0.3613).

Conclusions. WT1 expression levels may serve as a surrogate marker for MRD assessment, especially in elderly AML patients unfit for intensive regimens. Reduced-dose venetoclax strategies in unfit AML patients do not appear to compromise response rates or survival outcomes, supporting a flexible, response-adapted dosing approach based on MRD dynamics and treatment-related toxicity.

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Acute myeloid leukemia

MONITORING ACUTE MYELOID LEUKEMIA AND EXTRAMEDULLARY RELAPSE FOLLOWING ALLOGENEIC STEM CELLS TRANSPLANTATION WITH LIQUID BIOPSY USING PLASMA FT-IR SPECTROSCOPY

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Relapse of acute myeloid leukemia (AML) remains a major cause of treatment failure. Among relapse patterns, extramedullary disease, known as myeloid sarcoma, representing a rare but clinically significant scenario, characterized by leukemic blast infiltration outside the bone marrow. Diagnosis is challenging and requires a multimodal approach integrating imaging, histopathology, and immunophenotyping. Prognosis is influenced by localization, disease burden, and therapy response.In this study, we employed a plasma-based liquid biopsy approach using Fourier-Transform Infrared (FT-IR) spectroscopy to analyze samples from AML patients at diagnosis, pre- and post-allogeneic hematopoietic stem cell transplantation (allo-HSCT), during bone marrow and extramedullary relapse, alongside healthy controls. Spectral data were normalized using standard normal variate and analyzed via multivariate and machine-learning methods (Random Forest) with leave-one-patient-out cross-validation.Comparison between healthy and pathological subjects demonstrated high discriminatory power (AUC=0.866; Accuracy=0.826), with optimized sensitivity of 100% and specificity of 80%, highlighting a distinct FT-IR spectral signature associated with healthy and AML patients (Fig. 1A). Analyses comparing diagnosis, bone marrow and extramedullary relapse samples revealed excellent discrimination (Fig 1B-C), as well as differences between medullary and extramedullary relapse (Fig 1D), suggesting distinct metabolic, molecular, and structural profiles linked to clinical presentation. Post-HSCT spectra showed gradual normalization toward physiological profiles, with 94.4% of samples reaching near-normal spectra at day +90, reflecting partial metabolic recovery, partially observed at day +30.These findings indicate that plasma FT-IR spectroscopy is a promising non-invasive tool for AML monitoring and detecting post-transplant relapse, demonstrating that biochemical changes accurately reflect the patient's biochemical and metabolic status. The method can discriminate disease phases and relapse types while capturing gradual metabolic normalization, supporting its potential clinical utility. FT-IR offers a sensitive approach to detect biochemical changes, providing complementary biomarkers for disease monitoring, ad potentially early relapse detection. Further studies are warranted to validate these spectral signatures and integrate FT-IR-based liquid biopsy into precision AML management strategies.

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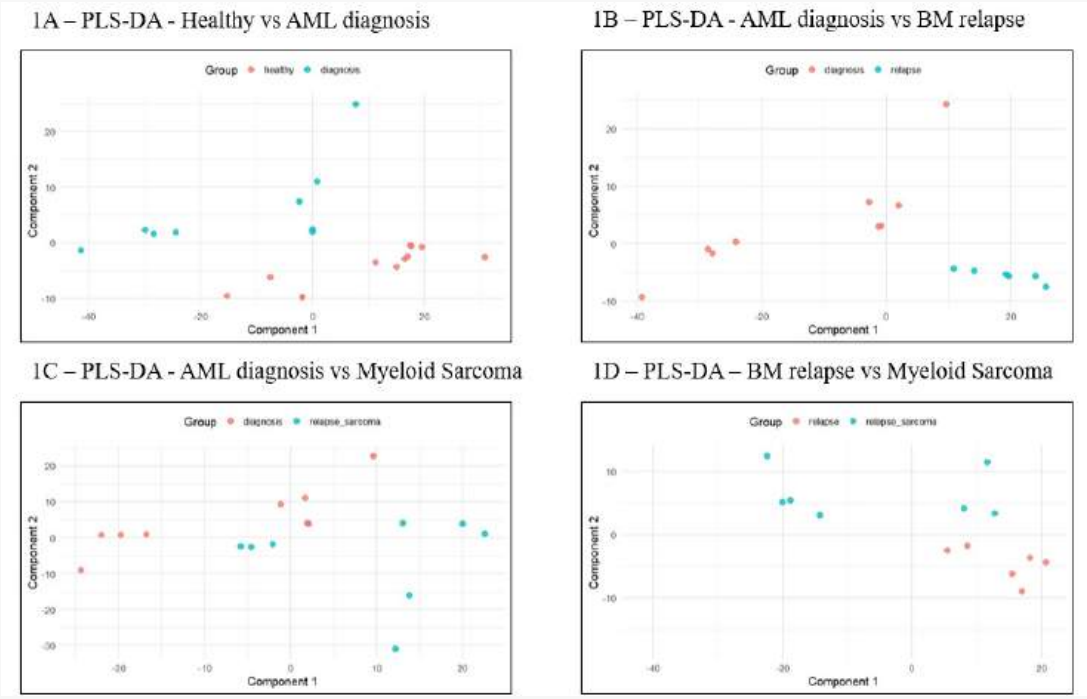

Acute myeloid leukemia

IN AML PATIENTS A FASTER PLATELET RECOVERY TIME DURING FIRST CYCLE OF VENETOCLAX-AZACITIDINE IS ASSOCIATED WITH IMPROVED OVERALL SURVIVAL

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Background. The combination of Venetoclax and Azacitidine (Ven-Aza) has been set up as the new standard first--line regimen in acute myeloid leukemia (AML) patients unfit for intensive chemotherapy (IC), with a median overall survival (OS) of 14.7 months (VIALE-A study). Delayed hematologic recovery is one of the main causes of therapy discontinuation. Platelet (PLT) recovery during Ven-Aza is variable and the impact of a faster PLT recovery time within the first cycle is unknown. In this single-center retrospective study, we analyzed in this setting the relationship between timing of PLT recovery and outcome.

Methods. We collected data of consecutive IC ineligible patients with AML diagnosed between January 2020 and July 2025 treated first-line with standard dose Ven-Aza at our institution. PLT recovery at day 21 and 28 from the beginning of the first cycle of treatment was analyzed; reference levels for PLT response analysis were established as $50x10^9$/L and $100x10^9$/L. The primary objective of the study was OS. Secondary objectives included event-free survival (EFS), PLT transfusion independence (PTI, i.e. absence of a PLT transfusion for at least 56 days between first and last day of treatment) and complete remission rate (CR).

Results. 47 patients (23 males, 49%), median age 76.6 years (range 46-85), 33 patients (70%) ≥75 years old were analyzed; 24 (51%) had de novo AML. Baseline percentage of bone marrow blasts was <30% in 11 patients (23%), 30-50% in 14 (30%) and >50% in 22 (47%). Intermediate and poor cytogenetic risk were in 17 (36%) and 26 (55%) patients, respectively. Out of 24 assessable patients, 4 (9% of the cohort), 2 (4%), 3 (6%), 6 (13%) had IDH1 or IDH2, FLT3-ITD or -TKD, NPM1, TP53 mutations. Baseline median PLT count was $52x10^9$/L; 4 (9%) were PLT transfusion dependent. The results of therapeutic outcome are summarized in Figure 1. Briefly, at a median follow-up of 325 days the median OS and EFS were 325 and 266 days, respectively. OS and EFS curves were significantly higher in those patients who had a faster platelet recovery, either at day 21 or 28.

Conclusions. In patients with AML treated first-line with Ven-Aza a more rapid recovery of PLT count appears to be a possible positive predictor of OS and other treatment outcomes.

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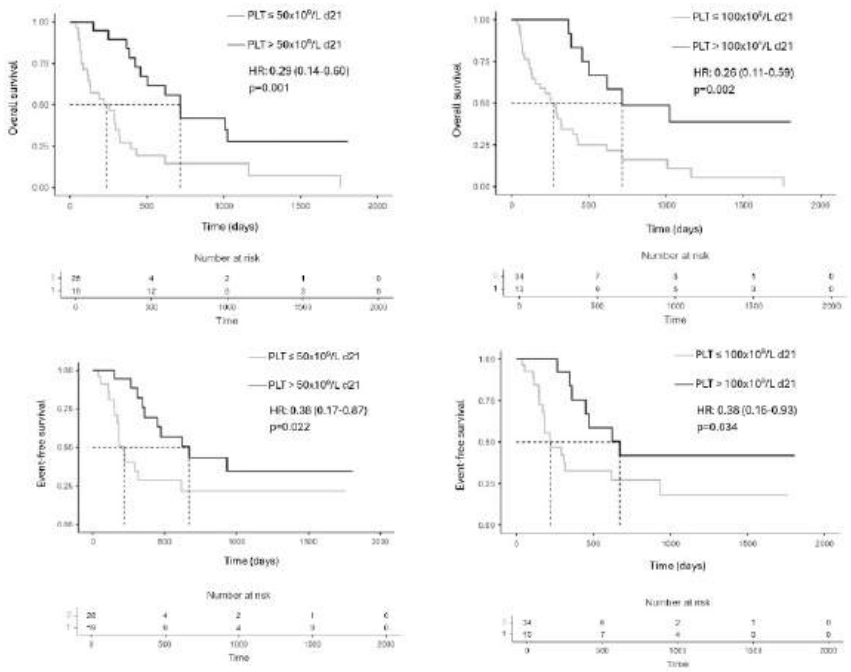
Figure 1.



	PLT recovery	PLT ≤ 50 x 10^9L	PLT > 50 x 10^9L	PLT ≤100 x 10^9L	PLT >100 x 10^9L
Patients	**Day 21**	28	19	34	13
	Day 28	18	29	27	20
Median OS, days (range)	**Day 21**	238 (38-1759)	652 (152-1806)	261 (38-1759)	688 (273-1806)
	Day 28	141 (38-618)	502 (65-1806)	266 (38-1162)	617 (65-1806)
Median EFS, days (range)	**Day 21**	161 (38-1759)	471 (149-1806)	175 (38-1759)	621 (266-1806)
	Day 28	134 (38-618)	359 (65-1806)	268 (38-1162)	602 (65-1806)
CR, n. (%)	**Day 21**	14 (50)	13 (68)	15 (44)	12 (92)
	Day 28	7 (39)	20 (69)	12 (44)	15 (75)
PTI, n. (%)	**Day 21**	23 (82)	19 (100)	29 (85)	13 (100)
	Day 28	13 (72)	29 (100)	22 (81)	20 (100)

PLT: platelet; OS: overall survival; EFS: event-free survival; CR: complete remission; PTI: platelet transfusion independence

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Acute myeloid leukemia

RAPID SCREENING OF FLT3 MUTATIONS IN ACUTE MYELOID LEUKEMIA USING THE TAPESTATION SYSTEM

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Background. FLT3 gene mutations are among the most frequent molecular alterations in acute myeloid leukemia (AML), occurring in 25–35% of cases and playing a key role in disease pathogenesis. Internal tandem duplications (FLT3-ITD) are detected in 20–30% of patients, while tyrosine kinase domain mutations (FLT3-TKD), most commonly affecting codon D835, occur in 5–10%. FLT3 is a major therapeutic target, making mutation detection essential for prognostic stratification and treatment decisions. Capillary electrophoresis (CE) remains the gold standard for FLT3-ITD detection.

Aim. To evaluate the performance of an automated gel-based electrophoresis system (Agilent 4150 TapeStation) for the detection of FLT3-ITD and FLT3-TKD mutations.

Methods. DNA samples from 28 AML patients previously tested in routine diagnostics for FLT3 mutations by PCR followed by CE were analyzed. PCR assays targeted FLT3-ITD (exons 14–15) and FLT3-TKD (exon 20) using 20 ng DNA input. For TKD analysis, PCR products were digested with EcoRV. Subsequently, 2 µL of each PCR (or digested) product was mixed with sample buffer and loaded onto ScreenTape High Sensitivity D1000 with a ladder. Samples were analyzed using the Agilent 4150 TapeStation according to the manufacturer's instructions. Each run included a 5% positive control, a negative control, and a no-template control. Results were compared with CE and/or NGS.

Results. TapeStation analysis identified 12 FLT3-ITD cases (size range: 24–444 bp) and 16 wild-type cases. Concordance analysis using Cohen's kappa coefficient yielded a value of 0.93, indicating strong agreement with CE and/or NGS. Two discordant samples showed a variant allele frequency of 2–4% by NGS, consistent with the assay's ~5% sensitivity limit.For TKD analysis, 6 samples were negative and 2 were mutated, with 100% concordance with CE. Following digestion, mutated samples showed three fragments, whereas wild-type samples displayed two fragments.

Conclusions. The TapeStation system provides a rapid, simple, and reliable method for FLT3 mutation analysis, requiring only 2 µL of PCR product and approximately 2 minutes per sample. Given its widespread availability in NGS laboratories, it represents a practical tool for routine screening, with high concordance compared to established methods.

Acute myeloid leukemia

A STANDARDIZED FLOW CYTOMETRIC ASSAY TO EVALUATE THE MEASURABLE RESIDUAL DISEASE IN ACUTE MYELOID LEUKEMIA AN INITIATIVE BY THE RETE EMATOLOGICA LOMBARDA

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Measurable Residual Disease (MRD) monitoring is a critical component in the management of acute myeloid leukemia (AML), to inform prognosis and to guide therapy. MRD, evaluated by multiparametric flow cytometry (MCF) assay and/or by molecular methods is used as a key endpoint indicator in clinical trials. However, assessment of MRD in AML is a technical challenge. Many efforts have been done to harmonize the various published approaches.The European LeukemiaNet MRD Working Party has promoted standardization and harmonization of MRD, providing several recommendations. Taking advantage from these recommendations, a multicenter working group of the Rete Ematologica Lombarda (REL) developed and standardized an ad hoc MCF assay for the evaluation of MRD in AML.This MCF assay is composed of two 12-colors tubes. The panel includes 5 backbone markers: CD33, CD34, CD45, CD117, HLADR, seven AML-associated aberrant immunophenotype (LAIP): CD2, CD7, CD11c, CD19, CD25, CD56 and CD123, three markers of myeloid maturation: CD13, CD11b and CD10 and three of monocytic maturation: CD64, CD4 and CD14. This panel allows to identify the largest possible number of AML phenotypic variants and all the minor bone marrow populations. It is also useful in the evaluation of the bone marrow quality, by identifying B lymphocyte precursors and plasma cells, by the expression of CD10, CD19 and CD38, and of basophils, mast cells and dendritic cells, by the expression of CD123, CD117 and HLADR.Spiking experiments were performed to obtain a LOQ value of 0.01%. Ten bone marrow samples and four External Quality Assessment exercises (samples from UK NEQAS MRD scheme) were analyzed in parallel by in-house methods and REL assay with a concordance of 100%. The results of UK NEQAS samples, analyzed by the REL assay, were compared with the consensus mean of over 100 participants.In conclusion, although these data are preliminary, the standardized REL MRD assay seems endowed with high diagnostic accuracy, high sensitivity, a high degree of correlation with the in-house methods and is fully applicable to the UKNEQAS MRD External Quality Assessment exercises.

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Acute myeloid leukemia

A PHASE 3 STUDY OF REVUMENIB IN COMBINATION WITH INTENSIVE CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED *NPM1*-MUTATED ACUTE MYELOID LEUKEMIA (REVEAL-ND NPM1): TRIAL IN PROGRESS

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Background. There are no approved targeted therapies for newly diagnosed (ND) acute myeloid leukemia (AML) harboring a nucleophosmin-1 mutation (*NPM1*m), which occurs in ~30% of ND adult AML cases. In *NPM1*m AML, the NPM1m/XPO1 protein complex binds to DNA to sustain the interaction of menin and wild-type KMT2A that drives upregulation of *HOX/MEIS* gene expression, resulting in hematopoietic differentiation arrest and leukemogenesis. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy showed clinically meaningful response rates and was generally well tolerated in relapsed/refractory *NPM1*m AML. Standard AML treatment for younger, non-frail adults is based on intensive chemotherapy (IC) regimens and hematopoietic stem cell transplant (HSCT). The addition of revumenib to standard IC may improve treatment responses in the ND setting. This study is designed to assess the safety and efficacy of revumenib in combination with IC in pts with ND *NPM1*m AML.
Methods. REVEAL-ND NPM1 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT07211958). Eligible pts are ≥12 years of age, weigh ≥40 kg, and have treatment-naive ND AML with locally determined (centrally confirmed) *NPM1*m. Pts will be randomized 1:1 to revumenib or placebo in combination with IC. Induction consists of 1 to 2 cycles of revumenib or placebo (dosed orally) alongside IC with cytarabine and daunorubicin or idarubicin (dosed intravenously). Consolidation consists of 1-3 cycles of revumenib or placebo plus cytarabine. HSCT may be performed after initial induction or consolidation. Treatment with revumenib or placebo monotherapy will continue for ≤2 years, with long-term follow-up until death, withdrawal of consent, or study closure. Dual primary endpoints are event-free survival and measurable residual disease-negative complete remission (CR) in the bone marrow. A key secondary endpoint is overall survival. Additional investigator-assessed endpoints include CR rate, composite complete remission (CRc) rate, overall response rate, duration of response (CR, CRc), safety, and quality of life. Overall, ~468 pts will be enrolled. As of April 30, 2026, the study is open to enrollment.©2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting. All rights reserved.

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Acute myeloid leukemia

ORAL AZACITIDINE AS BRIDGING THERAPY FOR INTERMEDIATE/HIGH-RISK AML PATIENTS AWAITING ALLO-HSCT: A SINGLE-CENTER EXPERIENCE

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Background. Delays in performing allogeneic hematopoietic stem cell transplantation (allo-HSCT), often due to donor unavailability or patient-specific clinical factors, significantly increase the risk of relapse in patients with intermediate/high-risk acute myeloid leukemia (AML). Given that both the quality of complete remission (CR) and the timing of the transplant are critical determinants of clinical outcomes, implementing a standardized bridging strategy during these intervals is vital. This report evaluates the safety and efficacy of oral azacitidine as a bridging therapy between the final consolidation cycle and allo-HSCT in patients with AML in CR.

Methods. From July 2024 to October 2025, 11 patients (median age 48, range 29–67; 6 males, 5 females) with intermediate/high-risk AML (ELN 2022) received oral azacitidine during allo-HSCT delays. Inclusion criteria: hematological CR, off therapy for >2 months post-second consolidation, and temporary donor unavailability or clinical issues. Azacitidine was administered at 300 mg/day for 14 days per cycle.

Results. Unrelated donor unavailability was the primary cause of delay (64% of cases). In this cohort, 7 (64%), 2 (18%), and 2 (18%) patients received 1, 2, or >2 cycles, respectively. At baseline, 6/11 (54%) were in MRD-positive CR and 5/11 (45%) were FLT3-mutated. Excluding one patient who became ineligible due to frailty, 10/11 (91%) were evaluable: 9/10 (90%) underwent allo-HSCT in hematological CR, 4 of whom (44%) were MRD-negative. All patients who were MRD-negative before bridging maintained this status until allo-HSCT. The median time from start of azacitidine to allo-HSCT was 2.9 months (95% CI: 2.36–3.43). No grade ≥2 adverse events (CTCAE) occurred. With a median follow-up of 15.13 months (IC 13.03-17.22), DFS and OS post-allo-HSCT were 77.8% and 90.9%, respectively.

Conclusions. Oral azacitidine as a bridging therapy to allo-HSCT in intermediate/high-risk AML patientsis feasible and appears effective in maintaining hematological and molecular CR, including in FLT3-mutated cases. No patients were excluded from transplant due to azacitidine-related adverse events. Although our experience is limited to a small series, these data are encouraging for the use of oral azacitidine when allo-HSCT is delayed.

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Table 1: Cause of Bridging Therapy

Patient Id/UPN	Cause of bridging therapy Donor/Patient	Days between last CHT and allo-HSCT*	N of oral Azacitidine cycles
1/229.1	Temporary Unavailability/IFI	111	1
2/237.1	Multiple donors' unavailbility /-	92	1
3/NA	- /E. coli spondylodiscitis, IFI	*567	7
4/242.1	Temporary Unavailability/-	109	1
5/249.1	Temporary Unavailability/-	106	1
6/250.1	Temporary Unavailability/-	330	1
7/263,1	-/IFI	138	2
8/267,1	First unrelated donor ineligibility/-	181	2
9/274,1	-/Fungal skin infection	135	1
10/in progress	No donors identification/-	*158	4
11/278.1	-/IFI	118	1

Legend: Id= Identification; UPN= Unique patient number; Invasive Fungal Infection; NA= Not Applicable; * days to last follow up

Myelodysplastic syndromes

INFLAMMATORY BURDEN, COMORBIDITIES AND FUNCTIONAL STATUS MAY REDEFINE CLINICAL RISK IN LOW-RISK MYELODYSPLASTIC SYNDROMES: A REAL-LIFE APPLICATION OF TRIPLE A AND TRIPLE A+ MODELS

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Background. Low-Risk Myelodysplastic syndromes (LR-MDS) frequently show clinical heterogeneity. Since most patients (pts) are often elderly and with comorbidities we evaluated the applicability of ET-derived risk models [TripleA (AAA: age-ANC-ALC) and AAA+ (+monocytes/clinical variables: hypertension/arterial thrombosis)], to refine clinical risk categories.

Methods. We retrospectively analyzed 59 pts with LR-MDS (WHO/ICC 2022), followed at our Centre from 1996 to 2025 [M/F:34/25), median age at diagnosis: M 70.9yrs (r:45-90) and F 65.1yrs (r:29-91). AAA and AAA+ scores were calculated on CBC- and host-related parameters; inflammatory status was assessed by neutrophil-to-lymphocyte ratio (NLR).

Results. Most pts had MDS with low blast count (78%); comorbidities were: hypertension (69%), vascular disease 24%, (arterial thrombosis 86%). A great proportion of pts (91%) had lower IPSS-R risk (36% and 42% reclassification according to IPSS-RA and IPSS-M respetively). AAA distributed pts across all risk groups (71% low-intermediate, 29% high-risk) whereas AAA+ increased the high-risk allocation (29% vs 69.5%, p<0.000001; 85% of IPSS-R low-risk resulted high AAA+). Across AAA groups, increasing risk was associated with older age (p<0.001), higher comorbidity burden (CCI, p=0.0003), reduced functional status (ADL, p<0.001), and higher inflammatory profile (NLR, p=0.038). As for AAA+ application, significant differences were observed in age (p<0.001), comorbidity burden (CCI p<0.001; CIRS p=0.01), functional status (ADL p<0.001), and inflammatory profile (NLR p=0.03). AAA+ score correlated with AAA (ρ=0.72), CCI (ρ=0.67), inversely with ADL (ρ=−0.71), and moderately with both NLR (ρ=0.43) and CIRS (ρ=0.41) (all p≤0.001) (Table 1). ECOG status was not discriminatory for both scores. Lastly, ESA loss of response clustered in AAA+ high-risk. Patients with higher AAA+ due to arterial disease were not high IPSS risk, supporting clinical vulnerability beyond biological risk.

Conclusions. Integration of clinical variables into AAA+ model modifies risk stratification toward higher risk categories. Data extrapolated from comorbidity burden, functional status, and inflammation might support the validation of integrated prognostic models beyond traditional scoring systems and will be helpful in defining a subgroup of pts with low biological risk but increased clinical vulnerability.

TABLE 1

A	Clinical Data according to triple A score				
Parameter	**Low (n=4)**	**Int-1 (n=26)**	**Int-2 (n=12)**	**High (n=17)**	**P value**
Age, median (IQR)	41.5 (37–44)	63 (59–66.5)	78 (75–79.5)	79 (77–84.3)	**<0.001**
CIRS, median (IQR)	4 (3–5)	7.5 (5–10)	8 (5.5–9)	7 (6–10)	0.14
CCI, median (IQR)	2.5 (1.8–3)	4 (3–5)	5 (4–5.5)	6 (5–7)	**0.0003**
ADL, median (IQR)	95 (95–96)	85 (76–95)	70 (60–77.5)	65 (60–70)	**<0.001**
ECOG ≥2, n (%)	0 (0%)	3 (11.5%)	2 (16.7%)	1 (5.9%)	0.70
NLR, median (IQR)	1 (1–1.5)	1 (1–2.75)	3 (2–3)	2.5 (2–3)	**0.038**
B	**Clinical Data according to triple A+ score**				
Parameter	**Low (n=4)**	**Intermediate (n=15)**		**High (n=40)**	**P value**
Age, median (IQR)	48.5 (42.2–55.2)	60 (53–64)		77 (69–79)	**<0.001**
CIRS, median (IQR)	5 (4.5–6.8)	5 (3.5–8)		8 (6–10)	0.01
CCI, median (IQR)	3 (2.8–3.2)	3 (2–4)		5 (5–6)	**<0.001**
ADL, median (IQR)	95 (95–96.2)	95 (87.5–100)		65 (60–75)	**<0.001**
ECOG ≥2, n (%)	0	2 (13%)		6 (15%)	NS
NLR, median (IQR)	1 (1–1)	1 (1–3)		2 (2–3)	0.03

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Myeloproliferative Neoplasms

BASELINE PREDICTORS OF SURVIVAL AND SPLEEN RESPONSE IN RUXOLITINIB-TREATED MYELOFIBROSIS: DEVELOPMENT OF THE RUXOLITINIB-PROGNOSTIC SCORING SYSTEM IN A REAL-WORLD COHORT

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Background. In Myelofibrosis (MF), currently, there is a lack of baseline tools specifically tailored to predict outcomes upon JAKi initiation, as the RR6 score provides post-6-month-treatment guidance.

Aims. To evaluate the rate of IWG-MRT defined-SR and OS of a real-life RUX-treated MF cohort and to identify baseline clinical factors as predictors of SR and OS.

Methods. We analyzed a single-center cohort of 235 JAKi naïve RUX-treated MF patients (pts). Eligibility was based on national indications. For survival analysis pts undergoing allo-HSCT were censored at transplant date.

Results. Median age at RUX-start was 65.9 years. PMF accounted for 109 cases, SMF for 126. After a median follow-up of 66.5 months, the overall SR rate was 49.8%, with 93 deaths (39.6%) and an estimated cohort median OS of 82.5 months.Multivariate analysis identified these baseline factors as independent predictors of shortened OS: age ≥68 years (HR 2.94), BM Fibrosis Grade 3 (HR 2.41), anemia (M<11 g/dL, F<10 g/dL) (HR 2.41), PLTs < 150×10^9/L (HR 2.27), PB Blasts 1–2% (HR 2.23) and ≥3% (HR 4.05). The R-PSS was developed by assigning weighted points to the identified predictors, and pts were classified into four distinct risk categories: Low (0-2), Int-1 (3-5) HR 6.77 (95% CI 2.51–18.26, p<0.001), Int-2 (6-7) HR 15.42 (95% CI 5.66–41.97, p<0.001) and High (≥8) HR 61.89 (95% CI 22.45–170.57, p<0.001). Internal validation via bootstrapping (1000 samples) confirmed the robustness of the model, with p=0.001 for all risk tiers. The R-PSS demonstrated a higher C-index (0.807) compared to both baseline DIPSS (0.737; p=0.004) and RR6 score (0.735; p=0.004) and achieved the lowest AIC (696.1 vs 737.0 for RR6 and 758.7 for DIPSS). At 60 months, the R-PSS significantly improved the accuracy of risk assignment over DIPSS by 50.3% (NRI 0.503, P=0.003) and over RR6 by 39.9% (NRI 0.399, P=0.011), as well as model's overall predictive power by 17.2% over DIPSS (IDI 0.172, p<0.001) and by 20.0% over RR6 (IDI 0.200, p<0.001).Interestingly, R-PSS showed a high accuracy in predicting the absence of overall SR, with an AUC of 0.772, superior to the DIPSS (0.732) and statistically non-inferior to the RR6 score (0.817, p=0.09).

Conclusions. RUX remains an effective standard of care for MF. In this context, the clinically-based tool R-PSS may help in identifying pts at high risk of treatment failure, allowing optimal patient selection for novel therapies and/or allo-HSCT referral soon after RUX-start.

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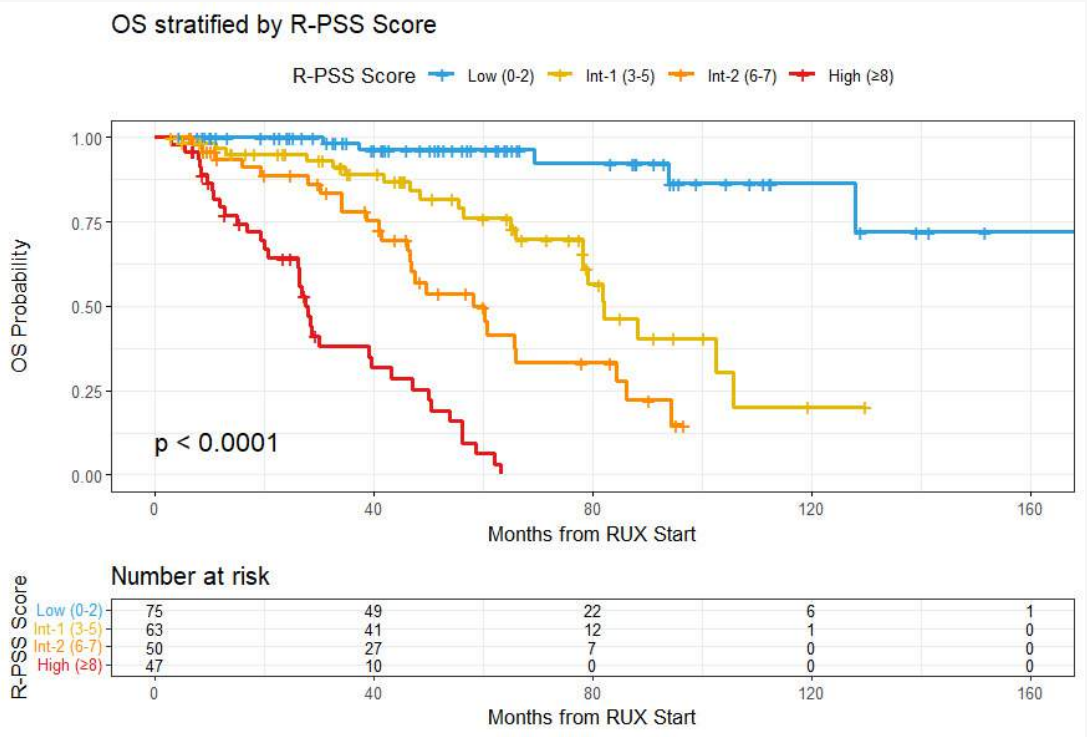

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Myeloproliferative Neoplasms

EARLY DYNAMICS OF THE SYSTEMIC INFLAMMATION RESPONSE INDEX PREDICT OUTCOMES IN MYELOFIBROSIS PATIENTS TREATED WITH RUXOLITINIB

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Background. Chronic inflammation is a hallmark of MF pathogenesis. Conventional prognostic scores do not consider the systemic inflammatory state. However, inflammatory biomarkers represent robust candidates for refining risk stratification and predicting clinical outcomes. Hence, monitoring the early dynamics of the SIRI during RUX may help to identify MF patients at higher risk of treatment failure and poor survival.

Methods. In this single-center retrospective study, we analyzed 235 consecutive JAKi-naïve MF patients treated with RUX from 2011 to 2026. Eligibility to RUX was based on national guidelines. SIRI was calculated at RUX-Start and at 6 months using the formula: (Neutrophils x Monocytes)/Lymphocytes.

Results. Median age at RUX-start was 65.9 years, with 52.8% males. PMF accounted for 109 (46.4%) cases, SMF for 126 (53.6%). After a 66.5-month median follow-up, the overall SR rate was 49.8%, with 93 deaths (39.6%) and a whole cohort median OS of 82.5 months.Baseline SIRI values did not correlate neither with aggressive disease phenotype nor with poorer outcomes. Nevertheless, 6-month SIRI was significantly associated with shorter OS [HR 1.05 (95% CI, 1.02-1.08) p<0.001]. Univariate and multivariate analysis showed that an increase of 6-month SIRI from baseline [HR 2.07] and a 6-month SIRI value ≥ 5 [HR 2.35] (both cut-offs identified by restricted cubic splines), significantly predicted a shorter OS. Therefore, patients presenting neither of these two 6-month SIRI parameters (Low Risk) presented a median OS of 102.5 months. Patients with only one 6-month SIRI factor (Int Risk) had a median OS of 63.0 months [HR 2.04 (95% CI, 1.28-3.27) p=0.003], while those with both factors (High Risk) showed a median OS of 34.0 months [HR 4.99 (95% CI, 2.71-9.19) p<0.001]. Furthermore, patients with one or both risk factors were significantly less likely to achieve SR (p<0.001) and presented a more aggressive disease phenotype, as evidenced by their higher 6-month DIPSS scores (p<0.001).

Conclusions. Baseline SIRI fails to predict outcomes in patients starting RUX, likely because most candidates present with a high inflammatory burden. Conversely, 6-month SIRI dynamics, with the failure to reduce inflammation and/or high inflammatory state, may help to identify patients with suboptimal drug response, significantly poorer survival and need to switch to a second line treatment. These data may integrate the predictive strength of RR6 prognostic score.

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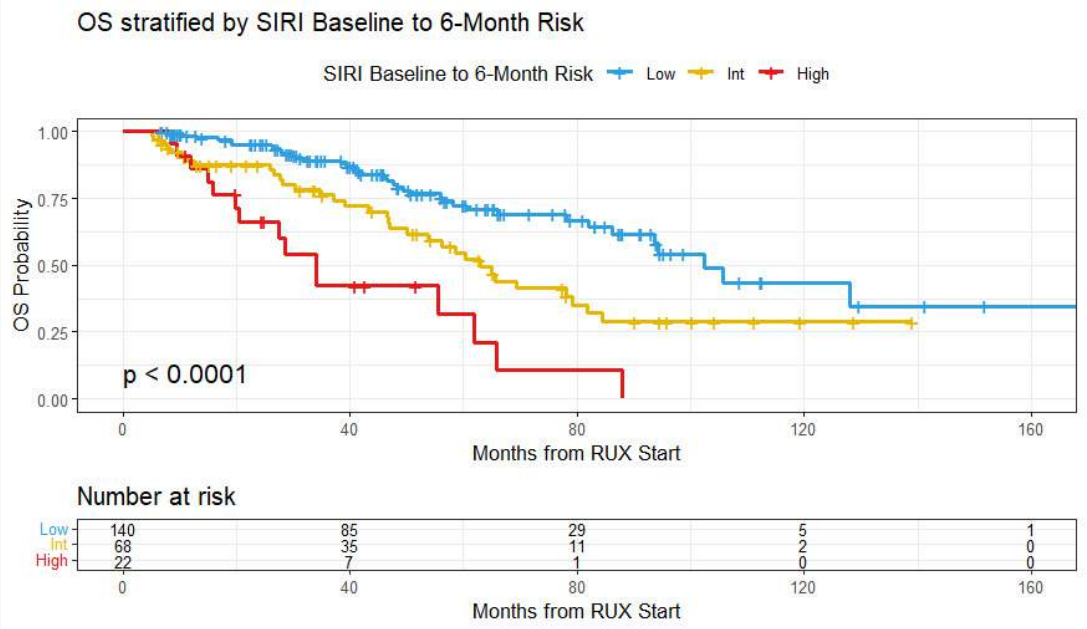

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Myeloproliferative Neoplasms

PRESENTATION AND LONG-TERM OUTCOMES IN ONE THOUSAND PATIENTS WITH POLYCYTHEMIA VERA

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Background. Polycythemia vera (PV) is associated with thrombosis, myelofibrotic (MF) and blast-phase (BP) progression, and reduced survival. Identification of clinical predictors and the role of *JAK2* V617F variant allele frequency (VAF) may improve risk stratification.

Aims. To characterize clinical features, long-term outcomes, and predictors of vascular events, disease progression, and survival in a contemporary PV cohort.

Methods. We retrospectively analyzed 1,000 PV patients followed at the Center for Research and Innovation in MPN (CRIMM), University of Florence, AOU Careggi, from 1980-2026, with median follow-up of 7.6 years. Diagnoses followed 2022 ICC criteria. Predictors were assessed using univariate and multivariable Cox regression; cumulative incidence (CI) of arterial (AT) and venous thrombosis (VT), MF, and BP was estimated with death as competing event.

Results. Median age was 61 years; 57% were male and 63% had cardiovascular (CV) risk factors. *JAK2* V617F was detected in 99% (median VAF 40%), while *JAK2* ex 12 mutations occurred in 1% and were associated with younger age (53 vs 61 years; p=0.04), lower leukocytes (7.3 vs 9.8×10^9/L; p=0.02) and platelets (300 vs 484×10^9/L; p=0.01). Splenomegaly, G1 fibrosis, and abnormal karyotype occurred in 30%, 25%, and 12%, respectively, similar between *JAK2* V617F and ex 12 cases. According to conventional thrombotic stratification, 63% were high-risk and showed higher thrombotic incidence, confirming score validity. Thromboses occurred in 23% at diagnosis (arterial 12%, venous 11%) and during follow-up in 9% and 8%, respectively. The CI of AT was 9%, 15%, and 18%, and VT 8%, 14%, and 17% at 10, 20, and 30 years. Age ≥60 years and CV risk factors independently predicted AT (HR 1.7; p=0.04 and HR 2.0; p=0.01), while VAF ≥50% predicted VT (HR 2.4; p<0.01). Overall, 16% progressed to MF and 3% to BP. The CI of MF was 11%, 33%, and 54%, and BP 1%, 4%, and 12% at 10, 20, and 30 years. Neutrophil-to-lymphocyte ratio (NLR) >3.3 and VAF ≥50% independently predicted MF (HR 3.4; p=0.02 and HR 2.6; p=0.02), while leukocytes $>15\times10^9$/L predicted BP (HR 3.3; p<0.01). Age ≥60 years (HR 4.8; p<0.01) and leukocytes $>11\times10^9$/L (HR 2.3; p<0.01) predicted inferior survival.

Conclusions. Clinical variables and *JAK2* V617F VAF significantly influenced thrombosis, progression, and survival. VAF ≥50% identified patients at increased risk of adverse outcomes (Fig.1), supporting its integration into clinical risk stratification.

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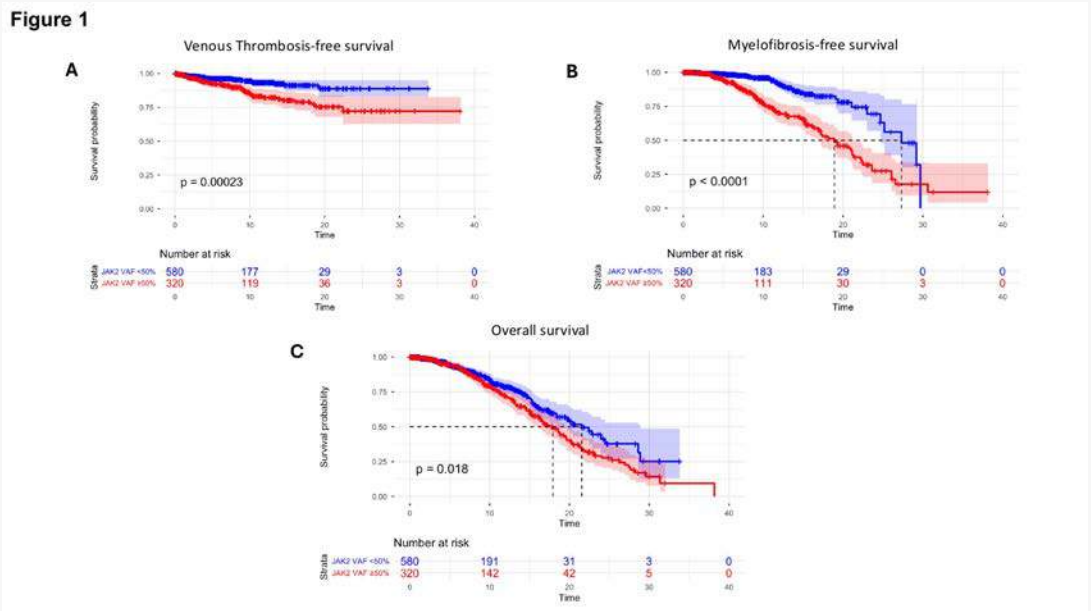
Figure 1



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Chronic myeloid leukemia

MORE THAN 40% OF CHRONIC-PHASE CML PATIENTS STARTING TYROSIN KINASE INHIBITORS ACHIEVE AND MAINTAIN A DURABLE TREATMENT FREE REMISSION AND CAN BE CONSIDERED POTENTIALLY CURED: A REAL LIFE EXPERIENCE FROM A SINGLE CENTER

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Background. Few data in literature are available about how many pts starting TKIs for a newly CP-CML diagnosis reach the criteria to discontinue TKIs.
Aim. to evaluate how many CP-CML pts starting TKIs in our center achieve a durable TFR and are potentially cured.
Methods. We evaluated all consecutive CP-CML pts treated with TKIs in our center in TKIs era, from 2000 to the end of 2025. The main criteria for 1st TKI discontinuation (DISC) were at least 5 years (y) of TKI therapy and at least 2 y of sustained deep molecular response (sDMR).Even for 2ndTKIs DISC a sDMR of at least 2 y was required.
Results. The total number of CP-CML pts treated with TKI was 332, 19 of them have received IFN before. Sixty two(19%) pts died- median age 83 y(58-95); 6 pts were lost at follow up (f. up); 264 pts are presently in TKI treatment or in TFR. Our analysis focuses on pts with a f. up of 5 y or more, that are 222/332. Among these 222 pts, 145(65%) reached TFR criteria and discontinued TKIs (TFR group), while the remaining 77(35%) didn't reach TFR criteria and continued treatment (no-TFR group). The characteristics of the 2 groups are summarized in table 1. In univariate analysis, they showed statistically different features, in detail: pts in TFR group had a longer f. up, better overall survival, a higher percentage of e14a2 transcript type compared to e13a2, a higher percentage of frontline 2GTKI. In the no-TFR group more pts needed TKIs beyond 1st line therapy and more pts were treated with reduced TKIs dosage. Between "TFR group" and "no-TFR group" there were no significant differences of age at the moment of CML diagnosis and of the 3 different Sokal risk score category. At the last contact, 99/145 pts (68%) in TFR group remain in TFR, that is 99/222 (45%) of the pts with a f. up of at least 5 y. Fourteen out of 99 pts reached a persistent TFR after a 2nd TKI DISC attempt. In the TFR group, median f. up from CML diagnosis to the last contact was 157(64-460) months (mo), median f. up from the start of TKIs treatment 100 mo(60-266), median f.up from TKIs DISC 45 mo (4-138) -for pts with 2nd TKI stop we considered follow up from 2nd DISC attempt.
Conclusions. According to our experience, more than 40% of newly diagnosed CP-CML pts starting TKIs can be considered potentially cured because they reach and maintain a durable TFR. Frontline 2GTKIs, full dosage TKIs treatment and the presence of the e14a2 transcript type are associated to a higher probability of achieving this goal

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	TFR group	no TFR group	p
Pts, n	145	77	
M/F	66/79	42/35	0.2
Age at CML diagnosis, years: median (range)	52 (13-80)	58 (27-82)	0.09
Follow up from CML diagnosis to the last contact, months: median (range)	157 (60-460)	109 (37-322	0.00021
Died pts, n.	17	20	0.0084
Sokal score risk • Low, n • Intermediate, n • High, n • Not available, n	 50 41 23 31	 16 22 13 26	0.7
Type of transcript • e13a2, n • e14a2, n • e14a2+a13a2, n • Atypical/not available, n	 42 97 2 4	 39 36 1 1	0.0020
Frontline TKI • Imatinib, n • 2GTKI, n	 93 52	 61 16	0.022
Interferon before TKI, n	16	3	0.081
Pts treated with ≥2nd line TKI	50	39	0.0021
TKI dosage (before TKI discontinuation or at last follow up for pts in no TFR group) • full dosage • reduced dosage	 73 71	 15 62	0.0001

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Myeloproliferative Neoplasms

COMPARISON OF CONVENTIONAL KARYOTIPE AND MOLECULAR KARYOTYPE BY REPROSEQ PGS KIT, A HELPFUL TOOL IN TP53 GENE LOSS IDENTIFICATION

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Introduction. Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by bone marrow fibrosis, extramedullary hematopoiesis and driver mutations in the JAK2, MPL, and CALR genes. Additional mutations may involve myeloid genes such as TET2, ASXL1, EZH2, SRSF2 and SF3B1. The TP53 gene is mutated in approximately 10% of MF cases. Double-hit TP53 mutations negatively impact prognosis and overall survival. A double-hit mutation is defined as the involvement of both alleles, which may occur as two single nucleotide variants (SNVs) or as one SNV combined with deletion of the second allele. Identification of double-hit TP53 mutations can be achieved through NGS gene panels and karyotype analysis. However, due to bone marrow fibrosis, karyotype analysis is not always feasible because of punctio sicca or an insufficient number of cells. Emerging methods, such as NGS-based molecular karyotyping, are now available and may help define the mutational status of these patients (pts).

Methods. We analyzed the mutational status of 117 MF pts by NGS gene panel, and performed molecular karyotyping (MK) with the ReproSeq PGS kit. We then compared the results of 74 conventional karyotypes (CK) with MK to evaluate the performance of ReproSeq. We also confirmed TP53 gene loss by ddPCR.

Results. In our cohort, the most frequently mutated genes were JAK2 (81 pts), CALR (34 pts), ASXL1 (27 pts), and TET2 (22 pts). Only five pts harbored TP53 mutations as detected by NGS, and conventional karyotype data were available for only two of them. Therefore, we performed molecular karyotyping on the remaining three samples and identified one patient harboring a TP53 gene deletion, which was subsequently confirmed by ddPCR assay. In summary, the most representative chromosomal alteration was the duplication of chr8 (8p23.3q24.3), found in 5 pts, followed by chr9 duplication (9p24.3q34.3) found in 4 pts. When comparing MK with CK we obtained a concordance of 84%. In detail, 9 patients were positive by both techniques, 9 were positive only by CK, 3 were positive only by MK, and 53 were negative by both.

Discussion. ReproSeq PGS kit is not intended to detect chromosomal balanced translocations ad it requires a small dna amount (0.5ng), which may explain its lower sensitivity vs CK. Yet, increasing dna input may improve sensitivity to match CK. It also provides karyotype data and TP53 mutational status from peripheral blood DNA, offering an alternative when CK is not feasible.

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Myeloproliferative Neoplasms

REAL-WORLD EFFECTIVENESS OF MEPOLIZUMAB IN PATIENTS WITH HYPEREOSINOPHILIC SYNDROME: A SINGLE-CENTER EXPERIENCE

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Background. Hypereosinophilic syndromes (HES) comprise a broad spectrum of rare disorders characterized by persistent hypereosinophilia [i.e., an absolute eosinophil count (AEC) >1.5 $\times 10^9$/L] associated with eosinophil-mediated organ damage and/or dysfunction. Although systemic oral corticosteroids (OCS) are the conventional first-line approach, with up to 85% of patients (pts) experiencing a positive response within one month of treatment, a substantial proportion of pts suffer from significant side effects attributable to OCS or treatment resistance. Mepolizumab (MEP), an anti–IL-5 monoclonal antibodies, is the only biologic approved for the treatment of pts with inadequately controlled HES in the absence of identifiable non-hematologic secondary cause.

Aim and Methods. To evaluate the efficacy and safety profile of MEP in a real-world series of 12 HES pts who initiated treatment between March 2024 and February 2026.

Results. Main clinical-laboratory features of the pts are shown in Table 1. In detail, no cytogenetic or molecular abnormalities were detected, with the sole exception of a variant of unknown significance in the KIT gene in one pt, which led to a diagnosis of idiopathic HES in 7 (58.4%) pts, while the remaining cases were classified as lymphocyte-variant HES (L-HES).All cases had previously been treated with OCS for a median time of 1.9 years (range, 0.2–16.6). Despite this, at MEP start, 4 (33.3%) pts still had an AEC >1.5 $\times 10^9$/L.MEP was administered according to the standard schedule of 300 mg subcutaneously every 4 weeks. After a median time from treatment initiation of only 22.5 days (range, 18–37), all pts achieved a sustained AEC normalization, allowing OCS discontinuation in 75% of the cases. No treatment-related adverse events were reported.After a median follow-up of 8.5 months (range, 1.4–24.5), 10 (83.3%) pts obtained a clinical response and were still receiving active treatment with MEP, with no significant differences between subgroups (including L-HES). Only 2 (16.7%) pts discontinued MEP, one for personal reasons and the other due to an inadequate clinical response (a pt treated with L-HES who continued to suffer from recurrent angioedema episodes, despite persistent AEC normalization).

Conclusions. MEP confirmed its high efficacy, particularly in terms of rapid hematologic response, and excellent tolerability even in a real-world setting, with consistent activity in different HES subtypes and a marked steroid-sparing effect.

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Table 1. Clinical-laboratory features of the patients.

	Patients n. 12
Male/female	3/9
Age at HES diagnosis, median (range)	50.9 (39.2 – 78.2)
HES subtype, n (%)	
- Idiopathic	7 (58.4)
- Lymphocyte-variant	5 (41.6)
AEC (x10^9/L), median (range)	4.6 (1.91 – 10.78)
Eosinophils (%), median (range)	38.8 (13.0 – 68.9)
Hb (g/dL), median (range)	12.9 (11.5 – 15.0)
WBC (x10^9/L), median (range)	13.8 (7.34 – 34.3)
PLT (x10^9/L), median (range)	284 (178 – 388)
LDH (IU/L), median (range)	241 (179 – 337)
Total IgE (kUA/L), median (range)	45 (5 – 4631)
Serum tryptase (mcg/L), median (range)	7 (3 – 13)
CRP (mg/L), median (range)	2.9 (0.6 – 43.8)
Beta2microglobulin (mg/L), median (range)	2.1 (1.6 – 3.8)
Constitutional symptoms, n (%)	7 (58.3)
Organ involvement, n (%)	
- Gastrointestinal	3 (25.0)
- Heart	2 (16.7)
- Skin	5 (41.6)
- Pulmonary/Upper respiratory	2 (16.7)

Abbreviations: HES, hypereosinophilic syndromes; AEC, absolute eosinophil count; Hb, hemoglobin; WBC, white blood cells; PLT, platelets; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Myeloproliferative Neoplasms

INTEGRATION OF SYSTEMIC INFLAMMATION INTO DIPSS IMPROVES RISK STRATIFICATION IN MYELOFIBROSIS: DEVELOPMENT OF THE DIMOL SCORE

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Background. Chronic inflammation is a key driver of myelofibrosis (MF) pathogenesis, contributing to clonal evolution, bone marrow fibrosis, constitutional symptoms, and cardiovascular complications. However, widely used prognostic models such as DIPSS and MYSEC-PM do not incorporate inflammatory status. Emerging evidence suggests that systemic inflammatory indices—including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic inflammation response index (SIRI)—may predict survival in MF.

Aims. To evaluate the prognostic impact of inflammatory indices in MF patients treated with ruxolitinib and to develop an inflammation-integrated prognostic model.

Methods. We retrospectively analyzed 166 consecutive MF patients (98 primary MF; 68 secondary MF) treated with ruxolitinib at the Hematology Units of Pisa and Catania (Italy) between 2013 and 2023. Diagnosis was established according to WHO 2008/2016 criteria. Inflammatory indices (NLR, MLR, PLR, WLR, SII, SIRI) were calculated at diagnosis. Overall survival (OS) was estimated using Kaplan–Meier analysis. Variables significant in univariate Cox regression were included in multivariate models. Based on independent predictors, a novel prognostic score combining DIPSS and MLR (DiMoL score) was developed.

Results. Median age was 68 years (M:F=1.2). Driver mutations were distributed as follows: JAK2V617F 76%, CALR 16%, MPL 1%. According to DIPSS, 11% were low-risk, 36% intermediate-1, 40% intermediate-2, and 13% high-risk. Median OS was 84 months; 6-year OS was 54%.In univariate analysis, OS was significantly associated with DIPSS category, age >65 years, and symptom burden, but not with gender, splenomegaly, or driver mutation. Among inflammatory markers, elevated MLR ($p<0.01$) and SIRI ($p<0.008$) were associated with inferior OS. In multivariate analysis, only MLR retained independent prognostic significance (HR 1.80, $p=0.03$).Combining DIPSS with MLR dichotomized at the cohort median (0.55), assigning 1 point for MLR ≥ 0.55 and 0 for MLR < 0.55; the DiMoL score (DIPSS + MLR) stratified patients into three risk groups with 6-year OS of 90% (low), 52% (intermediate), and 22% (high), improving discrimination compared with DIPSS alone (Figure 1-2-3).

Conclusions. Systemic inflammation, as reflected by MLR, independently predicts survival in MF patients treated with ruxolitinib. Integration of MLR into the DiMoL score refines risk stratification and identifies more homogeneous prognostic subgroups than DIPSS alone. These findings support the incorporation of simple inflammatory biomarkers into clinical practice and provide a rationale for prospective studies evaluating inflammation-targeted strategies in MF.

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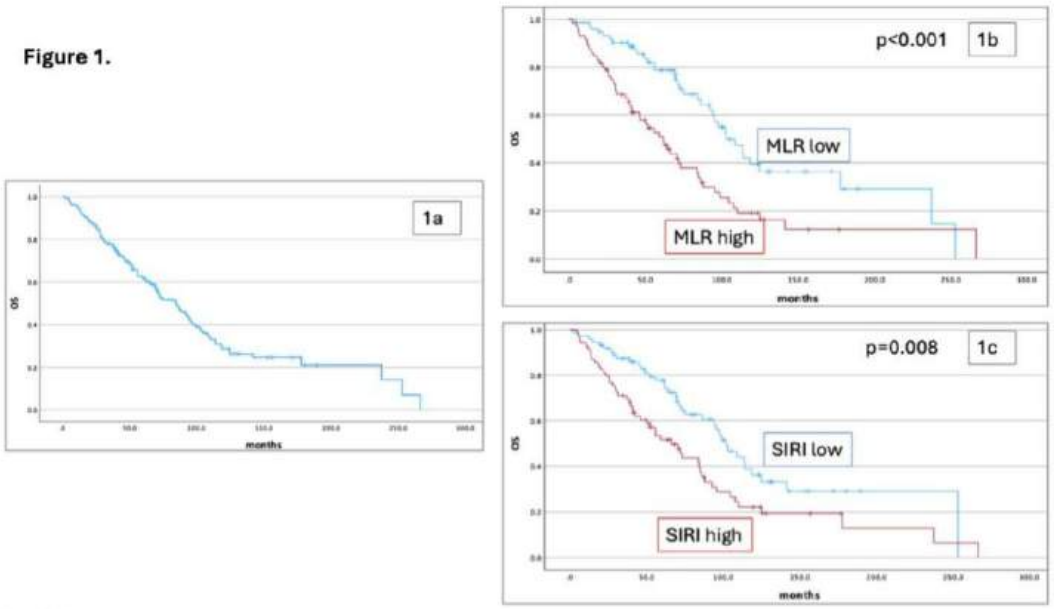
Figure 1.



LEGEND:
OS of the whole population (1a); OS according to monocyte/lymphocytes ratio (MLR) (1b), and according to Systemic Inflammation Response Index (SIRI).

Figure 2.

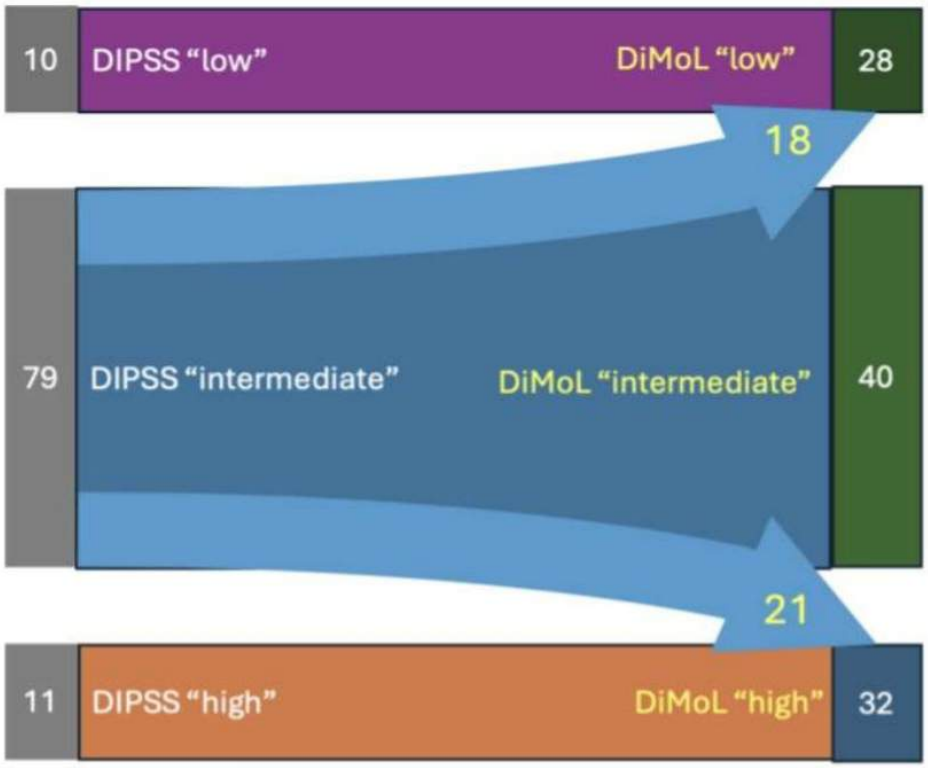
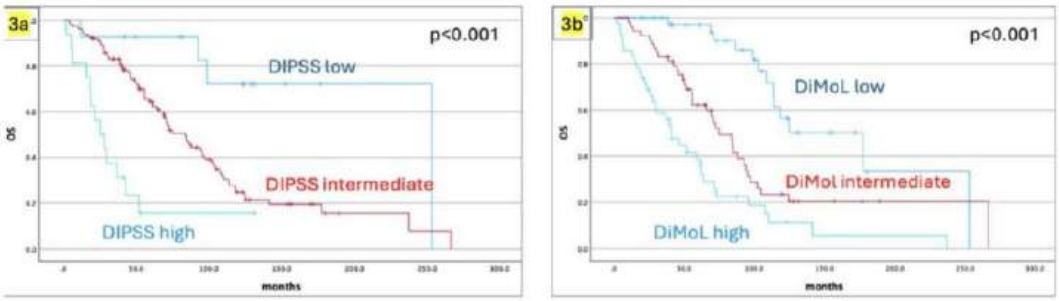


Figure 3.



Legend:

The Figure compares the OS rates according to DIPSS (3a) and DiMoL (3b) scores.

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Myeloproliferative Neoplasms

REAL LIFE OF MOMELOTINIB IN PATIENS WITH MYELOFIBROSIS: PRELIMINARY RESULTS OF MULTICENTER RETROSPECTIVE EXPERIENCE OF RETE EMATOLOGICA PUGLIESE-REP

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Introduction. Momelotinib(MOME) has shown clinical efficacy in patients with Myelofibrosis(MF), particularly in alleviating anemia and reducing transfusion dependence (TD). In this real-life retrospective analysis, we evaluated the efficacy and safety of MOME in JAK inhibitors (JAKi) naïve and exposed MF patients.

Methods. Data were collected from 8 centers of REP between July 2023 and March 2026. The primary endpoint was improvement in anemia at 12/24 weeks, according to IWG-ELN criteria. Secondary endpoints included spleen reduction, safety and transfusion independence (TI).

Results. A total of 138 patients were collected (median age 72 years). Baseline characteristics are summarized in Table1. Splenomegaly was present in 81% of patients. In JAKi exposed patients, more splenomegaly (89% vs. 53%, p=0.002) and increased LDH levels (83% vs 62%, p 0,01) were observed compared to naive patients. Median baseline Hb levels were 9.1 g/dl. 43% of patients were TD, 63% were categorized as intermediate-2/high DIPSS. The median time from MF diagnosis to MOME was 24 months(1-302).106 patients (77%) had prior exposure to JAKi (ruxolitinib 98%, fedratinib 25%).Sixty patients (43%) received concomitant erythropoietin. The median duration of MOME treatment was 5,6 months (0,5-30,8). The 12 week-overall response rate(ORR) in TD patients was 60% with 46% CR,and 70% with 63% CR in non-TD patients (p=ns).At 24 weeks of treatment CR was observed in 63% and 76% of TD and non-TD patients, respectively (p=ns).Spleen reduction was observed in 27% of patients.TI was achieved in 44% of TD patients. LDH, TD, driver or NGS mutation, DIPSS score were not predictive of responsiveness to MOME.Better response was observed in patients younger than 65 years(31% vs 4%, p 0.04). The ORR at 12 and 24 weeks was 71% and 70% in JAKi exposed patients,79% and 88% in JAKi naive patients, respectively(p=ns). At the time of last follow-up,16 deaths had occurred, mainly due to infections (n. 7) and disease progression (n. 3). Regarding safety, hematological adverse events were observed in 14% of patients.Infections were documented in 5 patients (fatal in 3 cases). At the last follow up, 83% of patients continued treatment, without differences between JAKi exposed/naive patients (p ns).

Conclusions. Although with the limitations of its retrospective nature and a short follow-up, our results confirm that MOME is effective and well-tolerated in real-world practice, in both JAKi exposed/naive patients.

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Table 1 Patient Characteristics, previous lines and baseline data prior Momelotinib start

	N= 138	JAKi exposed 106 (77)	JAKi Naive 32 (23)	P
Median age, years (range)	72 (40-88)			0,54
<= 65 years, n (%)	36 (26)	29 (27)	7 (21)	
Male, n (%)	84 (61)	65 (61)	19 (59)	0,84
Myelofibrosis subtype, n (%)				
Primary	85 (62)	65 (61)	20 (62)	
After ET / After PV	35 (25) / 12 (9)	29 (26) / 11 (10)	6 (19) / 1(3)	0,002
After MDS/MPN	6 (4)	1 (1)	5 (16)	
Driver Mutations, n (%)				
JAK2	87 (63)	67 (63)	20 (62)	0,94
CALR / MPL	29 (19) / 7 (6)	22 (20) / 4 (4)	5 (16) / 3 (9)	0,57
Trriple negative	20(17)	15 (14)	5 (16)	0,83
Additional NGS Mutations, n (%)	*Available in n=41 (30)*	*28 (26)*	*13 (40)*	0,12
ASXL1	10 (24)	5 (20)	5 (38)	0,17
EZH2 / SRSF2	3 (7) / 1 (2)	2 / /	1 / 1	//
No additional mutations	30 (75)	19 (71)	11 (85)	0,33
DIPSS, n (%)				
Intermediate-1	36 (26)	26 (25)	10 (32)	0,08
Intermediate-2 / High	87 (63) / 14 (10)	65 (61) / 14 (13)	22 (69)) / //	
Cytogenetics, n (%)	*Available in n=53 (38)*	41 (38)	12 (38)	
Unfavorable / Very high	4 (3) / 2 (2)	3 / 2	1	0,90
Median previous Lines, (range)		1 (1-2)		
Prior Therpies, n (%)				
Ruxolitinib		104 (98)		
Fedratinib		26 (25)		
Hydroxyurea		6 (5)		
Concomitant Therapies, n (%)				
Erythropoietin	60 (43)	44 (42)	16 (50)	0,39
Hydroxyurea / Iron chelator	34 (25) / 25 (18)	24 (23) / 18 (17)	10 (31) / 7 (22)	0,33 / 0,52

Table 2 Baseline data prior Momelotinib start according to JAKi pre treatment

Baseline data	N= 138	JAKi exposed 106 (77)	JAKi Naive 32(23)	p
Median Hemoglobin, g/dl (range)	9,0 (5,5-16)	9 (5,6-16)	9 (5,5-11,6)	
Hb<10 g/dl, n (%)	120 (87)	91 (86)	29 (90)	0,6
Median platelets,x10^9 cells /L (range)	180 (12-1693)	170 (12-1693)	235 (26-870)	
PLTs<50x10^9 cells /L, n (%)	17 (12)	13 (12)	4 (12)	0,59
Costitutional syntoms, n (%)	79 (57)	57 (54)	22 (69)	0,98
Median LDH, U/L (range)	470 (95-3166)	483 (141-3166)	384 (95-1284)	
Elevated LDH, n (%)	94 (78)	76 (83)	18 (62)	0,01
Transfusion Dependent, n (%)	60 (43)	46 (44)	14 (44)	0,97
Splenomegaly, n (%)	112 (81)	95 (89)	17 (53)	
Median size spleen, cm (range)	16,7 (10-26,5)	17 (10-26)	15 (11-23)	0,002

Abbreviations: ET, Essential Thrombocythemia; PV, Polycythemia Vera; MDS/MPN, Myelodysplastic / Myeloproliferative Neoplasms; DIPSS, Dynamic International Prognostic Scoring System; JAKi, JAK inhibitor

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Myeloproliferative Neoplasms

AI-BASED SCORE VERSUS CONVENTIONAL PROGNOSTIC SCORES IN MYELOFIBROSIS: A SINGLE-CENTER VALIDATION STUDY

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Background. Accurate estimation of overall survival (OS) in myelofibrosis (MF) is essential given marked clinical heterogeneity and limited curative options beyond allogeneic hematopoietic stem cell transplantation (allo-HCT). More recently, machine learning–based tools, such as the AIPSS-MF (Artificial Intelligence Prognostic Scoring System for Myelofibrosis) and the AlloRisk stratifier for patients who undergo allo-HCT, have been proposed to enable individualized risk assessment.

Methods. We retrospectively validated these models in 95 MF patients (WHO 2016/2022 criteria) and followed at IRCCS San Raffaele, Milan. AlloRisk was assessed in 35 patients undergoing allo-HCT. To minimize transplant-related bias, comparisons between AIPSS and conventional models were performed in non-transplanted patients.

Results. Median age at diagnosis was 59 years; 51 were male. Driver mutations were JAK2V617F 64%, CALR 27%, and MPL 8%. Among 49 patients with available NGS data, 32 had ≥2 high-risk mutations. After a median follow-up of 51.5 months, 32 patients died. In non-transplanted patients, AIPSS showed better discrimination than IPSS (C-index 0.73 vs 0.71). AIPSS predicted longer OS in 75% of cases (median gain +2.7 years), most pronounced in the IPSS low-risk group (+5.4 years). Among 36 patients with molecular data, AIPSS predicted longer survival than MIPSS70 in 81% (median Δ +2.6 years), identifying heterogeneity within high-risk categories. Using a 5-year OS threshold, 17% showed discordance; for those where AIPSS predicted >5-year survival despite conventional models suggesting <5 years, the observed 5-year OS was 80%. Among transplanted patients, 71% had an AIPSS-predicted OS >5 years; those with favorable AIPSS but high AlloRisk scores showed notable early transplant mortality.

Conclusions. In this real-world MF cohort, AIPSS provided individualized and often more favorable survival estimates than conventional scores. Clinically relevant discordance, particularly around the 5-year threshold used for transplant decisions, supports a complementary role for AIPSS in refining risk stratification and timing of allo-HCT. Prospective validation in larger cohorts is warranted.

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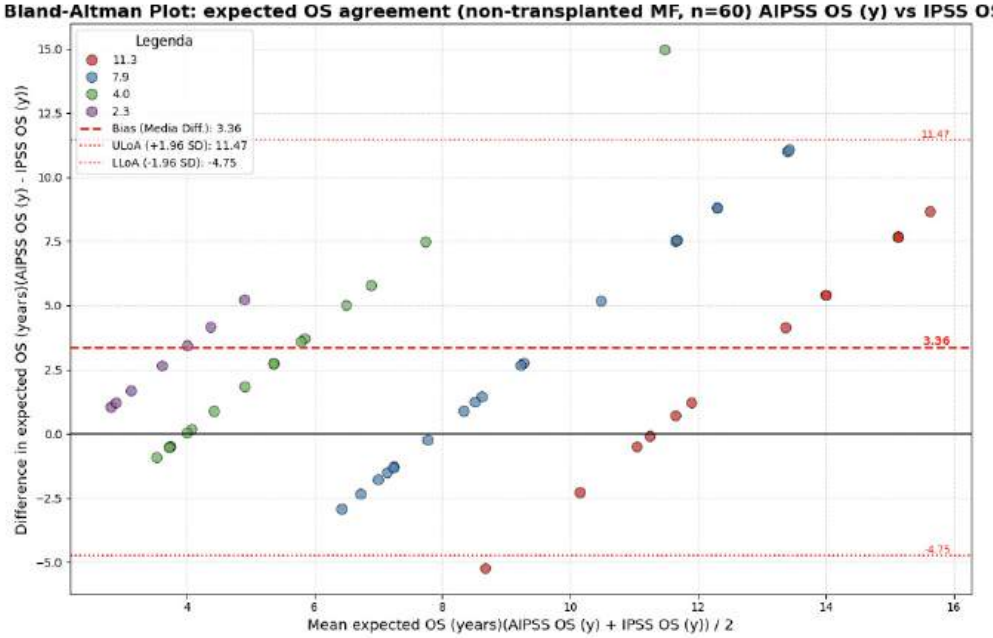

Figure 1. Bland–Altman analysis showed a positive systematic bias of AIPSS versus IPSS (mean difference +3.37 years) with wide limits of agreement (−4.73 to +11.47 years), indicating non-interchangeability of the two models at the individual level. The diagonal banding reflects the discrete nature of IPSS estimates and the continuous stratification provided by AIPSS.

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Myeloproliferative Neoplasms

OUTCOMES OF PATIENTS WITH JAK2V617F VAF ≤2% EVALUATED FOR SUSPECTED MYELOPROLIFERATIVE NEOPLASMS

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Università Politecnica delle Marche

Detection of the JAK2V617F mutation is central to the diagnosis of myeloproliferative neoplasms (MPNs). In clinical practice, a variant allele frequency (VAF) >2% is considered positive and is also used to define clonal hematopoiesis of indeterminate potential (CHIP). Current WHO/ICC recommendations advocate the use of highly sensitive methods to detect JAK2V617F when the VAF is below 1%. However, interpretation of low-level JAK2V617F positivity remains challenging, as the mutation can be detected in individuals withouthematologic disease and no validated diagnostic cut-off for MPNs has been established. Fifty-five patients evaluated for erythrocytosis (n=31) or thrombocytosis (n=24) and harboring a JAK2V617FVAF <2% were included. Median age was 64 years (range: 15–86). JAK2V617F analysis was performed on granulocyte DNA at diagnostic suspicion using quantitative PCR. At referral, median JAK2V617F VAF was 0.354% (range: 0.02–1.975), significantly higher in patients with thrombocytosis than in those with erythrocytosis (0.451% vs 0.25%, p=0.047). None of thepatients met diagnostic criteria for MPN at the time of the initial JAK2 assessment. Among patients with erythrocytosis, 4 (12.9%) were subsequently diagnosed with polycythemia vera and 1 with prefibrotic myelofibrosis. Among patients with thrombocytosis, 7 (22.5%) were diagnosed with essential thrombocythemia; CALR mutations were identified in three cases, all fulfilling ET criteria. The median time from first quantitative JAK2 assessment to MPN diagnosis was 21.1 months. Patients who later developed MPN had a higher median VAF at baseline compared with those who did not (0.532% vs 0.24%, p=0.02). Overall, 17 patients (30.9%) experienced thrombotic events, occurring a median of 4.3 months after molecular testing. Thrombotic rates were similar in patients with and without subsequent MPN diagnosis(25% vs 32.5%, p=0.57). However, patients with thrombosis had a significantly higher median JAK2V617F VAF than those without events (0.44% vs 0.23%, p=0.038). Comprehensive clinical and molecular evaluation of patients with erythrocytosis and/or thrombocytosis andJAK2V617F VAF ≤2% led to an MPN diagnosis in 21.8% of cases. Low-level JAK2V617F positivity is associated with a substantial thrombotic risk, correlated with allele burden, even in the absence of overt MPN.- Longitudinal studies are needed to refine diagnostic criteria and improve thrombotic risk stratification in this population

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Myeloproliferative Neoplasms

SHEAR-WAVE ELASTOGRAPHY FOR DYNAMIC ASSESSMENT OF SPLEEN RESPONSE IN MYELOFIBROSIS PATIENTS TREATED WITH MOMELOTINIB: A REAL-WORLD EVIDENCE

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Hematology Unit, University of Pisa

Background. In pivotal momelotinib (MMB) trials, spleen response is defined by MRI/CT-based spleen volume reduction (SVR35). While volumetric imaging represents the regulatory standard, it is not universally accessible and does not capture treatment-induced biomechanical remodeling of splenic tissue. In myelofibrosis (MF), splenic enlargement reflects complex changes in extramedullary hematopoiesis, vascular congestion, and stromal remodeling. Shear-wave elastography (SWE) enables quantitative assessment of splenic stiffness and may dynamically reflect microenvironmental modifications induced by JAK inhibition beyond mere dimensional changes.

Aims. To evaluate spleen response at 6 months in MF patients treated with momelotinib and to determine whether SWE-derived stiffness reduction correlates with anatomical spleen response, potentially serving as a dynamic surrogate imaging endpoint of treatment activity.

Methods. Twenty-three consecutive MF patients treated with momelotinib in a real-world setting were retrospectively analyzed. Spleen longitudinal diameter (cm) and stiffness (kPa) were assessed at baseline and 6 months using standardized high-resolution ultrasound with SWE performed by experienced operators. Percentage changes were calculated for both parameters. Spleen response was defined as ≥35% reduction in longitudinal diameter, consistent with SVR35 conceptual thresholds. Correlation analyses (Spearman), linear regression modeling, and exploratory predictor assessments were performed.

Results. Median age at MMB initiation was 67 years (range 52–82). Driver mutations included JAK2V617F (62%), CALR (25%), and triple-negative status (13%). At 6 months, 4/23 patients (17%) achieved ≥35% spleen reduction, while the majority demonstrated measurable splenic shrinkage (Figure 1), supporting overall treatment activity. Percentage spleen reduction strongly correlated with stiffness decline (p=0.0001), indicating a robust monotonic association between anatomical and biomechanical changes. Linear regression confirmed that 38% of stiffness variability was explained by spleen reduction (Figure 2). Responders exhibited significantly greater stiffness reduction compared with non-responders (p=0.044, Figure 3), reinforcing the biological coherence of elastographic changes with clinical response. Notably, baseline spleen size and baseline stiffness were not predictive of response, suggesting that dynamic stiffness modulation — rather than static baseline measurements — reflects treatment sensitivity. Hemoglobin improved in 18/23 patients (78%), and 12/17 (70%) transfusion-dependent patients experienced reduced transfusion requirements.

Conclusions. SWE captures biologically meaningful, treatment-induced alterations in splenic biomechanics and closely parallels anatomical spleen reduction in MF patients receiving momelotinib. These findings support stiffness decline as a dynamic surrogate imaging endpoint that may complement conventional MRI-defined SVR35 assessment. Prospective multicenter validation is warranted to determine whether elastography-based parameters can enhance response monitoring and serve as pragmatic imaging endpoints in both clinical trials and routine practice.

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Figure 1.

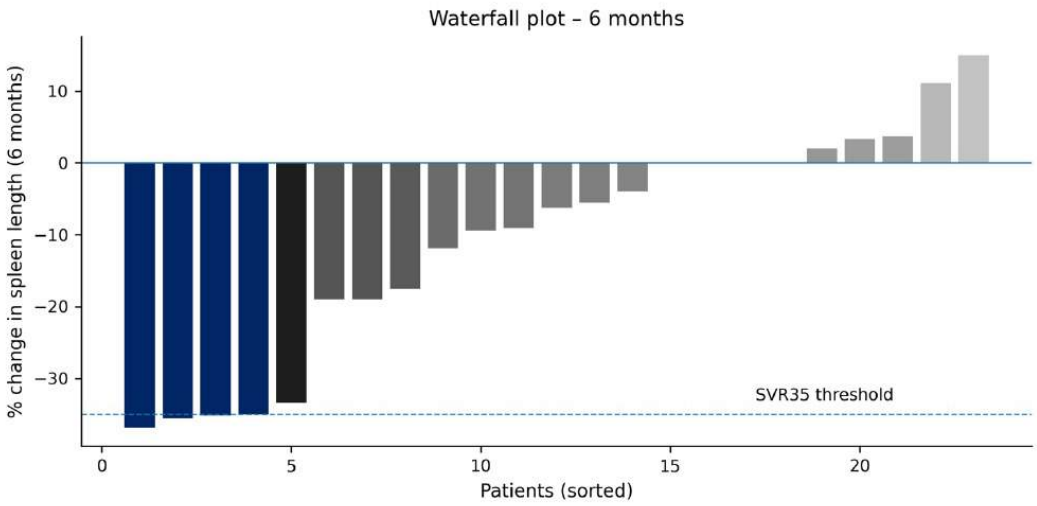

Waterfall plot – 6 months
% change in spleen length (6 months)
10
0
−10
−20
−30
SVR35 threshold
0
5
10
15
20
Patients (sorted)

Figure 2.

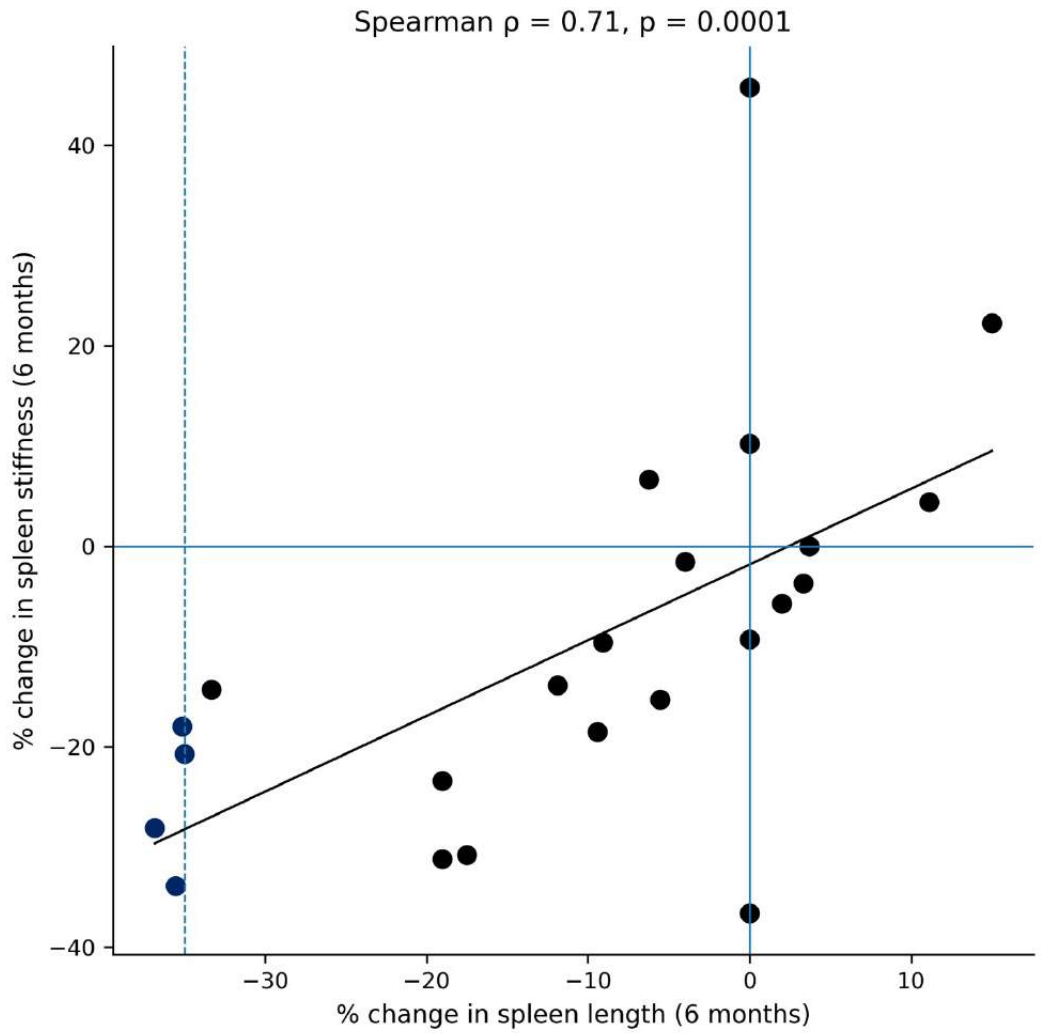
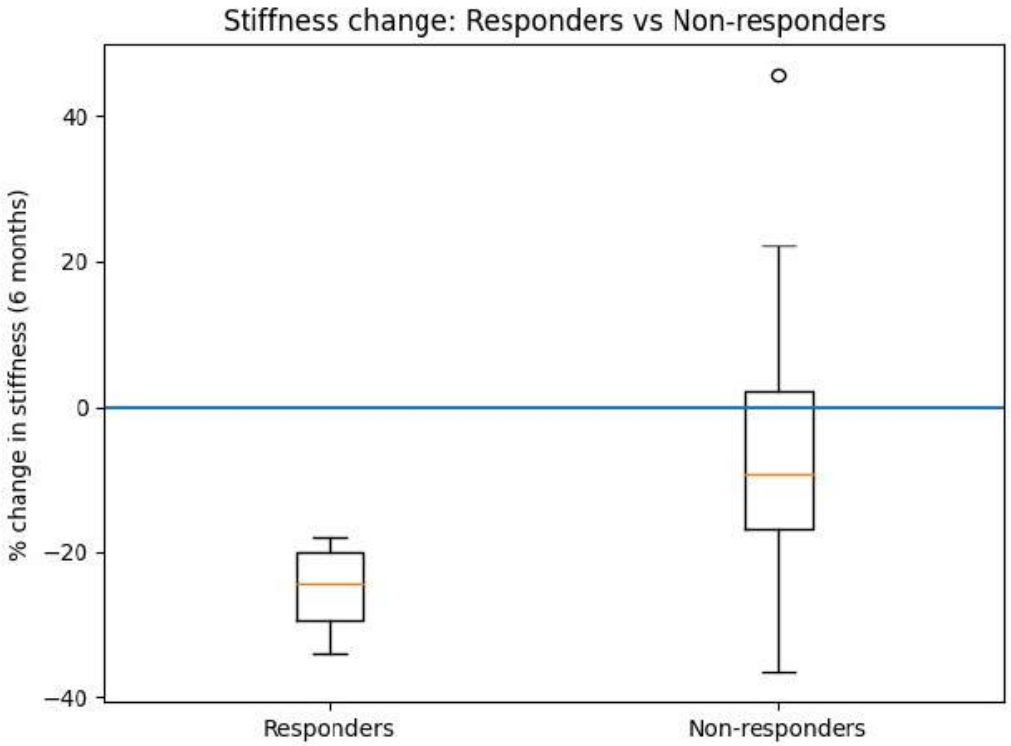

Spearman ρ = 0.71, p = 0.0001
% change in spleen stiffness (6 months)
% change in spleen length (6 months)
40
20
0
−20
−40
−30
−20
−10
0
10

Figure 3.


Stiffness change: Responders vs Non-responders
% change in stiffness (6 months)
40
20
0
−20
−40
Responders
Non-responders

Myeloproliferative Neoplasms

DOSE MATTERS: PROGNOSTIC ROLE OF TIME-WEIGHTED RUXOLITINIB EXPOSURE IN MYELOFIBROSIS

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Hematology, Department of Translational and Precision Medicine, Policlinico Umberto I - Sapienza University

Background. Ruxolitinib (RUX) has represented the main treatment of myelofibrosis (MF) for over a decade. While RUX efficacy is known to be dose-dependent, clinical practice often requires dose titrations based on platelet counts per label, frequently leading to sub-optimal dose intensity. However, the relative impact of the maintained dose intensity over time on outcomes remains poorly defined.

Methods. In this single-center retrospective study, we analyzed 235 consecutive JAKi-naïve MF patients treated with RUX. To evaluate the impact of RUX exposure over time, we calculated the weighted mean dose (WMD) at different timepoints, along with the Relative Dose Intensity (RDI), and used the 6-month landmark analysis. Optimal WMD dose cut-offs were identified using restricted cubic splines.

Results. Median age at RUX-start was 65.9 years, with 52.8% males. PMF accounted for 109 (46.4%) cases, SMF for 126 (53.6%). After a median follow-up of 66.5 months, overall spleen response (SR) rate was 49.8%, with 93 deaths (39.6%) and a whole median OS of 82.5 months.While overall RDI was not associated with OS (p=0.99), the overall WMD showed a significant correlation (p=0.040). Specifically, a 6-month landmark analysis revealed that patients with a RUX WMD ≤ 20 mg/die (≤ 10 mg BID) presented a median OS of 61.9 months (95% CI, 46.7-88.0), significantly inferior to those receiving > 20 mg/die (102.5 months; 95% CI, 81.8-NR), resulting in a more than two-fold increase in mortality risk [HR 2.21 (95% CI, 1.42-3.42) p<0.001]. In a multivariate Cox model adjusted for baseline DIPSS score, baseline platelet count, and adherence to label-recommended starting dose, a RUX WMD ≤ 20 mg/die at 6 months showed an HR of 1.90 (95% CI, 1.10-3.31) (p=0.022). Moreover, patients with a RUX WMD ≤ 20 mg/die at 6 months were associated with higher RR6 risk classes (p<0.001), an inferior rate of overall SR (39.3% vs 57.7%) [OR 2.11 (95% CI, 1.22-3.66) p=0.008] and significantly shorter median time to RUX discontinuation (45.3 vs 129.8 months) [HR 2.24 (95% CI, 1.47-3.41) p<0.001].

Conclusions. Our data suggest that long-term prognosis may be driven by the feasibility of maintaining dose intensity (> 20 mg/day) during early phases of treatment, which are the most critical to achieve a SR. Therefore, a proactive management of AEs and treatment-emergent cytopenias to sustain dosage rather than reducing RUX dosage (at least in the early phases) may be important to maximize RUX clinical benefit.

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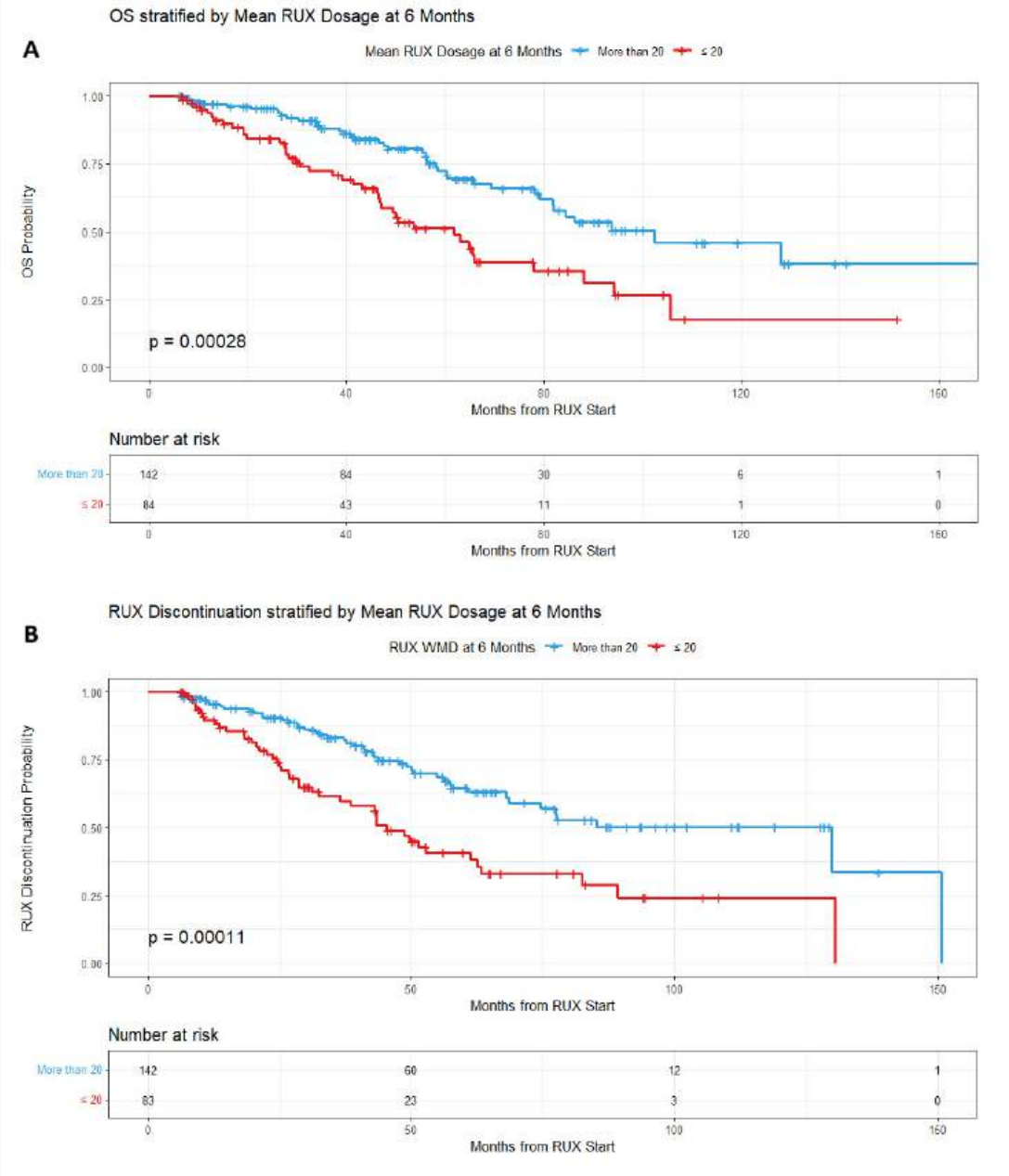
Myeloproliferative Neoplasms



Myeloproliferative Neoplasms

PREDICTING POST TRANSPLANT TRAJECTORIES IN MYELOFIBROSIS: THE PROGNOSTIC POWER OF SPLEEN SIZE AND DISEASE BURDEN

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Background. Myelofibrosis (MF) is a Philadelphia chromosome–negative myeloproliferative neoplasm characterized by progressive marrow fibrosis, splenomegaly and risk of leukemic transformation. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy, but outcomes are affected by graft failure(GF), poor graft function(PGF) relapse and transplant related morbidity.

Methods. Retrospective multicenter study of 45 adult MF patients transplanted between June 2012 and December 2024 at 4 Italian centers in Piemonte. Demographics, disease, donor and transplant variables, spleen size, circulating CD34+ cells, chimerism and molecular markers were collected. Endpoints included overall survival (OS), cumulative incidence (CI) of relapse, non-relapse mortality (NRM), GVHD, GvHD-relapse-free survival (GRFS), engraftment, GF/PGF. Statistical analyses included Kaplan–Meier, competing risks cumulative incidence, Fine–Gray models for multivariable logistic regression, ROC analysis and Cox models.

Results. The median age at HSCT was 61 years, 37 patients had prior JAK inhibitor exposure. After a median follow up of 50 months, 5 year OS was 59.7% and the CI of relapse 21.3%. The CI of NRM was 8.8% at 6 months and 22.5% at 24 months; the 5 year GRFS was 31.3%. Primary GF occurred in 3 patients, PGF in 5. Patients who developed GF were older (median age 64.5 vs. 61 years, p=0.05) and presented with larger spleens (20 vs. 17 cm, p=0.032). In multivariable analysis, only splenic size was independently associated with GF/PGF (OR=1.3, 95% CI: 1–1.7, p=0.05). The only factor associated with 2-year NRM was patient age (HR=1.11, 95% CI: 1.02–1.21, p=0.02). Spleen size and circulating CD34+ cells were associated with CI of relapse, and both were confirmed in multivariable analysis (HR=1.33, p=0.02; HR=0.36, p=0.01, for spleen size and circulating CD34+, respectively). Of note, neither early donor chimerism nor molecular clearance, the latter available in 12 patients only, provided predictive value for relapses in this cohort, although their relevance has been highlighted in previous studies.

Conclusions. These results highlight how disease characteristics and transplant factors jointly determine post HSCT outcomes and emphasize timely transplantation for suitable patients. Pretransplant spleen size and circulating CD34+ percentage are practical predictors of graft dysfunction and relapse and can guide risk stratification and pretransplant management.

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Red blood cell pathologies

PROPER LONGITUDINAL CHARACTERIZATION OF CAD: REDUCTION IN TIME TO DIAGNOSIS AND IMPROVEMENT IN THERAPEUTIC APPROPRIATENESS IN A REAL-WORLD, SINGLE-CENTER EXPERIENCE

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Background and Aims. Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia characterized by complement-mediated hemolysis and frequently associated with lymphoproliferative disorders. This study evaluates the clinical features at diagnosis and the impact of a structured multidisciplinary diagnostic pathway on disease characterization and therapeutic management over time at our center.

Methods. We retrospectively analyzed 11 patients diagnosed with CAD between 2016 and 2026. Median age was 72 years, with a female predominance (64%). At diagnosis, 5 patients (45%) had an associated lymphoproliferative disorder, while 3 (27%) had at least one concomitant autoimmune disease. No patients had active malignancy at diagnosis. Clinical presentation was heterogeneous, although most patients showed laboratory evidence of active hemolysis.Bone marrow evaluation was performed in 5 patients (45%), confirming hemolytic anemia with erythroid hyperplasia; in one case, monoclonal B-cell lymphocytosis was identified.We subsequently divided the patients into 2 cohorts based on the time of diagnosis (pre-2020 and post-2020), when a structured multidisciplinary diagnostic pathway was implemented with dedicated clinical assessment and advanced laboratory testing.

Results. Median time from initial diagnosis of unspecified autoimmune hemolytic anemia to confirmed CAD was 4 months overall. A significant difference emerged between cohorts: 72 months in the pre-2020 group versus 1,5 months in the post-2020 group. Similarly, median time to initiation of rituximab (RTX) therapy was 6 months overall, with 18 months in the pre-2020 cohort and 2 months post-2020.- Most patients received first-line therapy with corticosteroids, but 8 (73%) required second-line treatment with RTX. Only 2 patients needed 3 or more treatment lines and were also treated with sutimlimab, with one still on therapy.

Conclusions. In conclusion, despite the small cohort, our findings suggest that a structured multidisciplinary diagnostic approach significantly reduces time to CAD diagnosis and enables earlier initiation of effective therapies. This approach minimizes prolonged corticosteroid exposure and its associated toxicity while improving overall disease management. The availability of new treatments such as sutimlimab further highlights the importance of early and accurate diagnosis, allowing timely patient selection and appropriate preventive measures, including vaccination strategies.

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POPULATION	11 (100%)
DEMOGRAPHIC	
Female	7 (64%)
Male	4 (36%)
Median age at diagnosis (years old)	72
First AEA suspect	
- before 2020	5 (45%)
- after 2020	6 (55%)
Median time to CAD confirmation (months)	4
- before 2020	72
- after 2020	1,5
Patients with associated lymphoproliferative disorder	5 (45%)
Patient with concomitant cancer	0 (0%)
Patients with autoimmunity disorder	3 (27%)
Patients with CV risk factors	8 (73%)
LABORATORISTIC VALUES AT DIAGNOSIS	
Median Hb at diagnosis (g/dl)	9,3 [range 4,5 - 10,5]
Median Indirect Bilirubin at diagnosis (mg/dl)	2,2 [range 0,2 - 4,7]
Median LDH at diagnosis (U/L)	373 [range 228 - 779]
Not detectable haptoglobin at diagnosis	100%
Median reticulocytes at diagnosis (%)	5 [range 3,2 - 19,2]
BOM	5 (45%)
THERAPY	
First line	
- CCS	10 (91%)
- None	1 (9%)
Second Line	
- Rituximab	8 (73%)
≥Third Line	
- Sutimlimab	2 (18%)
- Other	2 (18%)
Median time from diagnosis to RTX initiation *(months)*	4,5
- Before 2020	28,5
- After 2020	2,3
Ongoing CCS	1 (8%)
Associated therapy	
- ESA	3 (27%)

Red blood cell pathologies

DISTRIBUTION AND CLINICAL CORRELATES OF HFE GENE MUTATIONS IN A REAL-WORLD COHORT OF PATIENTS EVALUATED FOR HEREDITARY HEMOCHROMATOSIS

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Background. HFE gene pathogenic variants underlie a wide phenotypic spectrum, from isolated biochemical abnormalities to multi-organ involvement. Non-C282Y variants (H63D, C65S) are frequently underestimated in clinical practice.

Aims. To characterize the HFE mutational profile and its relationship with iron parameters, hepatic involvement, and metabolic comorbidities in an unselected population with suspected iron overload.

Methods. Retrospective analysis of 200 consecutive patients undergoing HFE genotyping. Serum ferritin, transferrin saturation (TSAT), and clinical evidence of organ involvement were recorded. Liver MRI was obtained where phlebotomy was contraindicated. Results: H63D was the predominant variant: 84 patients (42%) heterozygous and 56 (28%) homozygous (total 140, 70%). C282Y in 40 subjects (20%); C65S in 20 (10%). Organ involvement, confined to the liver, was documented in 80 patients (40%), all with elevated ferritin. TSAT >45% was mainly confined to C282Y carriers; borderline elevations in 11 H63D (7.9%) and 4 C65S (20%). Approximately 25% of patients with moderate-to-severe steatosis showed hyperinsulinism and/or mild hyperglycaemia. No cardiac or pancreatic involvement was identified on MRI. Liver MRI, performed in 20 H63D patients (14.3%), demonstrated mild-to-moderate iron loading in all cases.

Conclusions. Non-C282Y variants account for a substantial share of suspected HH cases. Coexistent steatosis lowers the threshold for hepatic injury and is associated with early metabolic dysregulation. Genotyping, quantitative MRI, and metabolic profiling should be integrated into the diagnostic pathway.

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Red blood cell pathologies

CLINICAL AND MOLECULAR CHARACTERIZATION OF HB COIMBRA [HBB: C300T>A P(ASP100GLU)] IN A THREE-GENERATION ITALIAN FAMILY: FROM DIAGNOSTIC PITFALLS TO VASCULAR RISK

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Secondary erythrocytosis due to high oxygen-affinity hemoglobin (HOAH) variants is a rare cause of congenital polycythemia. Hb Coimbra [HBB: c.300T>A p.(Asp100Glu)] is a variant that stabilizes the Relaxed (oxy) state of hemoglobin, leading to a marked left-shift in the oxygen dissociation curve. We report the first Italian three-generation family carrying this variant, highlighting the diagnostic process and the significant lack of standardized management protocols for pediatric carriers.The 5-year-old proband (III-1) was referred for hematological evaluation due to the known history of HOAH in her father and paternal grandfather. She presented with stable erythrocytosis (Hb 15.9 g/dL, HCT 47%) and an inappropriately normal erythropoietin level (6.9 mIU/mL). Targeted workup revealed two striking diagnostic pitfalls: a spurious HbA2 peak of 38.9% on electrophoresis (due to co-migration of the variant) and a pseudo-carboxyhemoglobinemia of 2.2% (Ref: 0.0-0.8) on CO-oximetry. Diagnosis was confirmed by molecular analysis (HBB:c.300T>A) and a reduced p50 (estimated from a venous pO2 of 22.9 mmHg at SO2 61.9%).The clinical spectrum across the kindred underscores the management dilemma. The grandfather suffered two previous strokes; the father (HCT 60.4%) requires periodic erythrocytapheresis (EEX). Currently, the 5-year-old proband remains asymptomatic with unremarkable screenings (ophthalmologic and abdominal ultrasound). This non-invasive "wait-and-watch" strategy is feasible due to her current pediatric status and the low baseline thrombotic risk in the pre-pubertal period.However, in the absence of established guidelines, it remains difficult to determine the optimal timing for transitioning to active management. As the patient approaches puberty and adulthood, defining the exact clinical or laboratory triggers to initiate antithrombotic prophylaxis or EEX—to prevent the severe vascular complications documented in her kindred without exacerbating tissue hypoxia—remains a significant challenge for the clinician.

Red blood cell pathologies

COMBINED APHERESIS APPROACH AND ENDOTHELIAL-INFLAMMATION MODULATION IN PEDIATRIC SICKLE CELL STROKE COMPLICATED BY CENTRAL VENOUS THROMBOSIS

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Ischemic stroke in sickle cell disease (SCD) is a multifactorial emergency driven by erythrocyte sickling, hypercoagulability, and inflammation. While erythrocytapheresis (EEX) remains the gold standard for rapid HbS reduction, severe presentations with massive cerebral edema or features suggestive of thrombotic microangiopathy (TMA) may benefit from adjunctive therapeutic plasma exchange (TPE) to modulate cytokine-mediated endothelial injury and alternative complement pathway activation.A 10-year-old girl with SCD (baseline HbS 74%) presented with acute left hemiplegia and aphasia. Neuroimaging revealed a massive right middle cerebral artery infarction, rapidly progressing to malignant cerebral edema with uncal herniation (Fig. 1), requiring emergency right decompressive craniectomy. Immediate EEX reduced HbS to 17% (Hb 10.4 g/dL). Due to persistent severe endothelial dysfunction, adjunctive TPE was initiated. Six TPE sessions were performed with the aim of removing proinflammatory mediators and stabilizing the humoral response. Monitoring included ADAMTS13 activity to evaluate TMA-like endothelial stress, along with strict reticulocyte control given their enhanced adhesiveness to activated endothelium. The clinical course was complicated by eccentric thrombosis of the left external iliac vein, likely related to the high-flow central venous catheter (CVC) required for apheresis. In the context of SCD-associated hypercoagulability and recent neurosurgery, anticoagulation with therapeutic enoxaparin was initiated, while antiplatelet therapy was deferred due to the high risk of intracranial bleeding.TPE was discontinued following radiological stabilization and clinical improvement. The patient was transferred to a specialized rehabilitation center for intensive motor and speech therapy, with progressive functional recovery. She is currently on a high-intensity secondary prevention regimen combining chronic EEX and hydroxyurea, aiming at synergistic control of sickling, blood rheology, and vascular inflammation. This case highlights that in life-threatening SCD-related stroke, EEX alone may be insufficient. Adjunctive TPE may represent a valuable strategy to target the humoral and inflammatory components of disease. Furthermore, proactive management of CVC-related thrombotic complications is essential. A multidisciplinary approach—integrating hematology, neurosurgery, and intensive rehabilitation—is critical to optimize outcomes in complex pediatric cases.

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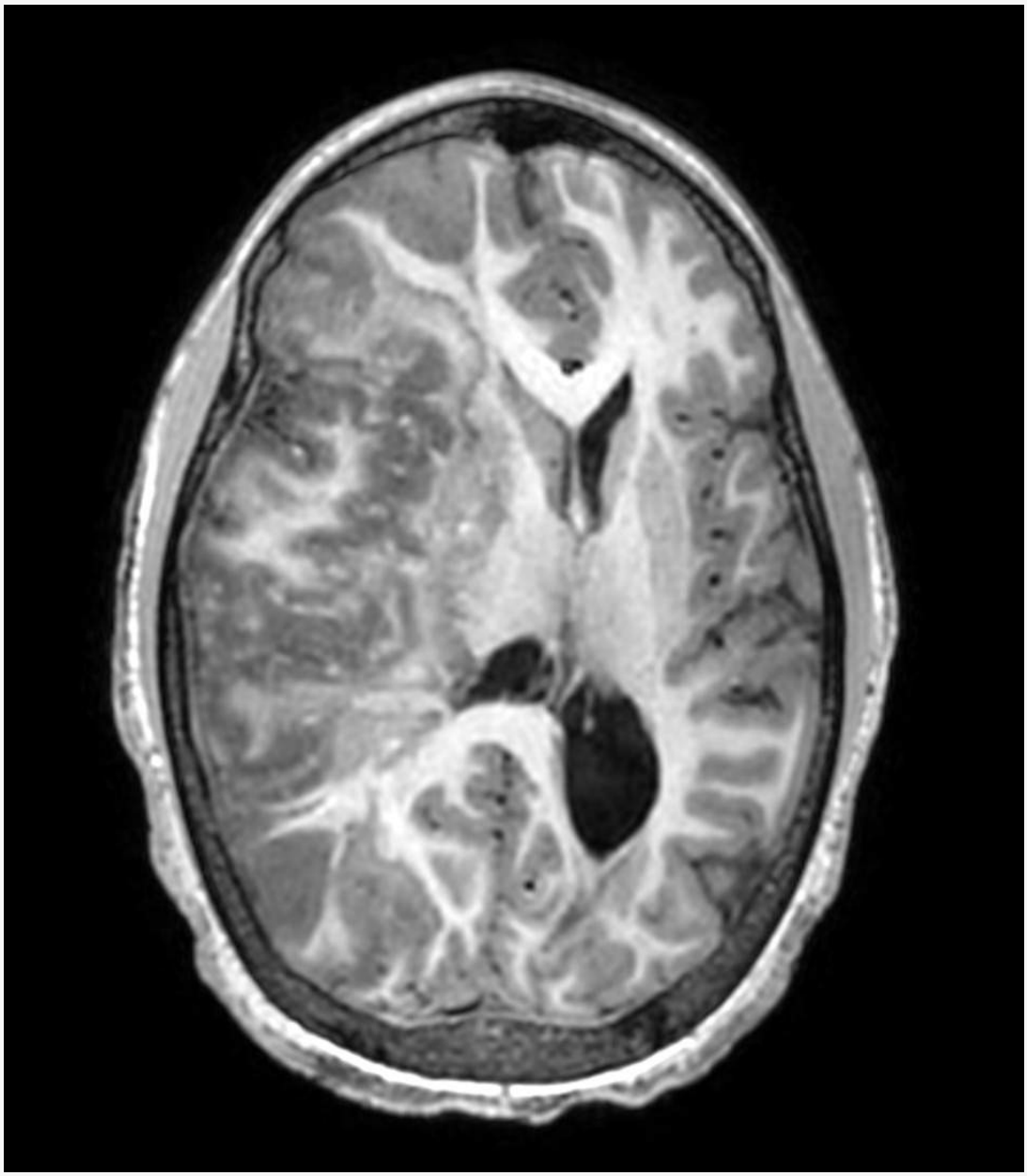
Red blood cell pathologies



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Red blood cell pathologies

SAFETY OF DARATUMUMAB-BASED REGIMENS IN MULTIPLE MYELOMA PATIENTS WITH G6PD DEFICIENCY

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Introduction. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells worldwide. It is inherited in an X-linked recessive manner and is therefore more frequently and more severely expressed in males. Despite the well-established association between several drugs and hemolytic crises in G6PD-deficient individuals, limited data are available about the safety of daratumumab-based treatments in similar patients with multiple myeloma (MM). At our Institution all patients with an anamnestic history of possible congenital hemolytic anemias are regularly screened for G6PD-deficiency. Among them, two patients with confirmed G6PD-deficiency and newly diagnosed MM have been so far treated with daratumumab-based regimens.

Case 1. In November 2023 a 62-year-old male was diagnosed with IgA lambda MM (R-ISS, stage I). First-line induction therapy with 4 courses of daratumumab, bortezomib, thalidomide, and dexamethasone (DVTd) was administered, followed by stem cell mobilization with cyclophosphamide (2 gr/sqm) and G-CSF. In August 2024, the patient underwent conditioning regimen with melphalan (200 mg/sqm) and autologous stem cell transplantation (ASCT). Two additional cycles of DVTd were administered and maintenance therapy with lenalidomide (10 mg/day) was started in July 2025. No evidence of hemolysis was reported throughout the course of treatment.

Case 2. In September 2025, a 79-year-old male was diagnosed with IgA lambda MM (R-ISS, stage I). First-line therapy with daratumumab, lenalidomide, and dexamethasone (DRd) was started. To date, after 8 cycles of DRd, no signs of hemolysis were observed. In both patients, drugs belonging to combination (DVTd or DRd) were started one at a time to quickly recognize a possible trigger of hemolysis. About pre-daratumumab medications recommended to reduce infusion-related reactions, anti-histamines and dexamethasone were regularly employed, while paracetamol, reported among drugs triggering hemolysis, was excluded. For the same reason, sulfamethoxazole/trimethoprim was avoided and atovaquone was instead prescribed for the first 6 months after ASCT as anti-Pneumocystis prophylaxis. Anti-viral prophylaxis with acyclovir was normally adopted for the prevention of Herpes Zoster virus reactivation.

Conclusions. Our experience suggests that daratumumab-containing regimes may be safely managed and administered in MM patients with G6PD-deficiency.

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Red blood cell pathologies

INFLAMMATORY CHRONIC ANEMIA IN GASTRIC MALIGNANCY: CLINICAL EVIDENCES WITH LACTOFERRIN TREATMENT

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Background. Cancer is a global health challenge and its development is closely linked to iron metabolism. Cancer cells need ironfor their proliferation and tissue invasion. Recently, the use of nutraceuticals as natural compounds supporting standard anti-cancertherapy is emerging as a promising strategy. Lactoferrin (Lf), a glycoprotein with a high iron-chelating capacity can inhibit theavailability of this ion to cancer cells, limiting their growth and progression. By chelating free Fe3+ ions Lf reduces oxidative stressand inhibits the mechanisms that promote carcinogenesis. Additionally Lf exhibits immunomodulatory and anti-inflammatoryeffects and may enhance the body antitumor response, thus representing a promising tool for cancer prevention and treatmentespecially in combination therapies.Case series: we present a retrospective case series of four patients with gastric cancer. At baseline all patients showed anemia,elevated ferritin levels, high C-reactive protein (CRP) values and low levels of serum transferrin, indicating an increasedinflammatory status. In addition to pharmacological therapies all patients started treatment with bovine lactoferrin (bLf) at aninitial dose of 600 mg/day. After one month the dosage was tapered to 200 mg/day for other three months.

Results. At the end of the treatment period all patients showed improvement in hemoglobin levels and red blood cells (RBC)count with a decrease of ferritin values. In univariable linear mixed-model analyses, hemoglobin and RBC count significantlyincreased by 0.62 g/dL and 0.18 million/μL per month respectively and both changes were high statistically significant ($p < 0.001$and $p=0.006$). Notably ferritin significantly decreased by 75 ng/mL per month ($p<0.001$). Serum iron and CRP levels showed atrend toward improvement over time ($p=0.089$ and $p=0.07$, respectively).

Conclusions. bLF supplementation, particularly following an initial higher-dose loading phase, was associated with improvedhemoglobin levels and RBC counts, often reaching or approaching normal levels. It was also associated with reduced ferritinlevels, suggesting relief of functional iron blockade (likely inflammation-mediated), modest increases in serum iron, indicatingimproved iron availability and mobilization, and CRP levels showed a decreasing trend, even if non significant, suggesting apotential anti-inflammatory effect that warrants confirmation in larger controlled studies.

Red blood cell pathologies

INCOMPLETE MARROW RECOVERY AFTER APLASIA: COMPLEMENTARY INSIGHT FROM MRI

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Background. Aplastic anemia is defined by bone marrow hypocellularity (<25%) and peripheral pancytopenia. Standard hematologic response criteria rely on peripheral blood counts, which may not adequately reflect the quality or spatial distribution of marrow recovery. The role of magnetic resonance imaging (MRI) in this setting remains poorly characterized.

Case presentation. We report the case of a 45-year-old woman who developed severe aplastic anemia following urosepsis complicated by renal abscess requiring nephrectomy. Following surgery, she developed severe pancytopenia (neutrophils 0.16x×10^9/L, platelets 15×10^9/L, hemoglobin 7.2 g/dL). Bone marrow biopsy showed marked hypocellularity (5-10%) with depletion of hematopoietic elements and CD34+ cells. Cytogenetic and molecular analyses were unremarkable, and no paroxysmal nocturnal hemoglobinuria clone was detected. In the absence of an HLA-matched related donor, the patient received immunosuppressive therapy with horse antithymocyte globulin (ATGAM), cyclosporine, corticosteroids, and eltrombopag. Hematologic recovery began at day +45 with normalization of neutrophil counts (2.5×10^9/L), while anemia and severe thrombocytopenia persisted, requiring ongoing transfusional support. The clinical course was complicated by recurrent multidrug-resistant bacterial sepsis and invasive pulmonary aspergillosis, occurring both during the aplastic phase and after neutrophil recovery. At day +55, non-contrast MRI of the spine and pelvis, performed to exclude infectious foci, revealed diffuse millimetric T1 hypointense and T2 hyperintense marrow lesions involving the axial skeleton and proximal femora. A repeat bone marrow biopsy at day +60 showed partial recovery (25-30% cellularity) with predominant myeloid reconstitution and persistent erythroid and megakaryocytic suppression.

Conclusions. Bone marrow recovery after aplasia may be spatially heterogeneous and functionally inadequate despite partial hematologic improvement. Notably, normalization of neutrophil counts did not translate into effective immune reconstitution, as reflected by ongoing severe infectious complications. Diffuse millimetric T1 hypointense and T2 hyperintense foci on MRI may reflect a patchy pattern of marrow recovery. Bone marrow MRI may provide clinically relevant insight into the spatial distribution of recovery, not fully captured by single-site biopsy, supporting its potential role as a complementary tool in post-aplastic marrow evaluation in selected patients.

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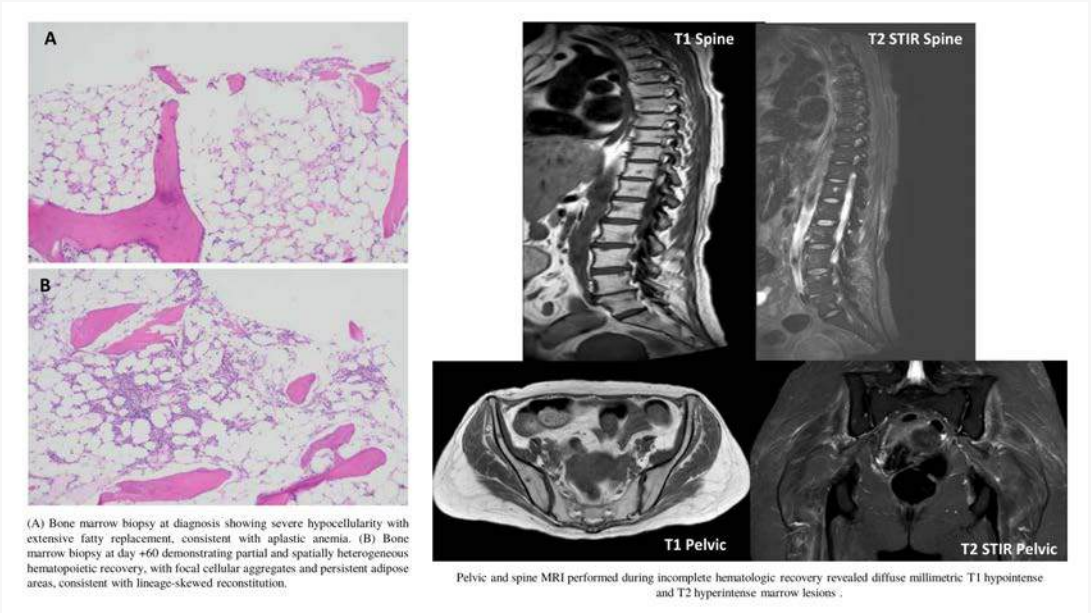

(A) Bone marrow biopsy at diagnosis showing severe hypocellularity with extensive fatty replacement, consistent with aplastic anemia. (B) Bone marrow biopsy at day +60 demonstrating partial and spatially heterogeneous hematopoietic recovery, with focal cellular aggregates and persistent adipose areas, consistent with lineage-skewed reconstitution.

Pelvic and spine MRI performed during incomplete hematologic recovery revealed diffuse millimetric T1 hypointense and T2 hyperintense marrow lesions .

Red blood cell pathologies

UNUSUAL CAUSE OF HEMOLYTIC ANAEMIA: GLUCOSE PHOSPHATE ISOMERASE DEFICIENCY COMBINED WITH THALASSEMIA CARRIER STATUS CASE REPORT AND NOVEL THERAPEUTIC OPTIONS

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Introduction. Glucose phosphate isomerase (GPI) deficiency is a rare autosomal recessive disorder causing hereditary nonspherocytic hemolytic anemia. It results from homozygous or compound heterozygous mutations in the GPI gene on chromosome 19q13 and represents the second most common glycolytic erythroenzymopathy after pyruvate kinase deficiency. Approximately 90 cases have been reported worldwide, mostly in homozygous individuals. To date, no cases describing combined enzymatic red cell defects with β-thalassemia carriers have been reported.

Materials and Methods. A 54-year-old male was referred to our Center in December 2023 for evaluation of microcytic anemia, splenomegaly, and a history of multiple transfusions, with a suspected diagnosis of thalassemia intermedia. Family history revealed β-thalassemia trait in his father and brother, and severe anemia in his son. Initial screening for hemoglobinopathies by high-performance liquid chromatography was consistent with β-thalassemia carrier status.

Results. Sanger sequencing identified a heterozygous mutation at codon 39 of the β-globin gene , NM_000518.5:c.118C>T p.(Gln40Ter) (cd39), while no α-globin gene alterations were detected. Peripheral blood smear showed marked anisocytosis. Due to laboratory evidence of hemolysis, targeted next-generation sequencing (NGS) of 124 genes associated with hereditary anemia was performed. This analysis revealed a heterozygous variant NM_000175.5:c.653 C>T in the GPI gene, consistent with GPI deficiency inherited as an autosomal recessive condition.DiscussionClinical severity of GPI deficiency ranges from mild to severe hemolytic anemia; in extreme cases, it may be incompatible with life. Patients with milder forms can survive into adulthood but remain at risk for hemolytic crises, often triggered by infections. The coexistence of β-thalassemia trait and GPI deficiency may contribute to the patient's complex phenotype.

Conclusions. NGS is a powerful diagnostic tool for identifying rare hereditary anemias and guiding appropriate management. The patient is currently managed with folic acid and vitamin B12 supplementation, with occasional transfusions when hemoglobin levels fall below 8 g/dL. He also underwent splenic artery embolization for aneurysm with clinical benefit. Emerging therapies targeting the glycolytic pathway, such as mitapivat, may represent promising future treatment options.

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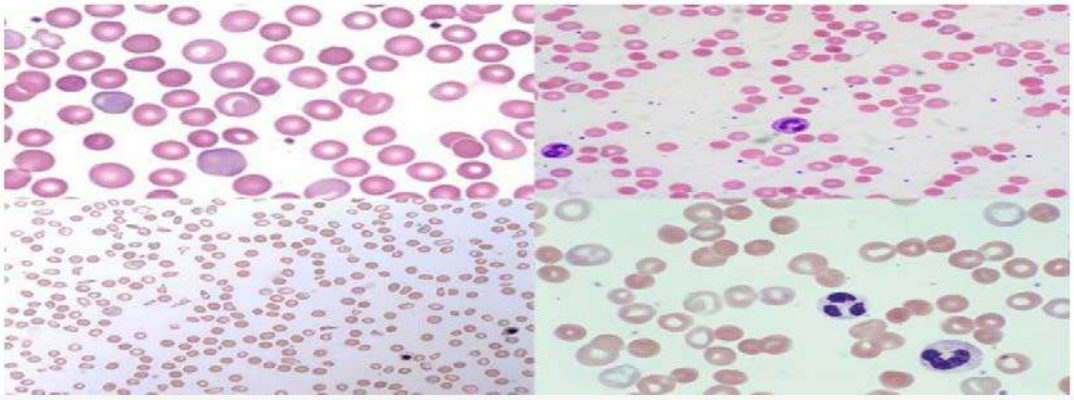
TABLE 1 : CLINICAL AND LABORATORY FEATURES OF THIS CASE REPORT

	AGE	DIAGNOSIS	SEX	COMORBIDITY	ETHNICITY	NEED OF TRANSFUSION	HEMOLYSIS INDICES	HEMOGLOBIN	RED CELL VOLUME	TRANSFERRIN SATURATION INDEX	HYPERFERRITINEMIA	BLOOD SMEAR MORPHOLOGICAL EXAMINATION	NEED FOR HOSPITALIZATION
PATIENT 1	54	Bthalassemia carrier plus GPI deficiency	M	-Aneurysmal dilation of the splenic artery -Gallbladder stones	Caucasian	Yes	Positive	9,5 g/dl	69	61	Yes	Severe anisocytosis	Yes

FIGURE 1: BLOOD SMEAR CHARACTERISTICS OF OUR PATIENT



Red blood cell pathologies

RAPID HEMATOLOGIC RESPONSE TO SUTIMLIMAB IN SEVERE COLD AGGLUTININ DISEASE REFRACTORY TO RITUXIMAB IN AN ELDERLY PATIENT

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Background. Cold Agglutinin Disease (CAD) is a rare subtype of autoimmune hemolytic anemia characterized by complement-mediated hemolysis driven by cold-reactive autoantibodies. The disease may occur as a primary clonal lymphoproliferative disorder or be triggered/exacerbated by infections. Management remains challenging, particularly in elderly patients with severe hemolysis and transfusion requirements. Recently, complement inhibition has emerged as a targeted therapeutic strategy.

Case Presentation. A 75-year-old woman with a medical history significant only for hypertension developed progressive fatigue and dyspnea following recurrent viral infectious episodes, including previous COVID-19 and a subsequent flu-like syndrome requiring Emergency Department admission and empiric antibiotic treatment. In January 2026, she was referred to our Hematology Unit for severe symptomatic anemia. Laboratory findings showed hemoglobin (Hb) 6.0 g/dL, lactate dehydrogenase (LDH) 1000 U/L, total bilirubin 5 mg/dL, and undetectable haptoglobin (<3 mg/dL), consistent with severe hemolysis. The patient required hospitalization and red blood cell transfusion support.Further diagnostic workup was consistent with CAD. Autoimmune screening, including ANA, ENA, LAC, anticardiolipin and anti-β2 glycoprotein antibodies, was negative. Molecular testing for MYD88 L265P mutation was negative. Bone marrow biopsy and immunophenotypic analysis excluded an underlying lymphoproliferative disorder. CT scan staging did not reveal lymphadenopathy or organomegaly. An initial empiric course of corticosteroids was administered without significant hematologic response. Subsequently, treatment with Rituximab was started; however, after two administrations, no clinical or laboratory improvement was observed. Due to persistent severe hemolysis and transfusion dependence, therapy with Sutimlimab was initiated, resulting in a rapid improvement in hematologic parameters after the first administration, with progressive stabilization of hemolysis and reduced transfusion requirement.

Conclusions. This case highlights the diagnostic and therapeutic challenges of severe complement-mediated CAD in elderly patients. In our patient, viral infections may have acted as triggering or exacerbating factors. The lack of response to corticosteroids and anti-CD20 therapy, together with the rapid hematologic improvement after complement inhibition, supports the emerging role of Sutimlimab as an effective and fast-acting treatment in refractory CAD. This case underlines the importance of prompt recognition and early access to targeted therapies in life-threatening hemolysis.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

FROM SEVERE THROMBOSIS TO SUCCESSFUL PREGNANCIES: ORTHOTOPIC LIVER TRANSPLANTATION IN INHERITED AFIBRINOGENEMIA WITH BUDD-CHIARI SYNDROME

G. Murante[1|2|3], S. Bergonzi[1|2|3], M. Capetta[1|2|3], F. Valeri[1|2], C. Dainese[1|2], A. Valpreda[4], R. Pastorino[1|3], F. Bocchi[1|3], R. Romagnoli[5], S. Martini[6], B. Bruno[2|3], A. Borchiellini[1|2]

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Background. Inherited FBG disorders are generally classified as quantitative or qualitative. Quantitative disorders include aFBG, which is characterized by the complete absence of FBG. Clinical manifestations vary from being asymptomatic to developing catastrophic life-threatening bleeds. Although the clinical phenotype is predominantly hemorrhagic, paradoxical thrombotic events have been increasingly reported, reflecting the complex pathophysiology of this condition.

Case report. We report the case of a 30-year-old woman diagnosed with inherited aFBG during infancy following severe gingival bleeding that required treatment with fresh frozen plasma (FFP) and red blood cell (RBC) transfusions. In adulthood, her clinical course was complicated by recurrent hemoperitoneum secondary to hemorrhagic corpus luteum rupture, requiring surgical intervention and transfusion support. Combined oral contraceptives were subsequently introduced to prevent recurrence. In January 2018, following a spontaneous haematoma of the abdominal wall treated with FFP, a CT scan revealed splenomegaly, an enlarged and distorted liver, no visualization of the right suprahepatic vein, leading to a diagnosis of partial Budd–Chiari syndrome. In the absence of identifiable thrombophilic conditions, the event was attributed to a multifactorial prothrombotic state associated with aFBG, estrogen exposure, and repeated FFP administration. The progression to advanced chronic liver disease, with a MELD score of 30, prompted the indication for OLT. In June 2018, a chronic right subdural haematoma was incidentally discovered during a brain CT scan performed as part of pre-OLT screening. Taking into account the complex nature of the case, there was no indications for evacuation, and it was treated conservatively. Prophylaxis with Human fibrinogen concentrate (HFC) (4 grams, every 72 hours) was initiated. On 27 November 2018, OLT transplant was performed after infusion of 4 g of HFC 1 hour before surgery. FFP, RBC transfusions, and tranexamic acid were administered during OLT. The postoperative course was uneventful, with rapid normalization of FBG levels the same day of OLT. Thromboprophylaxis with low-molecular-weight heparin was initiated on the first postoperative day. She successfully completed two pregnanciesunder appropriate antithrombotic prophylaxis.

Conclusions. We report one of the few cases of inherited aFBG, complicated with Budd-Chiari syndrome successfully treated with OLT.

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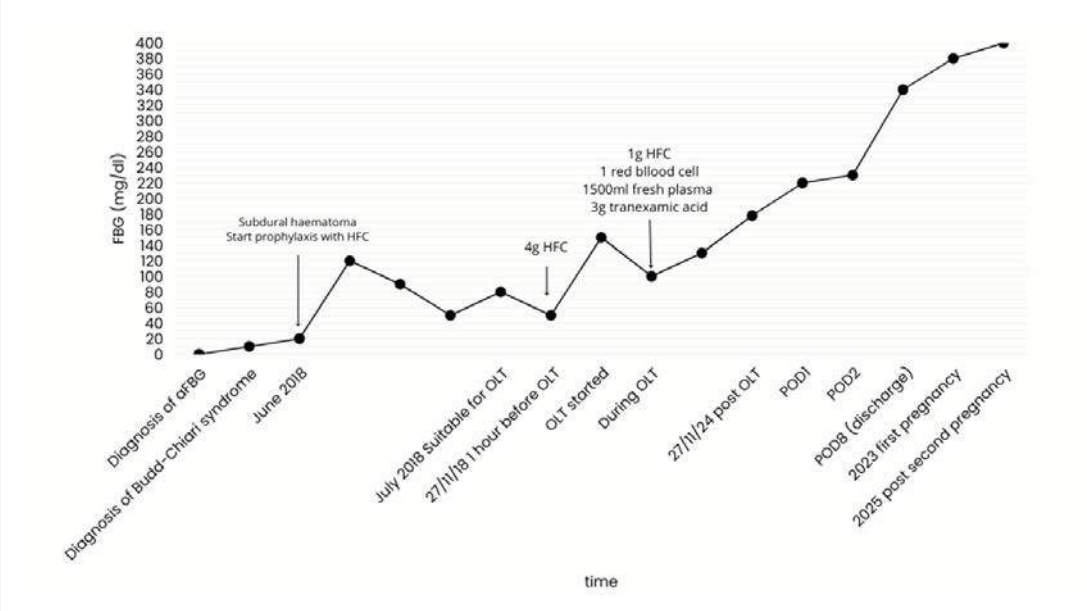
FBG (mg/dl)
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
Subdural haematoma
Start prophylaxis with HFC
4g HFC
1g HFC
1 red bllood cell
1500ml fresh plasma
3g tranexamic acid
Diagnosis of dFBG
Diagnosis of Budd-Chiari syndrome
June 2018
July 2018 Suitable for OLT
27/11/18 1 hour before OLT
OLT started
During OLT
27/11/24 post OLT
POD1
POD2
POD8 (discharge)
2023 first pregnancy
2025 post second pregnancy
time

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

POST KIDNEY TRANSPLANT PRESENTATION OF ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE OF PRE-EXISTING ADAMTS13 INHIBITORS

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Background and aim. Acquired TTP is a rare but critical complication after kidney transplantation. Its diagnosis is often masked by post-operative complications or drug-induced microangiopathic hemolytic anemia (TMA), requiring high clinical suspicion for timely intervention. The aim of this abstract is to report a rare case of early-onset post-transplant aTTP in a patient with no prior hematological history, highlighting the diagnostic process and the effectiveness of a multimodal therapeutic strategy including Caplacizumab (Cab).

Case report. A 56-year-old Caucasian woman with end-stage renal disease of unknown etiology underwent deceased-donor kidney transplantation in August 2025. The patient's medical history was unremarkable for any known autoimmune or hematological disorders.Immunosuppression was initiated with steroids, mycophenolate mofetil, tacrolimus, and anti-thymocyte globulin. Despite an initially stablenephrological course, the patient developed severe thrombocytopenia (18,000/mmc) and a drop in hemoglobin (10.1 g/dL) on post-operative day (POD). Laboratory findings on POD6 revealed TMA picture: hemoglobin 7.5g/dL, Platelets 18.000/mmc, schistocytes 1.6%, elevated LDH, indirect bilirubin 2.3 mg/dL and undetectable haptoglobin, with a negative direct Coombs test. Coagulation profiles and graft function remained stable. With a PLASMIC score of 5, ADAMTS13 testing was performed. Results confirmed aTTP, showing ADAMTS13 activity <0.01 U/mL and an inhibitor titer of 19.34 BU. Treatment started with daily plasma exchange (PEX) and Rituximab (RTX), alongside adjusted baseline immunosuppression to mitigate infectious risk. Due to post-operative haemorrhagic risk, Cab was started after 24 hours. Retrospective analysis of pre-transplant serum revealed positive ADAMTS13 inhibitors (20 BU). Clinical remission was achieved within 5 days, leading to PEX discontinuation. Following rapid ADAMTS13 recovery (0.71 UI/m) and inhibitor clearance, the final RTX dose was omitted. Cab was ceased after 30 days. The patient was discharged in full clinical and serological remission on POD 30 with stable graft function.

Conclusions. This case highlights the diagnostic challenge of post-transplant aTTP and the critical importance of early ADAMTS13 assessment. The retrospective finding of pre-existing inhibitors suggests that the surgical stress or induction therapymay have triggered the clinical manifestation of a previously silent autoimmune state.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

CONGENITAL THROMBOTIC THROMBOCYTOPENIC PURPURA: HOW TO MANAGE? - A CASE FROM REAL WORLD

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[1]Department of Clinical and Biological Sciences, University of Turin; [2]Department of Medical Sciences, University of Turin; [3]AOU Policlinico "G Rodolico San Marco"; [4]Haematology and Cellular Therapies Unit, A O Ordine Mauriziano

Introduction. Congenital thrombotic thrombocytopenic purpura (cTTP) is a rare autosomal recessive condition with an estimated prevalence of 0.5-2.5 cases per million caused by mutations in the ADAMTS13 gene that result in ADAMTS13 activity <10%. Since its proven safety and efficacy, recombinant ADAMTS13 (rADAMTS13) is functional to treat acute episodes or as prophylaxis in cTTP which can be triggered by infections, trauma, pregnancy and major surgery.

Case Report. A 46 year old female presented at our center in March 2026 in anticipation of elective major surgery. From childhood she suffered from cyclic thrombocytopenia with jaundice, treated by plasma transfusion. Notably, in 2016, because of multiple uterine fibroids, she underwent transverse laparotomic uterine myomectomy complicated by massive hemorrhage due to severe thrombocytopenia which required intensive care. In 2017 Coombs-negative hemolytic anemia occurred in addition to severe thrombocytopenia with deficiency of ADAMTS13 activity; therefore cTTP diagnosis was confirmed by molecular test. From April 2019 she started prophylaxis with fresh-frozen plasma (FFP) once per month with increased level of platelets and from September 2025 she started prophylaxis with rADAMTS13 (40 UI/kg equals to 2 vials of 1500 UI each one) every two weeks without any cTTP recurrence. As a precautionary measure, one vial was administered the day before the surgery and supplies of rADAMTS13 and FFP were stoked to deal with a possible relapse of cTTP. From the day of the surgery the patient was tested for blood count, hemolysis indices and ADAMTS13 activity, every day during the hospitalization and twice per week for the first month after the surgery. According to international guidelines, we decided to perform a vial of rADAMTS13 when ADAMTS13 activity was < 10%. It resulted in an administration of rADAMTS13 every two days for the first week after surgery and one administration per week for the first month after surgery.

Conclusions. cTTP is a very rare genetic condition: scientific literature does not set an optimal level of pre and postoperative ADAMTS13 activity. This case report evidences that rADAMTS13 is safe and improves the patient's QoL, especially while undergoing surgery. So if available we suggest intensifying rADAMTS prophylaxis (possibly weekly) and a close monitoring of ADAMTS13 levels which can be lower during the postoperative period.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

IMMUNOMODULATORY EFFECTS OF FOSTAMATINIB IN A PATIENT WITH EVANS SYNDROME, TRIPLE-POSITIVE ANTIPHOSPHOLIPID ANTIBODIES AND RELATED COAGULATION ABNORMALITIES

S. Bergonzi[1|2|3], G. Murante[1|2|3], M. Capetta[1|2|3], F. Valeri[1|2], C. Dainese[1|2], A. Valpreda[3|4], R. Pastorino[3|4], F. Bocchi[3|4], B. Bruno[2|3], A. Borchiellini[1|2]

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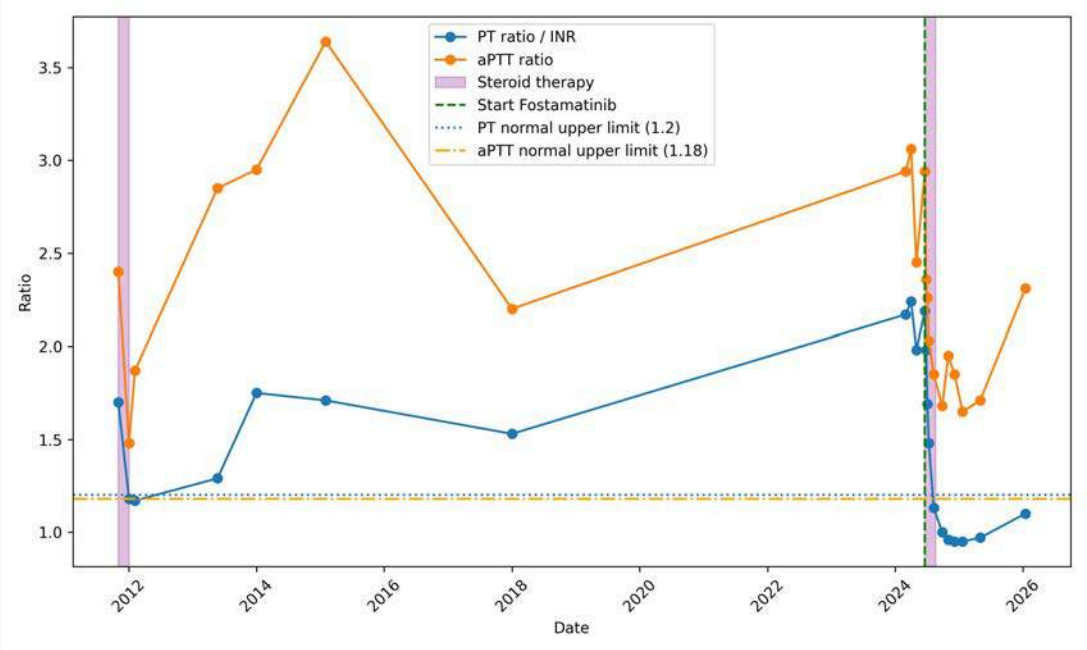
Background Fostamatinib is a spleen tyrosine kinase (Syk) inhibitor approved for immune thrombocytopenia, with emerging evidence suggesting a potential role in autoantibody-mediated disorders.

Case Report A 32-year-old man who, in 2011, following an infectious episode, presented with prolonged PT and aPTT and Coombs-positive hemolytic anemia. Further investigations showed triple positivity for antiphospholipid antibodies (aPL) (lupus anticoagulant, high-titer anticardiolipin and anti-β2GPI antibodies), medium-titer ANA, low C4 with normal C3. Steroid therapy was initiated, leading to complete resolution of hemolytic anemia and normalization of hemolysis markers, and was discontinued after two months. PT initially normalized and then showed progressive prolongation from 2013 onward. Concomitantly, thrombocytopenia was observed (nadir 69,000/mmc), along with mild splenomegaly and hilar lymphadenopathy. Bone marrow biopsy showed trilineage hyperplasia and features of hemophagocytosis; PET was negative, with a mild reduction in the CD4/CD8 ratio and no evidence of monoclonal gammopathy. Platelet count subsequently recovered spontaneously and remained stable (>100,000/mmc) for more than 10 years, with normalization of spleen size. aPL remained persistently positive in the absence of thrombotic events; primary prophylaxis with low-dose aspirin was initiated. Given the persistent prolongation of PT and aPTT, coagulation factor assays showed a concordant reduction of intrinsic pathway factors (VIII, IX, XI, XII), with normal FVII levels. No clinically relevant bleeding events occurred. In 2024, progressive thrombocytopenia recurred, together with the detection of medium-titer anti-prothrombin IgG antibodies. At a platelet nadir of 31,000/mmc, a short course of steroids and fostamatinib was initiated, resulting in platelet recovery; steroids were subsequently discontinued while fostamatinib was continued. Concomitantly, stable normalization of PT, negativization of anti-prothrombin antibodies, and normalization of coagulation factor levels were observed. (Figure 1)

Conclusions. Fostamatinib is a Syk inhibitor with immunomodulatory activity on autoantibody-mediated effector mechanisms. Its effect is predominantly functional rather than serological, as it modulates downstream signaling without directly eliminating autoantibodies. In this context, the present case suggests a potential role for Syk inhibition in modulating aPL-related coagulation abnormalities.

Stampa pp. 503-504


PT ratio / INR
aPTT ratio
Steroid therapy
Start Fostamatinib
PT normal upper limit (1.2)
aPTT normal upper limit (1.18)
Ratio
Date
3.5
3.0
2.5
2.0
1.5
1.0
2012
2014
2016
2018
2020
2022
2024
2026

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

AL AMYLOIDOSIS IN A PATIENT WITH SEVERE HEMOPHILIA A AND INHIBITORS WHO HAD A MONOZYGOTIC TWIN: SAME GENES, DIFFERENT OUTCOMES

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Sapienza, University of Rome

Background. Severe hemophilia A (HA) with inhibitors has been associated with high bleeding risk and complex management. AL amyloidosis is a rare plasma cell dyscrasia characterized by monoclonal light chain deposition with systemic involvement. We report a case of AL amyloidosis in a patient with severe HA and high-titer inhibitors, who had a monozygotic twin.

Case report. The patient and his brother were referred to our center in 1973 at the age of 10 for severe HA; the proband had also a high-titer inhibitor. Molecular analysis identified a F8 splice-site mutation (c.1537+1G>A). In 1991, the patient tested positive for HCV with spontaneous viral clearance. In 1995, an immune tolerance induction (ITI) attempt using the Malmö protocol failed. Thereafter the clinical course was complicated by multiple major bleeding events; nevertheless the patient repeatedly refused a new ITI course. After two iliopsoas hematomas, in 2010 and in 2014, he agreed to a second ITI course, initiated in July 2014 using pdFVIII/vWF concentrate (100 IU/kg/day). In August 2014 a severe episode of diffuse abdominal bleeding occurred, treated with large amount of rFVIIa in the emergency department. Thereafter, no further hemorrhagic events were reported, and the inhibitor titer progressively declined, reaching <1 BU in October 2016. Then, pdFVIII/vWF concentrate was tapered until reaching a dose of 40 IU/Kg/-day in March 2017. In August 2014, laboratory investigations revealed an IgD-λ monoclonal gammopathy, with a κ/λ free light chain ratio of 0.04 and urinary λ Bence-Jones protein excretion of 195mg/24h. The patient was a physician and at that time declined further evaluation. Two years later, in August 2016, the patient was diagnosed with heart failure with reduced ejection fraction and concentric left ventricular hypertrophy that led to a diagnosis of AL amyloidosis. Thereafter, treatment with VCD (bortezomib, cyclophosphamide, and dexamethasone) was initiated. A few days after starting therapy, in April 2017, the patient died from sudden cardiac death.His twin brother never developed an inhibitor and has a lambda monoclonal gammopathy without evidence of organ involvement. Last year he developed a cholangiocarcinoma.

Conclusions. This case shows the rare coexistence of severe HA with inhibitors and AL amyloidosis in a monozygotic twin, whose brother did never develop an inhibitor. This suggests that genetic background alone is not sufficient to determine the inhibitor event. Moreover, as regards the AL amyloidosis, we could speculate if previous treatment with cyclophosphamide, but also the immune stimulation during ITI may have contributed to clonal progression; otherwise his twin brother without inhibitor present a stable monoclonal gammopathy and developed a cholangiocarcinoma. Environmental factors could have had an impact on these divergent clinical histories: same genes, different outcomes.

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

TRANSIENT IDIOPHATIC ACQUIRED VON WILLEBRAND DISEASE: A RARE CHALLENGING CONDITION WITH A POSSIBLE RAPIDLY AND FAVOURABLE EVOLUTION

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Background and Aim. The AvWD is a rare but probably underestimated bleeding disorder characterized by laboratory findings and clinical presentations similiar to those of inherithed vWD. However, unlike the inherited disease, AvWS occurs in adults with no personal or family history of bleeding diathesis. Although AvWS is particularly frequent in lymphoproliferative or myeloproliferative disorders, it can also be associated with solid tumors, immunologic and cardiovascular disorders, and other miscellaneous conditions. The aim of this abstarct is to demonstrate the significance of follow-up in cases of AvWS without a recognised underlying cause, given the possibility of spontaneous clinical and laboratory resolution of the haemorrhagic condition.

Case report. We present a case of a 56 years-old woman that was referred to our centre in 2024 due to multiple episodes of epistaxis and easy bruising. She exhibited negative bleeding histories even in trigger conditions (surgery, childbirth) and no family history of bleeding diathesis. No comorbidities were present at diagnosis and both autoimmune evaluation and cancer screening were negative. One year after diagnosis, acomplete clinical and laboratory resolution was observed. As rare disease, the diagnostic process is complex and involves multiple steps, requiring an experienced and specialized laboratory. Despite pathological laboratory results, confirming the acquired nature of this disorder remains a significant diagnostic challenge. The first step routine coagulation tests and vWF screening were performed: factor VIII(FVIII:C) dosage, VWF Antigen(vWF:Ag), VWF activity (VWF:Ac), VWF ristocetin cofactor activity (VWF:RCo) and collagen binding assay (CBA). Afterwards, dilution and subsequent in vivo recovery test with plasma derived von Willebrand factor concentrate were performed. A genetic test was performed. Dilution and in vivo recovery tests strongly suggested an acquired form. Genetic analysis was inconclusive. One year after diagnosis, no more antibodies were found.

Conclusions. The AvWS is a rare bleeding disorder with a diagnostic work-up and optimal treatment highly individualized. The management remains challenging, particularly when discrepancies arise between laboratory findings and the patient's medical history. For this reason, especially in cases without an underlying cause, it is important to perform close follow-up for the possibility of rapid favorable resolution of the condition.

Parameter	2024	2025
FVIII:C	35%	120%
vWF Antigen (vWF Ag)	33%	90%
vWF Ristocetin Cofactor (vWF RCo)	8%	75%
vWF Collagen Binding Activity (vWF CBA)	22%	70%

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Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

CYTOMEGALOVIRUS INFECTION AS A CAUSE OF THERAPY REFRACTORY THROMBOTIC THROMBOCYTOPENIC PURPURA IN A PATIENT WITH STEROID INDUCED IMMUNOSUPPRESSION

V. Funari[1|2]

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I report a case of CMV infection occurring after steroid therapy in a patient with TTP, leading to early relapse and resistance to standard treatment.A 62 year old man presented to the Emergency Department of Trebisacce Hospital (Cosenza, Italy) in January 2026 with vomiting and jaundice. Initial laboratory investigations revealed severe anemia and thrombocytopenia, prompting transfer to the tertiary HUB Hospital of Cosenza. Further evaluation established the diagnosis of TTP based on Coombs negative hemolytic anemia, elevated hemolysis markers, and markedly reduced ADAMTS13 activity. The patient was admitted to the Internal Medicine Unit and started on high dose corticosteroid therapy and daily plasma exchange. Caplacizumab was added. Acute renal failure was managed with intravenous hydration, diuretics, and sodium bicarbonate.During hospitalization, inflammatory markers and procalcitonin levels progressively increased. A septic trigger of unknown origin was hypothesized, and empirical antibiotic therapy was initiated.After approximately three weeks without significant improvement, Rituximab was introduced, resulting in clinical and laboratory improvement within seven days, including rising hemoglobin and platelet counts and improved renal function.However, after a few days, laboratory tests demonstrated disease relapse despite ongoing combined therapy. The patient also reported severe asthenia, and inflammatory markers increased again despite persistently negative cultures. Virological testing revealed significant CMV viremia.Antiviral therapy with Ganciclovir was initiated alongside TTP specific treatment. Within four days, progressive clinical and laboratory improvement was observed, leading to discharge with continued corticosteroids and Caplacizumab.At early outpatient follow up, both clinical examination and laboratory tests confirmed continued improvement. Severe systemic manifestations of CMV infection predominantly affect immunocompromised patients, including those with drug induced immunosuppression such as corticosteroid therapy. Early identification of CMV infection is therefore crucial in patients with TTP, particularly in cases of therapeutic resistance or unexplained relapse. Further studies are needed to clarify whether effective preventive strategies against CMV should be implemented in patients with pharmacologically induced immunosuppression.

Hemostasis and thrombosis, Thrombocytopenia and thrombocytopathies

USE OF ROMIPLOSTIM IN LENALIDOMIDE INDUCED THROMBOCYTOPENIA : A SUCCESSFULL EXPERIENCE IN A MULTIPLE MYELOMA PATIENT

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Chemotherapy induced thrombocytopenia frequently complicates cancer treatment causing chemotherapy treatment delays, dose reduction and discontinuation. Also multiple myeloma's therapies like Lenalidomide induce thrombocytopenia. We described a pancytopenia occurred during Daratumumab-Lenalidomide-Dexamethasone (DaraRd) therapy successfully treated with Romiplostim(R). A 73 year old female patient affected by newly diagnosed multiple myeloma IgGlambda ISS II (cytogenetics: t(4;14),1 q21+) started first line therapy with DaraRd from August 2024 , at day 1 we observed leucocyte count 4,08 x10E9/L, neutrophil 2,60x 10E9/L, haemoglobin concentration (hb) 10 g/dl, platelet count 206x10E9/L. From October 2024 (III cycle) we prescribed Eritropoietin 10000UI weekly (Hb 9,3 g/dl) , G-CSF at day 22 and 23 of each cycle, we reduced Lenalidomide from 25 mg to 15 mg for fatigue. After the first cycle we detected a partial response of disease. On November 14th (IV cycle) a isolate severe anemia was found (hb 4,2 g/dl, plt 148x10E9/L) and we have carried out the following investigation: negative viral studies ,negative occult blood, normal hemolysis indices, reduced reticolocytes, no vitamin B12 and folate deficiency, high ferritin and sideremia. From January 2nd 2025 we discontinued DaraRd for pancytopenia (Neutrophil 0,92x10E9/L, Hb 5,8 g/dl, plt 25x10E9/L)The patient required blood and platelet trasfusion twice a week for severe persistent anemia and platelet count < 10x10^9/L. The bone marrow biopsy showed an average cellularity of 5-10%, a plasma cells infiltrate of 10%, high reduction of three hematopoietic lines, karyotyping and FISH fail. From February 26th Romiplostim was started according from 1 mcg/kg weekly starting dose until 10mcg/kg. From March 26th we started Carfizomib dexamethasone for newly bone lesions detected on CT scan. After 10 weeks of therapy platelet count was 57x10E9/L, after 4 months (in July) we observed a complete response of platelet count (192x10E9/L), we discontinued Eritropoietin and G-CSF, the patient achieved a very good partial response of multiple myeloma. We gradually reduced Romiplostim until 4 mcg/kg every 2 weeks, last platelet count was 123x10E9/L (on March 18th 2026) In conclusion romiplostim was effective for the management of Lenalidomide induced thrombocytopenia , in reducing platelet transfusion, in getting a lasting response(1 year), and allowing resumption of myeloma's therapy.

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Acute lymphocytic leukemia

PROGNOSTIC SIGNIFICANCE OF IKZF2::NOTCH1 REARRANGEMENT IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA: A CASE OF PRIMARY INDUCTION FAILURE CHALLENGING THE LBL/ALL DICHOTOMY

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Activating NOTCH1 mutations are frequent and generally favorable in T-ALL, whereas NOTCH1 fusions are rare (<1%). Genomic studies identify NOTCH1 fusions (e.g., IKZF2::NOTCH1) as a hallmark of T-Lymphoblastic Lymphoma (T-LBL), practically absent in leukemias. These fusions define a distinct subgroup characterized by specific gene expression and, particularly in IKZF2 rearrangements, chemotherapy resistance. We report a case of IKZF2::NOTCH1--positive T-ALL, discussing if this alteration identifies a distinct entity transcending the leukemia/lymphoma classification.A 16-year-old foreign female patient, diagnosed while temporarily in Italy, presented with pancytopenia and splenomegaly. Bone marrow (BM) revealed 44% blasts. Immunophenotyping confirmed cortical T-ALL (EGIL T-III, CD1a+, sCD3 dim). Induction started per AIEOP-BFM 2017. Despite an initial Prednisone Good Response (PGR) at Day +8, subsequent BM assessments showed induction failure. Flow cytometric MRD revealed 48.8% blasts at Day +15 and 25% at End of Induction (Day +33). Targeted FISH identified an IKZF2::NOTCH1 rearrangement (23% nuclei) and biallelic CDKN2AB deletion (9p21). She was later repatriated to her home country for further management.This case challenges the segregation of NOTCH1 fusions exclusively to T-LBL. Despite overt leukemic presentation, the patient harbored the IKZF2::NOTCH1 fusion. While formally T-ALL, this rearrangement defines a high-risk biological profile with intrinsic chemoresistance, shared by LBL. The clinical course showed a discrepancy between initial steroid sensitivity (PGR) and subsequent marrow refractoriness. Following repatriation, salvage attempts with nelarabine and daratumumab-based regimens proved completely ineffective. Evaluated for a CAR-T trial, she was deemed ineligible. She never achieved remission and died of progressive disease 6 months after onset. This profound refractoriness confirms that IKZF2 fusions confer a poor prognosis independent of favorable markers like the cortical immunophenotype-.IKZF2::NOTCH1 in T-ALL represents a transversal marker of high-risk disease. Regardless of the LBL/ALL distinction, this fusion predicted primary induction failure and resistance to targeted therapies. Screening for NOTCH1 rearrangements is crucial in T-ALL patients with discrepant responses (e.g., PGR but poor BM clearance) to identify candidates for early experimental approaches before clinical deterioration.

Acute lymphocytic leukemia

VENETOCLAX AND DECITABINE AS SALVAGE THERAPY IN RELAPSED T-CELL LYMPHOBLASTIC LYMPHOMA POST-ALLO-HSCT

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Background Relapsed T-cell Lymphoblastic Lymphoma (T-LBL) post-allogeneic hematopoietic stem cell transplantation (allo-HSCT) carries a poor prognosis with limited options. We present a heavily pretreated patient with Very High Risk (VHR) T-LBL who achieved a significant response to a salvage regimen of Venetoclax and Decitabine (VEN-DEC).
Case Report. In September 2020, a patient was diagnosed with VHR CD1a-negative T-LBL with central nervous system, but no bone marrow, involvement. Following 8 cycles of GIMEMA LAL1913 induction, lacking an available HLA-identical donor, he underwent consolidative autologous stem cell transplantation in December 2021. A bone marrow and lymph node relapse occurred in May 2022. Salvage therapy with Venetoclax and Navitoclax was initiated in June 2022. Due to disease progression in August 2022, re-induction with Nelarabine, Cyclophosphamide, and Etoposide was administered, yielding an excellent metabolic response. In October 2022, he received a haploidentical allo-HSCT. The post-transplant course was complicated by severe Veno-Occlusive Disease and chronic pulmonary Graft-versus-Host Disease (GvHD). In June 2025, a second relapse was confirmed by bone marrow minimal residual disease (MRD) positivity. As a second allo-HSCT was precluded due to donor unavailability and patient frailty related to comorbidities, the VEN-DEC regimen was initiated as salvage therapy.
Results. The patient showed an excellent response to VEN-DEC. A November 2025 PET-FDG scan showed regression of the mediastinal lesion, leaving a 1.8 cm residual tissue (SUVmax 1.1). Bone marrow evaluation confirmed the achievement of MRD negativity. The patient completed the 8th cycle in March 2026 and currently awaits a follow-up PET scan to evaluate consolidative mediastinal radiotherapy.
Conclusions. VEN-DEC proved to be an effective salvage strategy in a therapeutic scenario lacking consolidated alternatives for relapsed VHR T-LBL post-allo-HSCT. Notably, the patient achieved a significant metabolic response and MRD negativity. Furthermore, despite the heavy prior therapeutic burden and the presence of chronic GvHD, the treatment was well-tolerated with no significant complications.

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Acute lymphocytic leukemia

SEQUENTIAL IMMUNOTHERAPY AND TRIPLE ALLOGENEIC STEM CELL TRANSPLANTATION IN RELAPSED/REFRACTORY VERY HIGH-RISK B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background. We describe the clinical course of a 34-year-old male patient diagnosed in June 2018 with very high-risk (VHR) B-cell precursor acute lymphoblastic leukemia (ALL), whose initial presentation was complicated by spontaneous splenic rupture.
Clinical Course. Following induction chemotherapy, the patient achieved complete remission (CR) and underwent a first allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-identical sibling in December 2018. Three months later, the patient developed bone marrow and central nervous system (CNS) relapse. Following blinatumomab failure, a second CR was achieved with inotuzumab ozogamicin, and the patient underwent a second HSCT from a matched unrelated donor in December 2019. A second bone marrow and CNS relapse occurred in late 2021 and was successfully managed with CAR-T cell therapy (February 2022), yielding a third CR sustained for more than three years.In May 2025, a third relapse occurred with multi-site involvement encompassing bone marrow, CNS, and extramedullary disease (mediastinal mass with myopericardial infiltration). Following emergency pericardiocentesis, the patient received bridging chemotherapy with cytarabine (AraC) and high-dose methotrexate (HD-MTX). Given persistent MRD positivity, he underwent two further cycles of inotuzumab ozogamicin, achieving a fourth MRD-negative CR.Third HSCT and Follow-up: In November 2025, the patient underwent a third allogeneic HSCT from the same HLA-identical sibling donor, using CD34+-selected cells with regulatory T-cell (Treg)/conventional T-cell (Tcon) co-infusion. The early post-transplant course was complicated by mild sinusoidal obstruction syndrome (SOS/VOD), bacterial infection, and CMV reactivation. Approximately two months post-transplant, the patient developed post-transplant immune thrombocytopenia, successfully managed with eltrombopag. Subsequently, the patient developed an episode of ischemic colitis requiring partial intestinal resection.
Conclusions. Notwithstanding these severe complications, the patient currently remains in complete hematological remission with an adequate performance status. This case illustrates that a strategy of sequential novel immunotherapies combined with repeated allogeneic HSCT can achieve durable disease control in very high-risk, multiply relapsed ALL, and supports the feasibility of a third allogeneic transplant in carefully selected patients.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

BTK INHIBITORS IN CHRONIC LYMPHOCYTIC LEUKEMIA: A REAL-WORLD COMPARATIVE ANALYSIS OF EFFICACY AND TOXICITY ACROSS GENERATIONS

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Background. Bruton's tyrosine kinase inhibitors (BTKi) represent a cornerstone therapeutic approach in chronic lymphocytic leukemia (CLL). This study evaluates real-world outcomes of first- and second-generation BTKi (ibrutinib, acalabrutinib, zanubrutinib), focusing on efficacy and safety compared with pivotal clinical trials, with particular attention to cardiovascular and non-cardiovascular adverse events.

Methods This observational study included 71 CLL patients treated with BTKi (ibrutinib n=29, acalabrutinib n=29, zanubrutinib n=13). Clinical, biological, and treatment-related variables were analyzed, including age, sex, comorbidities, disease stage, IGHV, TP53, del(17p), line of therapy, and adverse events. Data were collected via case report form and analyzed descriptively (May–December 2025).

Results Zanubrutinib patients had a mean age of 77 years and 69% male prevalence; acalabrutinib patients had a mean age of 76 years (59% male), while ibrutinib patients had a mean age of 67 years (72% male). 71% had comorbidities. Hypertension was the most frequent comorbidity (37%), followed by diabetes (13%). Overall, 6 cardiovascular and 14 non-cardiovascular adverse events were recorded. In second-generation BTKi, non-cardiovascular events predominated (13 vs 2 cardiovascular). In contrast, ibrutinib showed more cardiovascular events (4 vs 1 non-cardiovascular), including two cases of atrial fibrillation requiring switch to second-generation BTKi. No severe hypertension and clinically significant bleeding events were observed.

Conclusions. The study population was comparable to registrational trials in age and sex distribution. Hypertension did not limit treatment initiation due to adequate cardiological monitoring. Although the sample size was smaller than pivotal trials, findings remain clinically relevant. Second-generation BTKi showed a predominance of non-cardiovascular toxicity, while ibrutinib was associated with more cardiovascular events, confirming the known safety profile of first-generation BTKi. The absence of severe hypertension and lower-than-expected cardiovascular events may reflect pre-existing comorbidities and optimized multidisciplinary management. Non-cardiovascular adverse events were generally manageable and rarely required hospitalization. Less common toxicities such as visual disturbances, hallucinations, hearing loss, nephroangiosclerosis, and acute renal failure were observed and may warrant further clinical attention.

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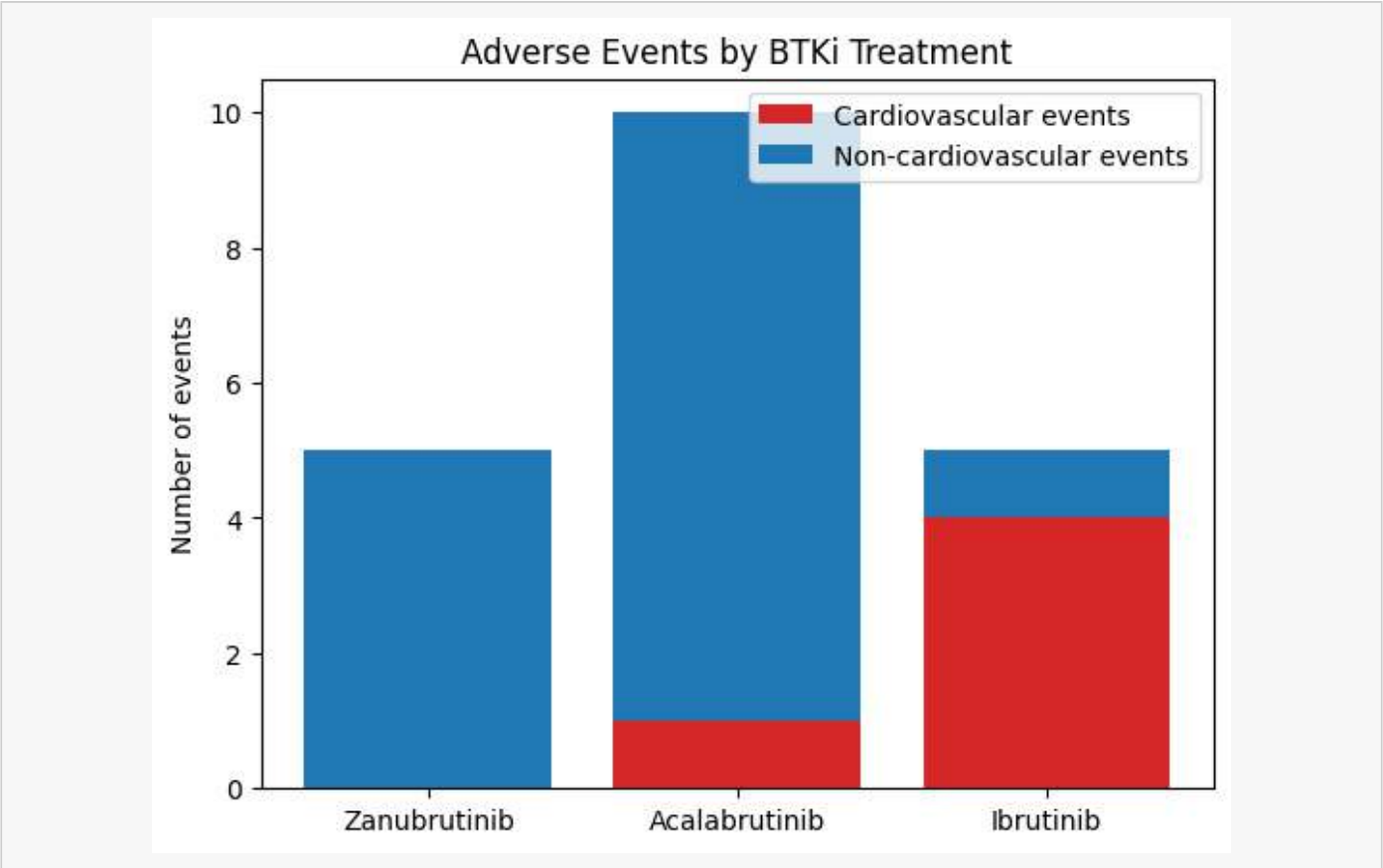
Adverse Events by BTKi Treatment
Cardiovascular events
Non-cardiovascular events
Number of events
0
2
4
6
8
10
Zanubrutinib
Acalabrutinib
Ibrutinib

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

CLINICAL AND ECONOMIC EVALUATION OF FIXED-DURATION ACALABRUTINIB-BASED REGIMENS IN FIRST-LINE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA IN ITALY

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Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, characterized by a median age at diagnosis of approximately 70 years and a prolonged clinical course associated with substantial healthcare resource utilization. The increasing availability of targeted therapies, particularly fixed-duration regimens, has introduced new opportunities to improve clinical outcomes while optimizing healthcare sustainability. This study aimed to assess the clinical and economic impact of introducing acalabrutinib-based fixed-duration regimens (Acalabrutinib + Venetoclax [AV] and Acalabrutinib + Venetoclax + Obinutuzumab [AVO]) as first-line treatment in Italy, from the perspective of the National Health Service (NHS).A cost-consequence analysis was performed using a state-transition model with three health states (progression-free, progressed disease, death), stratified by treatment status (on/off therapy), over a 20-year time horizon. Clinical inputs were derived from the AMPLIFY phase III trial, while post-progression survival was informed by the ASCEND study. For comparators not included in AMPLIFY, equivalent efficacy was assumed (HR=1). Direct healthcare costs included drug acquisition, administration, grade ≥3 adverse events, and subsequent treatments, based on Italian official tariffs. Two scenarios were evaluated: a base-case including all reimbursed therapies and an alternative scenario restricted to fixed-duration regimens.In the base-case scenario (1,000 patients), the introduction of AV/AVO resulted in total cost savings of €22.6 million over 20 years, mainly driven by reductions in drug costs (−€11.7 million) and subsequent treatment costs (−€10.5 million). The break-even point was reached between years 4 and 5, with costs shifting from +€0.66 million at year 4 to −€3.21 million at year 5, reflecting an early offset of initial treatment costs. In the alternative scenario, net savings amounted to €5.7 million despite higher upfront drug costs, due to reduced downstream resource utilization. The break-even point was achieved between years 6 and 7, with costs decreasing from +€0.12 million to −€0.96 million.Acalabrutinib-based fixed-duration regimens represent a clinically effective and economically sustainable strategy for first-line CLL management, contributing to improved patient outcomes, reduced healthcare burden, and more efficient allocation of NHS resources.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

COMPARATIVE MRD ASSESSMENT AND IMMUNE PROFILING IN R/R CLL TREATED WITH VENETOCLAX-RITUXIMAB: INSIGHTS FROM "DEDALUS"

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Background. Fixed-duration Venetoclax (Ven) combined with Rituximab (R) has revolutionized the management of relapsed/refractory chronic lymphocytic leukemia (R/R CLL), demonstrating substantial long-term survival and deep molecular responses. Precise monitoring of minimal residual disease (MRD) is paramount for predicting clinical outcomes. The "Dedalus" protocol sought to compare the performance of multiparametric flow cytometry (MFC) against next-generation sequencing (NGS) while investigating treatment-induced immunological shifts.

Methods. We evaluated 22 patients using ERIC-compliant MFC and Lymphotrack NGS (sensitivity threshold: 10^-5). Treatment response was monitored via advanced ultrasonography. MRD status and immune cell subsets were longitudinally assessed at months 1, 6, 12, and 18, or at the point of therapy cessation.

Results. Clinical efficacy was high, with 20 patients (90.9%) achieving complete remission (CR). At the initial assessment, 15 patients reached undetectable MRD (uMRD) by both methodologies. Notably, NGS identified residual IgH clonality (3–45 clonal cells per 10^6) in two cases of partial response where MFC remained negative. Beyond MRD, Ven-R therapy induced profound B-cell depletion and a contraction of the CD4+ T-cell compartment, resulting in a skewed CD4/CD8 ratio in 25% of the cohort. NGS findings demonstrated superior correlation with clinical progression, particularly in cases of low-level disease burden.

Conclusions. The R-Ven regimen confirms high efficacy in R/R CLL. While MFC remains a standardized and accessible tool, NGS provides enhanced sensitivity that better aligns with long-term outcomes. These data support further exploration of digital PCR for IgH monitoring and a deeper interrogation of Venetoclax-mediated immunomodulation.

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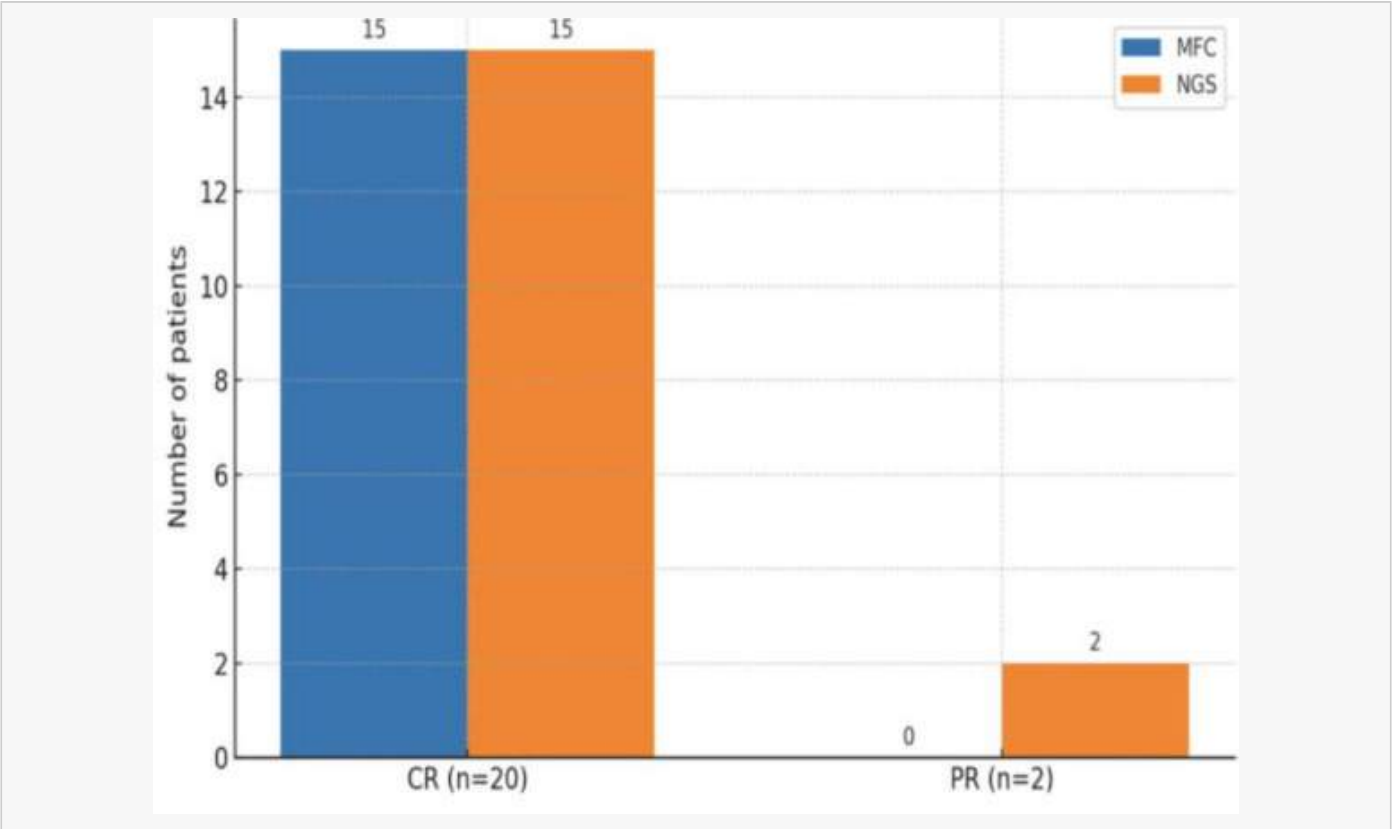

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD EXPERIENCE WITH ZANUBRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA: INTERIM RESULTS FROM THE COMPASSIONATE-USE RETROSPECTIVE COHORT OF THE AZALEA STUDY

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Background. Zanu, a highly selective BTK inhibitor, has demonstrated efficacy in patients (pts) with treatment naive (T-N) or relapsed/refractory (R/R) CLL. However, real-world evidence is limited. AZALEA (EMA RWD ID 1000000437) is an observational study of zanu treatment in pts with TN or R/R CLL in Italy.

Methods. AZALEA will enroll ≈350 pts in 2 cohorts: A (retrospective-prospective; ≤50 pts in the Italian compassionate use program [CUP]; May 2020-Oct 2023) and B (prospective; 300 pts in routine practice). Primary endpoint is time to treatment discontinuation (TTD). Secondary endpoints are reasons for discontinuation, dosing patterns (QD/BID), progression-free survival (PFS), overall survival (OS), discontinuation rates/causes, and safety. This interim analysis (IA) presents cohort A data.

Results. By 26Feb2025 data cutoff, 44 pts were enrolled in cohort A; 42 were evaluable. Median age was 78y (range, 53-93); 59.5% were male. Main baseline cardiovascular (CV) comorbidities were hypertension (61.9% [n=26]) and atrial fibrillation (AF; 33.3% [n=14]). Seven pts (16.7%) were on antiplatelet therapy and 14 (33.3%) on anticoagulants. Twenty-eight pts had R/R CLL, with a median of 3 prior therapies (range, 1-8). The most common starting dose was 320 mg/-day (n=30 [n=6 QD; n=24 BID]); 12 pts received reduced doses (160 mg/day n=10; 80 mg/day n=2). After a median follow-up of 22.9 months (95% CI, 19.9-27.9), median TTD was not reached; 17 pts (40.5%) discontinued zanu (3 TN [21.4%]; 14 R/R [50.0%]). Most discontinuations occurred within 6 months due to progression/relapse (n=4), death (n=4), adverse events (AEs, n=4), physician decision (n=3), and other (n=2). The most common treatment-emergent adverse drug reaction was neutropenia (n=6 [14.3%]; n=4 grade 3/4). AF occurred in 1 pt (2.4%; grade 2); 7 bleeding events were reported, all grade 1/2. Median PFS and OS were not reached. Eleven deaths occurred (n=2 TN; n=9 R/R).

Conclusions. This IA describes a real-world cohort of pts with CLL receiving zanu through CUP. In this population, characterized by a high burden of CV comorbidities precluding eligibility for other available targeted therapies, and heavily pretreated patients, zanu proved feasible, with only 4 discontinuations due to AEs and no unexpected safety signals. Early discontinuations and deaths may reflect the underlying characteristics of the cohort. Data from the larger prospective cohort will clarify treatment patterns, discontinuation and outcomes.

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NEUTROPHIL-TO-LYMPHOCYTE RATIO MIRRORS LEUKEMIC CLONE BURDEN BY FLOW CYTOMETRY AT DIAGNOSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Background. In chronic lymphocytic leukemia (CLL), peripheral blood lymphocytosis reflects expansion of a $CD5^+/CD19^+$ leukemic clone, usually assessed by flow cytometry (FC). The neutrophil-to-lymphocyte ratio (NLR) is often considered a marker of systemic inflammation, although in CLL it may also reflect changes in peripheral blood cell distribution. Its relationship with leukemic clone burden at diagnosis is still not well defined.

Methods. We retrospectively evaluated 33 patients newly diagnosed with CLL between 2024 and 2025. Immunophenotyping was performed by FC, and the percentage of $CD19^+/CD5^+$ leukemic cells was recorded. Hematological parameters were obtained from routine blood tests. Patients were stratified according to the median clone percentage, and correlations were assessed using Spearman's coefficient.

Results. Median lymphocyte count at diagnosis was 11,800/µL (range 2,320–142,900), with a median clone percentage of 82%. Hemoglobin and platelet values were generally preserved, and immunophenotypic features were consistent with typical CLL. An inverse correlation was observed between NLR and leukemic clone percentage ($\rho = -0.63$, $p = 0.003$). Patients with higher clonal burden showed lower NLR values (median 0.20 vs 0.53). This pattern may reflect a shift in peripheral blood composition related to lymphocyte expansion, with a relative reduction of neutrophils. A modest association between hemoglobin and age suggests that anemia at diagnosis was more related to patient factors than to disease burden.

Conclusions. At diagnosis, NLR appears to reflect leukemic clone burden in CLL, with an inverse relationship with clonal expansion. In this context, it may represent a simple parameter related to blood cell distribution rather than inflammation alone. Being readily available from routine blood tests, NLR could be considered alongside flow cytometry in the initial evaluation of CLL. Further studies are needed to better understand its clinical significance.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

REAL-WORLD USE OF TPO RECEPTOR AGONISTS IN SECONDARY IMMUNE THROMBOCYTOPENIA ASSOCIATED WITH INDOLENT LYMPHOPROLIFERATIVE DISORDERS: A 12-YEAR MONOCENTRIC EXPERIENCE

V. Innao, O. Bianco, V. Leotta, M. Di Giorgio, A. Barbagallo, A. Gorgone, M. Salerno, G. Uccello, A. Todaro, F. Lo Presti, R. Calogero, V. Uccellatore, U. Consoli

UOC Ematologia - ARNAS Garibaldi

Introduction. Immune thrombocytopenia (ITP) secondary to indolent lymphoproliferative disorders (LPDs), including chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL), and Waldenström macroglobulinemia (WM), represents a challenging clinical condition. In patients not meeting criteria for disease-directed therapy, management is focused on thrombocytopenia control. Thrombopoietin receptor agonists (TPO-RAs) are widely used in primary ITP, but data in secondary forms are limited.Patients and aim: We retrospectively evaluated efficacy and safety of TPO-RAs in 11 patients with ITP secondary to LPDs treated between March 2014 and March 2026. The cohort included 8 males and 3 females, with a median age of 68 years (range 52–81) and a median baseline platelet count of 18×10^9/L (range 4–36). Underlying diseases were CLL (n=6), MZL (n=3), and WM (n=2). None met criteria for LPD treatment (no cytopenias other than thrombocytopenia, no bulky disease, no B symptoms, IgM ≤6 g/dL). High-risk biological features were excluded (del17p/TP53 in CLL, TP53 in MZL, CXCR4 in WM). Among CLL patients, 5/6 had mutated IGHV. Three patients received romiplostim and eight eltrombopag (Fig. 1).

Results. Overall response rate (platelets ≥50×10^9/L) was 100%. Complete response (≥100×10^9/L) was achieved in 6/11 patients (55%), including 4 treated with eltrombopag and 2 with romiplostim. Median dose was 50 mg/day (range 25 mg alternate days–75 mg/day) for eltrombopag and 5 µg/kg/week (range 3–8) for romiplostim. No patients received avatrombopag. No new safety signals emerged. One arterial thrombosis (acute myocardial infarction) and one venous thromboembolism (deep vein thrombosis) occurred, both managed with standard therapy. No discontinuations were reported. No sustained response off-treatment (SROT) was observed (Fig. 1).

Conclusions. TPO-RAs are highly effective in controlling thrombocytopenia in secondary ITP associated with indolent LPDs not requiring immediate treatment. However, responses appear dependent on continuous therapy, with no SROT observed, likely reflecting persistent immune dysregulation. In the era of fixed-duration targeted therapies, the role of long-term TPO-RAs should be balanced against thrombotic risk and treatment burden. Larger studies are needed to confirm these findings.

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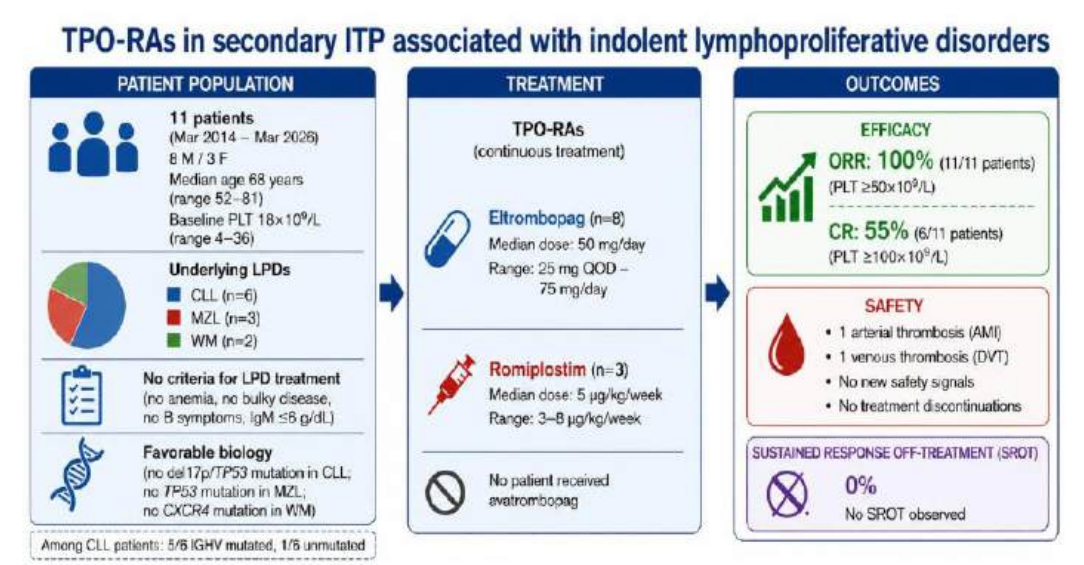

Figure 1. Real-world experience with thrombopoietin receptor agonists (TPO-RAs) in 11 patients with secondary immune thrombocytopenia (ITP) associated with indolent lymphoproliferative disorders (CLL, MZL, WM) not requiring disease-directed therapy. All patients achieved a platelet response (≥50×10⁹/L), with complete response in 55%. No sustained response off-treatment (SROT) was observed. Two thrombotic events occurred (one arterial and one venous), with no treatment discontinuations.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

FROM CONSENSUS TO PRACTICE: REAL WORLD IMPLEMENTATION OF FIXED-DURATION IBRUTINIB-VENETOCLAX IN CHRONIC LYMPHOCYTIC LEUKEMIA

V. Innao, V. Leotta, O. Bianco, M. Di Giorgio, A. Barbagallo, A. Gorgone, M. Salerno, G. Uccello, A. Todaro, F. Lo Presti, R. Calogero, V. Uccellatore, U. Consoli

UOC Ematologia - ARNAS Garibaldi

Introduction. Fixed-duration ibrutinib–venetoclax (Ven-I) represents an effective frontline strategy in chronic lymphocytic leukemia (CLL), combining deep responses with time-limited treatment. However, several practical aspects remain undefined in routine clinical practice. Recents Delphi consensus identified key domains influencing Ven-I use, including cardiovascular risk assessment, dose adjustments, and patient-centered decision-making.Patients and aim: We aimed to evaluate the real-world applicability of Delphi-derived recommendations through a monocentric experience with Ven-I. Sixteen consecutive CLL patients treated with first-line fixed-duration Ven-I between March 2024 and March 2026 were retrospectively analyzed (Tab. 1). Baseline characteristics, clinical outcomes, response kinetics, and safety were assessed and compared with the predefined Delphi domains.

Results. Responses deepened over time, with partial responses predominating at 3 months (93.8%), followed by a progressive increase in complete responses (25% at 6 months; 37.5% at 9 months; 25% at end of treatment). Treatment choice was driven by high efficacy expectations, patient preference for time-limited therapy, and a multidimensional evaluation including comorbidities, functional status, and lifestyle factors, consistent with Delphi findings and aligned with current guideline recommendations5. At a median follow-up of approximately 22 months, progression-free survival remained high, with no documented disease progression; one death unrelated to disease progression was recorded, due to pneumonia. The safety profile was manageable: grade ≥3 adverse events occurred in 31.3% of patients; atrial fibrillation was infrequent (6.3%) and no major bleeding events were reported. Dose reduction of ibrutinib was required in 6.3% of cases, while temporary treatment interruption occurred in 18.8%, without compromising overall outcomes.

Conclusions. This real-world experience confirms the feasibility and effectiveness of fixed-duration Ven-I, showing strong alignment with expert consensus domains. The progressive deepening of responses and favorable safety profile support its use in appropriately selected patients. Nonetheless, variability in clinical management highlights the absence of standardized algorithms and underscores the need for individualized strategies integrating clinical judgment, patient preferences, and consensus-based frameworks.

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Characteristic	All patients (N = 16)
Median age, years (range)	71.5 (51–78)
Age, n (%)	
< 65 years	5 (31.3)
≥ 65 years	11 (68.8)
Sex, n (%)	
Female	5 (31.3)
Male	11 (68.8)
Median time from CLL diagnosis, months (range)	44 (6–228)
ECOG performance status, n (%)	
0 – 1	10 (62.5)
2	5 (31.3)
> 2	1 (6.3)
Median CIRS score (range)	7 (3–22)
CIRS > 6, n (%)	13 (81.3)
< 65 years	3 (23.1)
≥ 65 years	10 (76.9)
Rai stage, n (%)	
0 – 2	3 (18.8)
3 – 4	13 (81.3)
Unmutated IGHV, n (%)	7 (43.8)
TP53 mutation, n (%)	0 (0)
Median time on treatment, months (range)	12 (9–12)
Patients completing treatment, n (%)	5 (31.3)
Treatment discontinuation, n (%)	3 (18.8)

Table 1. Baseline demographic and clinical characteristics of patients with chronic lymphocytic leukemia treated with first-line fixed-duration ibrutinib–venetoclax.
Abbreviations: CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; CIRS, Cumulative Illness Rating Scale; IGHV, immunoglobulin heavy-chain variable region; TP53, tumor protein p53.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

SONROTOCLAX (BGB-11417) + ZANUBRUTINIB *VS.* VENETOCLAX + ACALABRUTINIB IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA: A PHASE 3 RANDOMIZED TRIAL DESIGN (CELESTIAL-TNCLL-2)

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Background. Inhibition of B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) has emerged as an effective fixed-duration treatment (tx) strategy that can induce high rates of undetectable minimal residual disease (uMRD) in patients (pts) with TN CLL. AV is approved in the EU as a first-line fixed-duration tx for TN CLL. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib is a highly potent 2nd-generation BTK inhibitor approved in the US/EU for CLL. In an ongoing phase 1/1b trial (NCT04277637), SZ has had promising efficacy, with a 100% ORR (n=135) and high rates of blood uMRD at 10-4 sensitivity (uMRD4) in pts with TN CLL, including those with high-risk disease features. SZ was generally well tolerated, with neutropenia as the most common grade ≥3 TEAE and no laboratory or clinical TLS events observed. The phase 3 trial BGB-11417-304 (NCT07277231) was designed to directly compare fixed duration SZ vs AV in TN CLL to investigate whether SZ compared with AV, may improve efficacy in terms of achieved uMRD rate after completing treatment and PFS and potentially improve tolerability and safety.

Methods. BGB-11417-304 is a global phase 3, open-label, randomized study. Eligible adults have a confirmed diagnosis of previously untreated CLL requiring tx per iwCLL 2018 criteria, ECOG PS 0-2, and measurable disease confirmed by CT/MRI. ~500 pts will be enrolled and randomized 1:1 to arm A (3 lead-in cycles of oral zanubrutinib monotherapy followed by 12 cycles of oral SZ) or arm B (2 lead-in cycles of oral acalabrutinib monotherapy followed by 12 cycles of oral AV). Randomization will be stratified by age (<65 y vs ≥65 y), IGHV mutation status, and presence of del(17p) and/or TP53 mutations. The primary endpoint is PFS in arm A vs arm B, as determined by independent review committee (IRC), with an intermediate endpoint of uMRD4 rate in blood and bone marrow in arm A vs arm B, assessed by next-generation sequencing (clonoSEQ) at the first post-tx follow-up visit. Key secondary endpoints are PFS-IRC in high-risk subgroups and OS. Other secondary endpoints are ORR and complete response assessed by IRC and investigator (INV), uMRD5 rate (clonoSEQ), PFS-INV, duration of response by IRC and INV, time to next tx, pt-reported outcomes, and safety/tolerability. Enrollment is currently ongoing.

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Chronic lymphocytic leukemia and other lymphoproliferative syndromes

PROGNOSTIC IMPACT OF TP53 ABERRATIONS IN RICHTER TRANSFORMATION: A SINGLE-CENTER EXPERIENCE IN THE ERA OF TARGETED CLL THERAPIES

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Background. Richter Transformation (RT) represents a critical evolutionary milestone in chronic lymphocytic leukemia (CLL), posing significant therapeutic hurdles, especially post-targeted agent exposure. This study aims to elucidate the clinical landscape, molecular profiles, and survival outcomes of RT patients, with a specific emphasis on the role of TP53 disruptions.

Methods. We retrospectively reviewed 12 consecutive patients diagnosed with RT at our institution between 2012 and 2025. Analysis focused on clinico-biological markers, including IGHV status, del(17p), TP53 mutations, and karyotype complexity. Outcomes were assessed using Lugano 2014 criteria and overall survival (OS) from RT diagnosis.

Results. At RT diagnosis (median age 66), 91.7% of patients were pretreated for CLL, including 58.3% previously exposed to BTK inhibitors. High-risk features were prevalent: TP53 mutations (41.7%), del(17p) (33.3%), and complex karyotypes (25%). Histological subtypes were predominantly DLBCL-type (66.7%). Despite diverse salvage strategies (chemo-immunotherapy, targeted agents, or cellular therapies), the ORR was limited to 41.7%. Notably, TP53 aberrations significantly curtailed survival, with a median OS of 5.2 months versus 13.8 months in wild-type cases. All fatalities occurred within the high-risk DLBCL subgroup.

Conclusions. This real-life series underscores that TP53 aberrations remain the primary driver of poor prognosis in RT, even in the targeted therapy era. The dismal outcomes observed in pretreated patients highlight an urgent need for novel, non-chemotherapy-based therapeutic paradigms.

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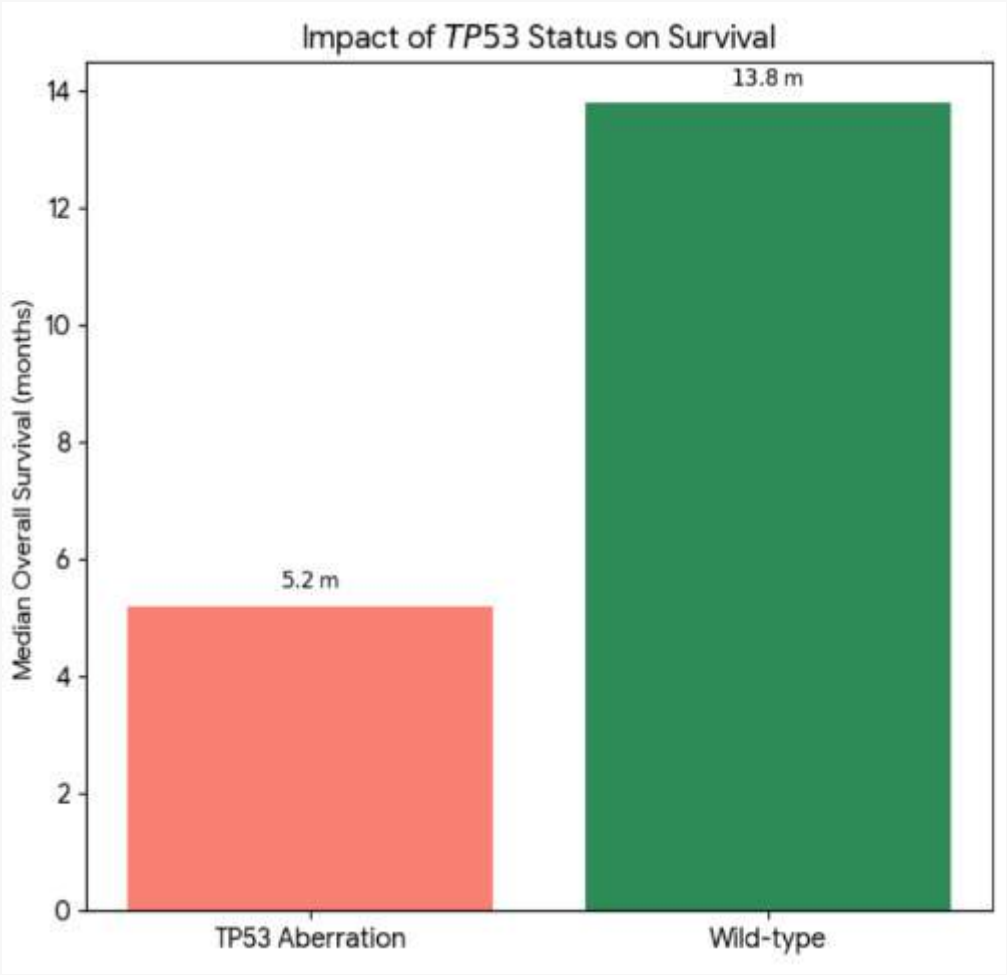

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Acute myeloid leukemia

OUTPATIENT CONSOLIDATION WITH CPX-351 IN AML: REAL-WORLD EVIDENCE SUPPORTING SAFETY, FEASIBILITY, AND DECREASED HOSPITALIZATION

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Background. CPX-351 is approved for high-risk acute myeloid leukemia (AML), including therapy-related AML and AML with myelodysplasia-related changes. Consolidation is usually administered in an inpatient setting due to concerns about prolonged cytopenias and infections. However, outpatient management may represent a safe and resource-sparing alternative.

Methods. We conducted a retrospective single-center study of AML patients treated with CPX-351 between April 2019 and January 2026. Data included response, infections, and hospitalization. Outpatient management was defined as day-hospital administration with admission only if clinically required.

Results. Fifty-nine patients (28 males, 31 females) with a median age of 59 years (range 22–75) received inpatient induction. During induction, infections occurred in 35 patients, including 6 deaths (3 of which associated with concomitant disease progression).Among 53 evaluable patients, 30 achieved complete remission (CR), 7 CR with incomplete hematologic recovery (CRh), 3 partial response, and 13 were refractory. Thirty patients received first consolidation: 15 outpatients and 15 inpatients; median hospitalization duration was respectively 0 and 21 days. Among outpatients, 7 required hospitalization (6 for prolonged cytopenias, 1 for fever), with a median stay of 11.5 days (range 6–14). Infectious complications occurred in 6 hospitalized patients (including 1 death due to COVID-19) and in only 1 outpatient. Response after first consolidation showed CR in 29 patients. Among these, 10 underwent allogeneic stem cell transplantation, 1 received alternative chemotherapy, 2 relapsed, and 16 proceeded to second consolidation. During second consolidation, 9 patients were treated as outpatients and 7 as inpatients; median hospitalization duration was respectively 0 versus 22.5 days. Among outpatients, 3 required hospitalization (1 for fever, 2 for cytopenias), with a median stay of 7 days (range 6–8). Infections occurred in 3 hospitalized patients and in 1 outpatient. All patients achieved CR after second consolidation. With a median follow-up of 8 months (range 0–76), 3-year progression-free survival (PFS) and overall survival (OS) were 20.2% (95% CI 10.6–38.7) and 32.9% (95% CI 21.5–50.4), respectively.

Conclusions. Outpatient CPX-351 consolidation is feasible and safe, with low infectious burden and reduced hospitalization. These findings support its use in selected AML patients.

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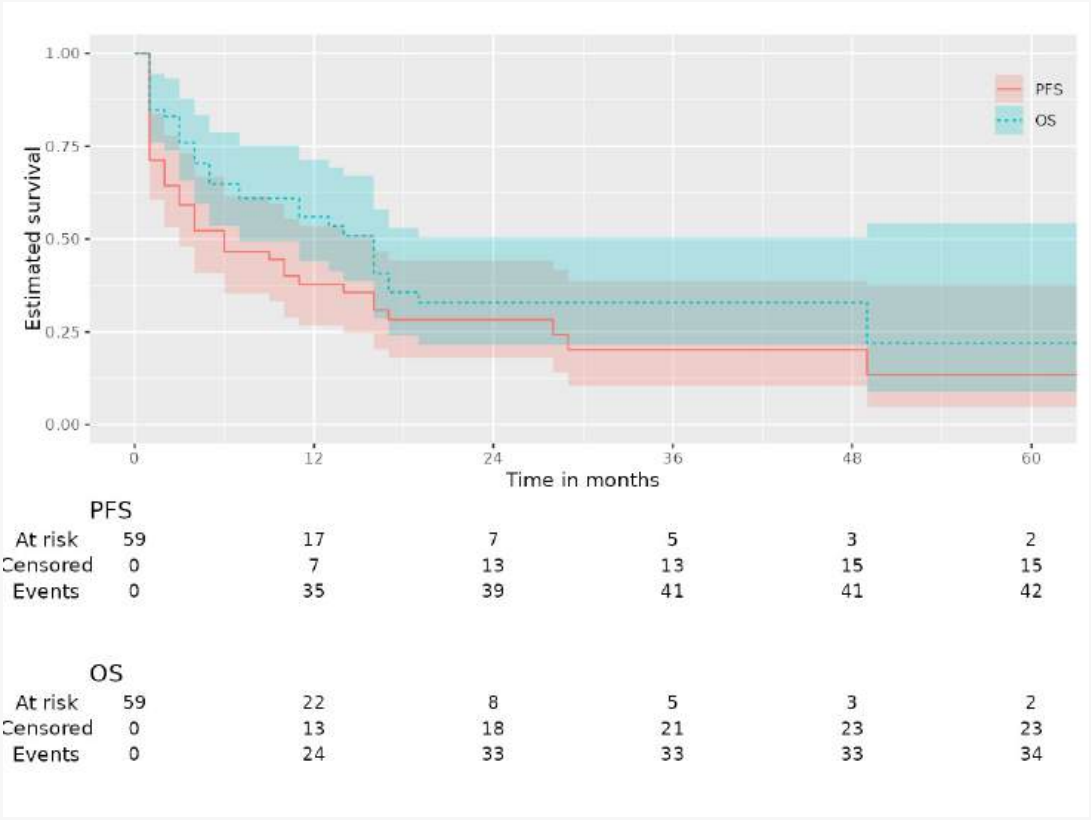
Acute myeloid leukemia



PFS						
At risk	59	17	7	5	3	2
Censored	0	7	13	13	15	15
Events	0	35	39	41	41	42

OS						
At risk	59	22	8	5	3	2
Censored	0	13	18	21	23	23
Events	0	24	33	33	33	34

Acute myeloid leukemia

REAL-WORLD OUTCOMES OF HYPOMETHYLATING AGENTS AND VENETOCLAX IN ACUTE MYELOID LEUKEMIA: A MONOCENTRIC EXPERIENCE

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Background. The combination of Hypomethylating Agents (HMAs) and venetoclax (VEN) is an established treatment for unfit patients (pts) with Acute Myeloid Leukemia (AML) ineligible for intensive chemotherapy. Although clinical trials show encouraging results, real-world data are needed to better define efficacy and safety in these patients.

Methods. We retrospectively analyzed 58 pts treated with HMAs+VEN at our institution, collecting clinical features, AML characteristics, antifungal prophylaxis, infections, and treatment response. Statistical analyses identified variables associated with response.

Results. Median age was 71.5 years (61–82), male/female ratio 0.62. According to ELN 2024, 48 pts (72%) were at intermediate risk, 15 (26%) adverse, and 1 favorable. Thirty--four pts (59%) were treated frontline and 24 at relapse (R/R). Azacitidine was used in 41 pts (71%) and decitabine in 17 (29%). Most pts (49/58, 84%) received antifungal prophylaxis (48/49 with posaconazole); no antibacterial prophylaxis was used. Infectious events occurred in 25 pts (43%), in 23 of bacterial origin and fungal in only 2 pts. Complete response (CR) rate was 50% (51% frontline, 48% R/R); 10% had partial response and 34% were refractory. Twelve pts (21%) underwent allogeneic hematopoietic stem cell transplantation (alloHCT)(3 as a first line and 9 in R/R). Median overall survival (OS) was 10.4 months: 9.1 months in frontline setting and 7.4 months in R/R (fig1). Disease-free survival (DFS) was 12.3 and 9 months, respectively. Overall, 40/58 pts (69%) relapsed and 34 (59%) died.At univariate analysis, CR achievement was the only factor significantly associated with OS and DFS in frontline and R/R pts. Antifungal prophylaxis, which led to VEN dose reduction, did not significantly impact treatment response. At multivariate analysis, in frontline pts, both CR and alloHCT independently improved OS and DFS. In R/R pts, CR and decitabine (vs azacitidine) were associated with better OS; in this setting alloHCT, although associated with a trend, showed a non-significant improvement in OS (p=0.08). Notably, pts treated with decitabine were more likely to undergo alloHCT (p=0.04).

Conclusions. We report a real-world experience with HMAs in combination with VEN in a heterogeneous cohort of AML pts. Achievement of CR and subsequent alloHCT, in particular in frontiline pts, emerged as the main factors associated with prolonged OS. In contrast, antifungal prophylaxis did not affect outcomes.

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Acute myeloid leukemia

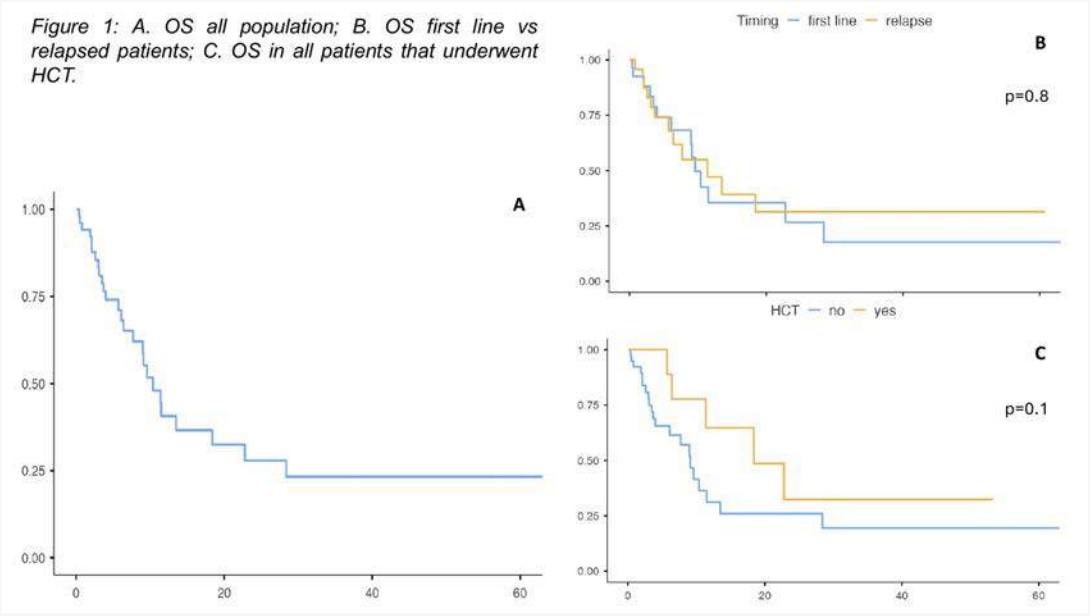

Figure 1: A. OS all population; B. OS first line vs relapsed patients; C. OS in all patients that underwent HCT.

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Acute myeloid leukemia

HMA + VENETOCLAX COMBINANTION IS EFFECTIVE AS SECOND LINE TREATMENT AFTER FAILURE OF CPX-351 IN S-AML PATIENTS

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Introduction. Acute myeloid leukemia evolving from a myelodysplastic syndrome or developing after chemotherapy (s-AML) is often characterized by high risk cytogenetic and molecular features. CPX-351 has been approved for the treatment of s-AML patients who are eligible for intensive treatment, but, despite achieving a complete response (CR) in the majority of patients, most patients will eventually relapseAn alternative treatment for fit elderly AML patients is Decitabine in combination with Venetoclax (HMA-VEN), followed by allogeneic stem cell transplantation (HMA-VEN). Although effective, relapse is often observed among s-AML patients treated with this combination.Scarce data are available on the best treatment for relapsed s-AML patients, and current option in Italy include intensive chemotherapy, HMA agents and HMA + VEN combinations, whereas CPX-351 cannot be administered outside first line treatment due to treatment regulation restrictions.The aim of this study was to evaluate if HMA-VEN is effective as a second line treatment after CPX-351.

Methods. This study included 25 patients (median age 70, range 61-76) who relapsed after (n=21) o were refractory to (n=4) CPX-351 were included in this study. Two patients had already received an HSCT and all patients were considered at high risk according to ELN 2022 criteria.All patients received HMA-VEN combination, for a median of 11 cycles (range 3-22). Response was CR in 11 patients (44%), PR in 2 (8%) and 12 patients did not respond (48%).

Results. No significant toxicities were reported and adverse event profile did not differ from what is expected with HMA-VEN combinations. Two patient received HSCT consolidation after a median of 4 HMA-VEN cycles, and are both alive and in a complete remission. Median follow up was 21 months (CI 95% 16-23) and median Overall and Relapse Free Survival after HMA-VEN treatment were 10 and 8 months, respectively.Survival was significantly higher among patients who achieved a CR (14 months compared to 6 months in non responder patients, $p<0.05$).

Conclusions. HMA-VEN is a safe and effective option after CPX-351 failure, allowing to achieve response in significant proportion of patients. The effectiveness of this strategy suggests that eligible s-AML patients may benefit from first line treatment with CPX-351 and HMA-VEN second line treatment if relapse is observed, allowing for the administration of two lines of treatment.

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Acute myeloid leukemia

CLINICAL AND GENETIC FEATURES OF ACUTE MYELOID LEUKEMIA HARBORING MECOM REARRANGEMENTS OR OTHER UNCOMMON CHROMOSOME 3 ABNORMALITIES: A SINGLE CENTRE RETROSPECTIVE EXPERIENCE

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Myeloid neoplasms with MECOM rearrangements represent a rare subgroup showing resistance to treatments and poor prognosis. Beyond classical inv(3)(q21q26) and t(3;3)(q21;q26), atypical rearrangements involving alternative partners are increasingly recognized and are often driven by enhancer hijacking mechanisms targeting GATA2, almost always leading to functional haploinsufficiency. Among 383 consecutive AML patients (pts) observed at our Institution over a 16-year period (2010-2025), we retrospectively described 13 cases (3.4%) with either MECOM rearrangements or other chromosome 3 abnormalities. Males were 5 and females 8 (mean age 67.5 years). At diagnosis, mean hemoglobin was 9 g/dL, WBC 12.7×10^9/L, platelets 107×10^9/L, with circulating and BM blast counts 5% and 46%, respectively. Dysplastic features were morphologically found in 8 pts (61.5%). Eight pts received less intensive treatments, mainly HMA plus venetoclax, while the remaining pts underwent intensive approaches, including alloHSCT in one case. CR was globally achieved in 6 pts (46.1%). At the last follow-up, survival outcomes were dismal with only 1 pt still alive. Cytogenetic findings included inv(3), t(3;3), t(3;21), t(3;6), t(3;13), t(3;16), and t(1;3). Additional chromosomal abnormalities were found in 4 cases (30.8%) To our knowledge, we reported the first case of a MECOM gene deletion by FISH analysis and also another rare t(3;13) arising in a pt with previous polycythemia vera, obtaining prolonged survival after two alloHSCTs. Only one similar case has been previously described, involving RB1 as a partner gene. NGS data were available for five pts. Of interest, an AML case harboring t(3;6) at evolution from MDS with SF3B1 and RUNX1 mutations was refractory to intensive treatments, representing the first reported case of an atypical MECOM rearrangement arising from a SF3B1-mutated MDS. Only a similar case of t(3;12) AML evolving from a JAK2-mutated neoplasm has been previously reported. A t(3;21) AML case with ASXL1 and DNMT3A mutations achieved a transient response to azacitidine-venetoclax. Overall, in addition to inv(3)/t(3;3), spliceosome mutations may also be linked to non-classical MECOM rearrangements, suggesting a potentially unexplored pathogenic connection, except for a small AML subgroup with t(3;8). Pre-existing molecular changes may promote genomic instability and support MECOM-driven leukemogenesis, warranting further molecular studies in this aggressive genetic subgroup.

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Acute myeloid leukemia

FAILURE OF CLOFARABINE AND INTERMEDIATE DOSES OF CYTARABINE TO OVERCOME VENETOCLAX RESISTANCE IN RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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Background. Resistance to Venetoclax (VEN)-based therapies is a significant therapeutic challenge in acute myeloid leukemia (AML), since most relapsed/refractory (R/R) patients (pts) lack actionable molecular targets, and conventional salvage chemotherapy offers limited benefit. Clofarabine in combination with cytarabine has previously shown activity in R/R AML; assessing its efficacy in the setting of VEN failure represents a clinically relevant question.

Methods. We analyzed two retrospective cohorts of adult R/R AML pts treated in a real world setting at Careggi University Hospital: a "VEN-failure" cohort (n=9), treated between 2017 and 2025 with clofarabine and cytarabine after VEN failure, and a "pre-VEN" cohort (n=33), treated between 2009 and 2019. Pts received clofarabine 22.5 mg/m^2/-day followed by cytarabine 1 g/m^2/day for 5 days.

Results. In the "VEN" cohort, pts had a median age of 57 years; 7 pts (78%) were classified as ELN 2022 adverse risk. All pts had previously been exposed to high-dose cytarabine. The median number of prior lines of therapy was 2 (range 2-4). Five pts (55%) received the treatment in the setting of relapse after HSCT. One pt (11%) achieved partial response (PR) and proceeded to HSCT, 8 (89%) were refractory (ORR 11%). At a median f-up of 2.0 months (95% CI, 0.0-4.9), the median OS was 2.0 months (95% CI, 0.0-4.9). Mortality within 30 days occurred in 3 pts (33%). In the “pre-VEN” era cohort the median age was 54 years; 19 pts (57%) were ELN 2017 intermediate-risk, 13 (39%) adverse and one (3%) favorable. Twenty-nine pts (88%) had received prior high-dose cytarabine–based therapy. Three pts (9%) were in relapse after allogeneic HSCT. The median number of previous treatment lines was 1 (range 1-4). Eleven patients (33%) achieved complete remission (CR), 2 patients (6%) PR (ORR 39%). At a median f-up of 87.0 months (95% CI, 37,0-101,0), the median OS was 4.0 months (95% CI, 0.6-7.3). Ten pts proceeded to allogeneic HSCT (77%). Early mortality was recorded in 1 pt (3%).

Conclusions. These real-world data suggest that while clofarabine showed moderate activity in the pre-VEN era (ORR 39%, CR 33%), its efficacy in VEN-exposed R/R AML pts was minimal (ORR 11%, CR 0%), with an unfavorable safety profile. Despite the retrospective nature of the study and the small sample size, the findings suggest that clofarabine does not overcome VEN resistance. Further efforts should focus on clinical trials for R/R pts after VEN failure.

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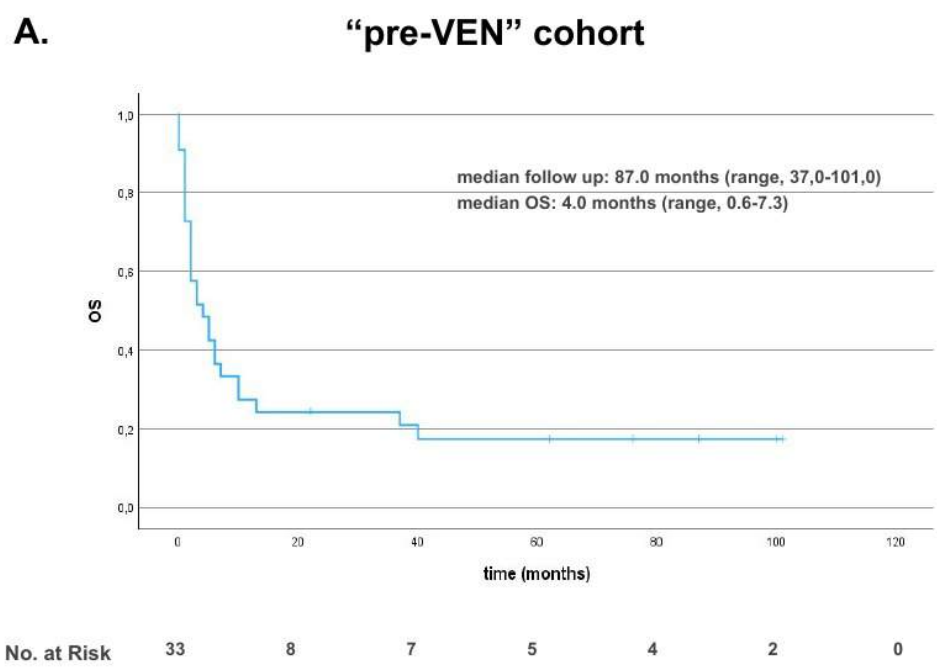

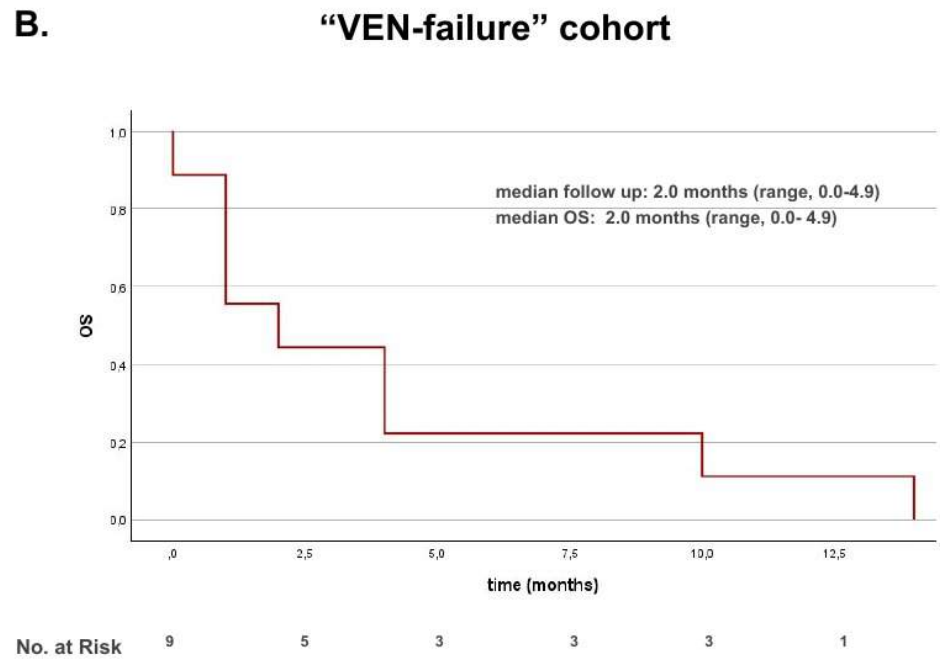

Figure 1. Outcome of patient of the "pre-VEN" cohort and the "VEN-failure" cohort: panel A: overall survival (OS) of patients of the "pre-VEN" cohort; panel B: OS of patients in of the "VEN failure" cohort

Acute myeloid leukemia

HYPOMETHYLATING AGENTS PLUS VENETOCLAX IN VERY ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS (≥80 YEARS), A SINGLE CENTRE EXPERIENCE

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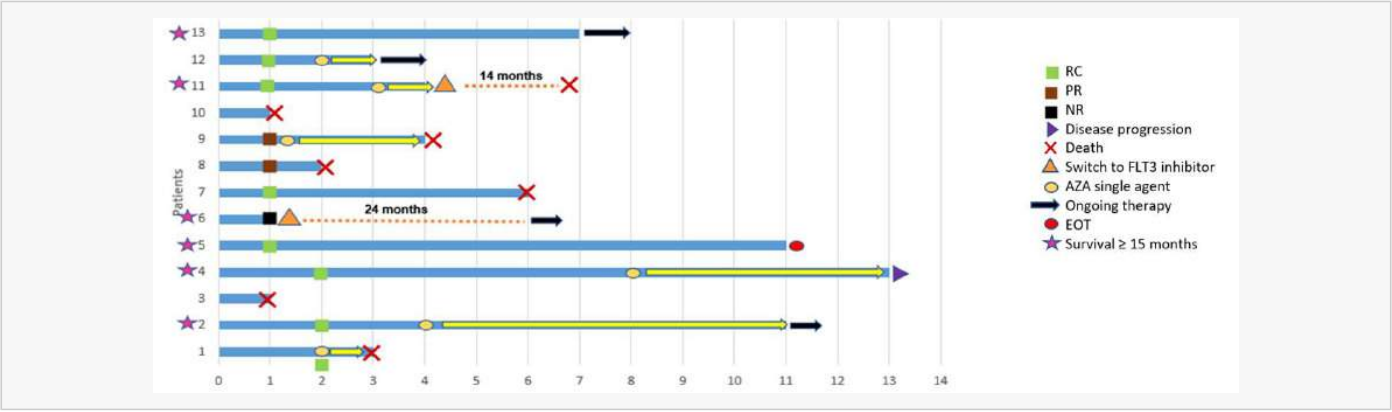
Hypomethylating agents in combination with venetoclax (HMA-VEN) are the current standard of care for elderly patients with acute myeloid leukemia (AML). However, evidences on efficacy and tolerability in the very elderly population remain limited. In this particularly vulnerable subgroup, clinical management is further complicated by reduced physiological reserve, high susceptibility to treatment-related toxicities and the frequent need for dose adjustments or treatment interruptions. Indeed, more data on feasibility of this treatment in such fragile population are strongly needed.We retrospectively evaluated the feasibility and outcome of HMA-VEN in very elderly AML patients (≥80 years) treated in our Centre between January 2020 and January 2026. Clinical characteristics, response rates, measurable residual disease (MRD), survival outcomes, and treatment-related toxicities were assessed. Thirteen patients were included, all of them received azacitidine plus venetoclax. All patients received antifungal prophylaxis with posaconazole 300 mg daily at least during cycle 1 (C1) and 2 (C2), and the dose of venetoclax was therefore adjusted to 100 mg daily. Bone marrow aspirate for disease assessment was performed after C1 and C2.Median age was 84 years (range 80–88), with 3 patients aged ≥85 years. Three patients had AML with NPM1 mutation. Four patients achieved CR/CRi after C1; 3 more achieved CR after cycle 2. Median duration of VEN during C1 was 20 days (range 7-28). Two NPM1-mut AML achieved molecular CR after C4. Median treatment duration was 14 months (range 1–27) with a median of 3 cycles (range 1-13). Infectious complications occurred in 61% of patients during C1, requiring hospitalization in 3/9 outpatient cases. Five responding patients proceeded with AZA alone due to severe cytopenias. Six patients showed survival ≥ 15 months (2 NPM1-mut in molecular remission, 2 NR patients who received second line salvage treatment with FLT3-inhibitor, 2 AML-MRC who achieved CR after C1.Our single Centre experience of HMA-VEN treatment in a cohort of very-elderly AML patients confirms a meaningful clinical activity. As durable responses can be achieved, careful dose adjustments are required to improve outcomes in this delicate setting.



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Acute myeloid leukemia

IMPROVED SURVIVAL OUTCOMES OF FLT3-MUTATED AML PATIENTS TREATED WITH INTENSIVE CHEMOTHERAPY AND MIDOSTAURIN ARE PREDOMINANTLY DRIVEN BY SUBSEQUENT ALLOGENEIC TRANSPLANTATION: A SINGLE-CENTRE REAL-WORLD EXPERIENCE

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Background. The increased risk of relapse in FLT3-mutated acute myeloid leukemia (AML) has significantly influenced therapeutic strategies, with a growing emphasis on hematopoietic stem cell transplantation (HSCT). First-generation FLT3 inhibitors, such as midostaurin (mido), have demonstrated improved overall survival (OS) and event-free survival (EFS) in pivotal trials, particularly in younger patients. These benefits are largely attributed to higher complete remission (CR) rates, enabling more patients to proceed to transplantation. However, in real-world settings, these advantages may be less evident due to more heterogeneous patient populations and barriers to completing the transplant pathway.

Aim. The aim of our study is to assess whether the addition of mido to intensive chemotherapy (IC) improves OS and EFS in routine clinical practice, compared with a historical cohort treated with IC alone.

Patients and Methods. We retrospectively analyzed patients with FLT3-mutated AML (ITD or TKD) treated between January 2017 and December 2025. Patients were divided into two cohorts based on treatment: standard “3+7” IC alone or IC+mido.

Results. Twenty-six and 36 patients had been treated with IC or IC+mido, respectively. The clinical and biological characteristics of the 2 groups did not show differences in terms of age, sex, blast counts, WBC, cytogenetics, ELN 2022 risk and NPM mutation, while the only significant difference concerned the distribution of de novo AML (81% vs. 100%; p =0.01) and age (46 vs. 49, p=0.02) in the IC and IC+mido groups, respectively. The overall response rate (CR+CRi+CRh) to treatment was 47% and 88% in the IC and IC+mido groups (p=0.001), respectively. The median OS and EFS in the IC+mido and IC-treated groups were not reached vs. 9.8 months (p=0.03, Figure 1a) and 15.5 vs. 1 month (p=0.002, Figure 1b). Of note, censoring for the transplant event did not show an advantage for patients treated with IC+mido (Figure 1c). Consequently, IC+mido-treated patients who underwent transplant showed the best OS when compared with patients who did not undergo transplant (Figure 1d). In multivariate analysis, achieving the response was the variable with an impact on OS (HR = 0.37; 95%CI:0.18-0.75, p=0.006) and EFS (HR=0.05; 95%-CI:0.02-0.13, p<0.0001), respectively.

Conclusions. The contribution of mido, although determining higher response rates, appears to be further improved only through completion of the transplant program.

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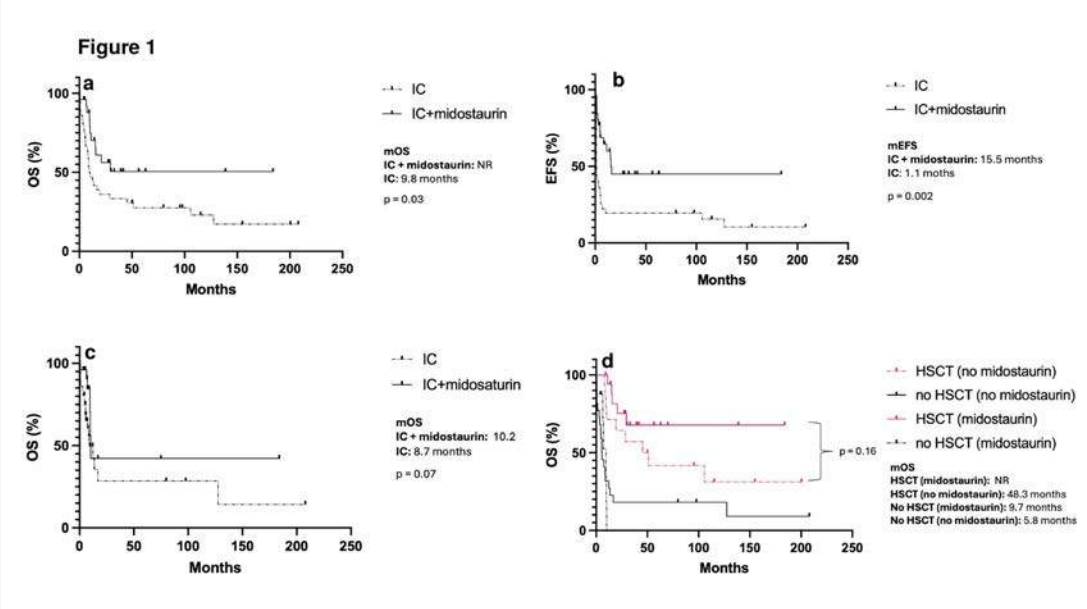
Acute myeloid leukemia



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Acute myeloid leukemia

TP53-MUTATED MYELOID NEOPLASMS A SINGLE CENTRE EXPERIENCE

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Background. The TP53 gene is a tumor suppressor gene located on chromosome 17. It is the frequently mutated gene in solid cancers and are found in 5% to 10% of de novo acute myeloid leukemia (AML), more frequently observed in patients with therapy-related AML. Despite recent advances in molecular profiling and targeted therapies, TP53-mutated myeloid neoplasms (MN) remains a challenge to treat. Indeed, current treatment strategies, including conventional chemotherapy, hypomethylating agents and venetoclax-based therapies, have shown limited efficacy in TP53--mutated MN, with low response rates and poor overall survival. Allogeneic hematopoietic stem cell transplantation is a potentially curative option; however, its efficacy in TP53-mutated MN depends on comorbid conditions and disease status at transplantation.

Patients and methods. We report the experience of our center's day hospital. Between December 2024 and April 2026, we observed 14 TP53-mutated patients: 5 with myelodysplasia (MDS) and 9 with AML (6 therapy-related AML). The median age was 68 years (range 45–78). Two patients had WT1 mutations and seven presented additional mutations detected by next-generation sequencing (NGS). Four patients with MDS were treated with azacitidine (HMA), while nine patients with AML and one younger patient with MDS received venetoclax-based therapies.

Results. Seven patients (50%) achieved complete remission (CR) after one or two cycles of therapy, with improved quality of life and transfusion independence. One patient is currently completing the first cycle of therapy and another achieved partial remission (PR). Five patients (35%) did not respond to HMA–venetoclax treatment. Among the responders, 2 out of 7 patients (14%) remain in complete remission, and one of them underwent transplantation. Five patients (35%) died due to disease progression or infection during treatment. Currently, 9 patients (65%) are alive, with a median survival of 5 months (range 1-11).

Conclusions. TP53-mutated MN presents a unique challenge in management due to resistance to both conventional and novel therapies. Survival is uniformly poor, and clinical benefit is limited. Allogenic stem cell transplantation is the only potentially curative option, although long-term post--transplant survival remains poor. Further studies are needed to define new therapeutic approaches.

Patients	age	diagnosis	date of diagnosis	Previous neoplasia	Molecular Biology	NGS	treatment	cycle	results	PFS months	relapse	last follow-up	OS months
1	78	MDS	05/20255		neg	SF3B1, ASXL1, RUNX1,TP53 (VAF 45%)	HMA	5	RC	6	yes	alive	11
2	74	MDS	12/2024		neg	TP53 (VAF 78%)	HMA	7	RC	7	yes	dead	9
3	73	LMMC	01/2026	PV, Multiple myeloma	neg	ASXL1, DNMT3A, JaK2, RUNX1, TP53 (VAF 20%)	HMA	2	PR	1	yes	alive	3
4	72	MDS	03/2026		neg	TP53 (VAF 23%)	HMA	1	NE	NE		alive	1
5	46	MDS	09/2025		neg	TP53 (VAF 46%)	HMA-ven	4	RC	8		alive	7
6	54	LAM-th	09/2025	ovarian cancer	**wt1**	TP53 (VAF 18%)	HMA-ven	2	Refractory	0		dead	5
7	63	LAM-th	02/2026	ovarian cancer	neg	TP53 (VAF 30%)	HMA-ven	2	Refractory	0		alive	2
8	68	LAM-th	06/2025	Multiple Myeloma	neg	TET2, TP53 (VAF 21%)	HMA-ven	4	Refractory	0		dead	5
9	74	LAM-th	01/2026	Multiple Myeloma	neg	TP53 (VAF 74%)	HMA-ven	1	Refractory	0		dead	1
10	69	LAM	02/2026		**wt1**	TP53 (VAF 34%)	HMA-ven	2	Refractory	0		alive	2
11	63	LAM	08/2025		neg	DNMT3A, PTPN11, TP53 (VAF 74%)	HMA-ven	5	RC	7	yes	alive	8
12	76	LAM-th	10/2025	lung cancer, urothelian cancer	neg	NF1, TP53 (VAF 42%)	HMA-ven	3	RC	4	yes	dead	6
13	72	LAM	02/2026	Myelofibrosis	neg	JAK2, SF3B1, TP53 (VAF 20%)	HMA-ven	2	RC	1		alive	2
14	76	LAM-th	09/2025	Essential Thrombocythemia	neg	CaLr, TP53 (VAF 54%)	HMA-ven	6	RC	6	yes	alive	7

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SUSTAINED MOLECULAR MRD-NEGATIVE REMISSIONS WITH AZACITIDINE PLUS VENETOCLAX IN NPM1-MUTATED ACUTE MYELOID LEUKEMIA: A SINGLE-CENTER EXPERIENCE

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Division of Hematology ARNAS Garibaldi

Introduction. NPM1-mutated acute myeloid leukemia (AML) is particularly sensitive to venetoclax-based regimens. The combination of azacitidine and venetoclax has demonstrated high response rates in patients unfit for intensive chemotherapy; however, real-world data regarding long-term durability of responses, particularly in terms of measurable residual disease (MRD), and treatment feasibility remain limited.

Methods. We conducted a retrospective single-center analysis of patients with NPM1-mutated AML treated with azacitidine plus venetoclax. Clinical outcomes, including response rates, MRD status, overall survival, and treatment tolerability, were assessed.

Results. Seven patients with NPM1-mutated AML were treated with azacitidine plus venetoclax. All patients achieved complete remission with molecular MRD negativity (7/7), typically after 4-6 cycles. Responses were durable, with five patients remaining on treatment for more than two years and three patients continuing therapy beyond three years while maintaining MRD-negative remission. Treatment was generally well tolerated, allowing prolonged administration of therapy without significant adverse events. In most patients, venetoclax schedule was subsequently adapted to 14 days per cycle to improve tolerability without compromising disease control. Only one patient experienced a treatment-related cutaneous rash, successfully managed by further reducing venetoclax exposure to ten days per cycle.

Conclusions. In this real-world single-center experience, azacitidine plus venetoclax demonstrated high efficacy in NPM1-mutated AML, complete remission achieved in all treated patients, sustained MRD negativity, and prolonged survival. The combination showed excellent tolerability, allowing long-term therapy with minimal toxicity and supporting its role as a feasible and durable treatment strategy.

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Acute myeloid leukemia

CLINICAL TRAJECTORY AND THERAPEUTIC EVOLUTION OF ORAL DECITABINE-CEDAZURIDINE IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA A CASE SERIES ANALYSIS

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Background. The current standard of care for patients with newly diagnosed acute myeloid leukemia (AML) who cannot undergo intensive chemotherapy involves a combination of a hypomethylating agent (HMA) and venetoclax. However, a considerable proportion of the older population with AML might not be physically or socially suitable for the administration of parenteral azacitidine or decitabine (DEC), which requires a hospital setting. In this regard, oral decitabine-cedazuridine (DEC-C) is an innovative bioequivalent alternative to the parenteral formulation of DEC, which might improve the treatment experience for the patients and the caregivers. This case series aims to present the first clinical experience with DEC-C in AML patients treated at our Institution.

Methods. This case series includes the clinical experience of seven patients with a median age of 80 (75-84) years who received oral DEC-C (35 mg DEC/100 mg cedazuridine) on days 1-5 of a 28-day cycle as monotherapy. The median number of administration cycles was 6 (1-15). Patients were re-evaluated after the second and the fourth cycle, respectively. Posaconazole was prescribed in case of severe neutropenia.

Results. Of the 5 patients evaluable for response, the overall response rate (ORR) to DEC-C in AML patients was 100%. Three patients achieved complete remission (CR), and two patients achieved CR with incomplete hematologic recovery, with a median time to best response of 2.5 months. Grade 3-4 neutropenia occurred in all patients, and treatment delays were necessary in 4/5 patients and in 32/41 courses of therapy (78%). As of April 2026, after a median follow-up of 6 (1-15) months, all patients were alive and on treatment. Of note, 4/5 (80%) evaluable patients achieved transfusion independence (TI) and functional restoration, suggesting a meaningful benefit in quality of life beyond the reduction in treatment burden. Three patients required hospital admission for pneumonia (1), cardiac failure (1), and febrile neutropenia (1), respectively. In conclusion, DEC-C in our hands resulted in an effective and well-tolerated treatment option for managing difficult-to-treat AML in older patients and those who may not be physically or socially suitable for treatment with parenteral HMAs. The oral formulation achieved high ORR and TI, along with other treatment goals that might improve patients' quality of life beyond merely reducing treatment-related inconvenience.

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LONG TERM EFFICACY OF GILTERITINIB MONOTHERAPY AS A POST-HSCT MAINTENANCE THERAPY AND POST TRANSPLANT RELAPSE TREATMENT

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Background. The relapsed/refractory Acute Myeloid Leukemia (R/R AML) setting remains, to date, very challenging, considering the limited available options, the resistance profile to salvage CHT regimens and the concomitant lack of multiple targeted therapy options. Gilteritinib is an oral, potent, selective FMS-like tyrosine kinase 3 gene (FLT3) inhibitor with single-agent activity in the FLT3-mutated AML subset which represents a valuable targeted therapy option in patients presenting this specific mutation.

Methods. We retrospectively analyzed 10 R/R FLT3-ITD mutated AML patients at our center, who received Gilteritinib in monotherapy following allogeneic stem cell transplant either as a maintenance therapy or as a relapse treatment. The two primary endpoints were overall survival and progression free survival in both groups to evaluate treatment efficacy. Response to treatment was evaluated with molecular MRD in patients with detectable markers (NPM1) and immunophenotyping and WT1 in patients not presenting any other quantifiable disease markers. Secondary endpoints comprehended the evaluation of the time to response and response depth after treatment.

Results. Gilteritinib monotherapy was administered to 5 patients as maintenance therapy after HSCT and 5 as post-HSCT disease relapse treatment. In both groups the AML presented similar disease characteristics with the ITD mutation present at diagnosis, 4/5 patients at INT risk and 1 at ADV risk (ELN2022). In the maintenance group, patients began therapy approximately 2 months after HSCT with response assessment before transplant showing CR in 4/5 cases and active disease in 1. After Gilteritinib only 1 patient relapsed whilst the others maintained or obtained a molecular remission at 48 months. In the relapse group, patients started therapy at a median of 13 months after HSCT, mostly as a third line, with a median time to complete remission of 2 months and 4 months to molecular remission. In the latter group 1 patient demonstrated resistance to Gilteritinib whilst the rest (4/5) obtained a molecular remission, sustained at 48 months. OS and PFS were, respectively, 60% at 48months in the relapse group and 80% at 48 months in the maintenance group.

Conclusions. With the limit of a small sample size, our data suggests that Gilteritinib is an efficient option, in both settings, as a monotherapy, and is able to maintain a pre-existing CR/MR pre-HSCT and obtain a CR/MR in a post-HSCT relapse setting.

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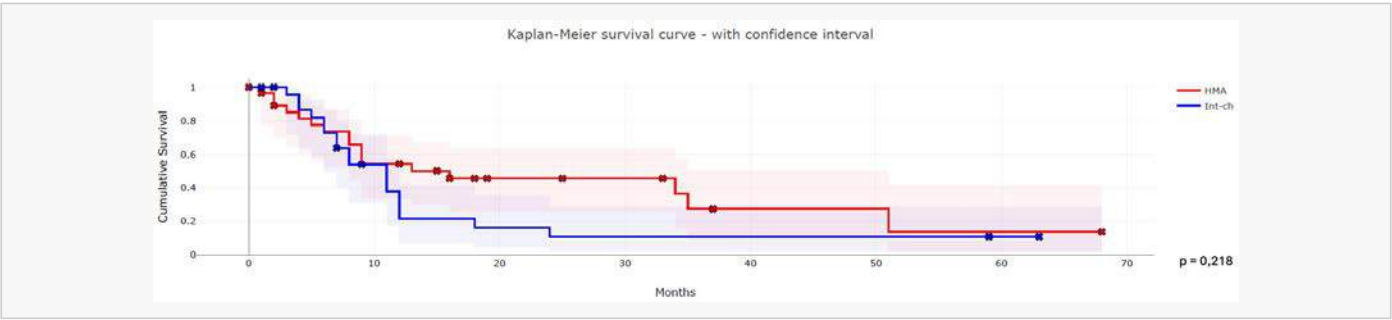
Acute myeloid leukemia

ACUTE MYELOID LEUKEMIA: A SINGLE-CENTER CASE SERIES INTENSIVE AND NON-INTENSIVE THERAPY

M. P. Flagiello, G. Piras, M. Schirru, A. Calvisi, R. Asproni, M. Monne, A. Uras, M. Bacciocchi, S. Chiriu, A. Cucca, L. Deiana, L. Malloci, M. Murineddu, A. Virdis, A. D. Palmas

SC Ematologia, CTMO, Laboratorio Specialistico

Acute myeloid leukemia (AML) is a neoplastic disease characterized by the uncontrolled proliferation of immature cells (blasts), often resulting from the development of somatic mutations; the estimated 5-year median survival rate is around 30% across all age groups and subtypes.Patients are typically classified as fit or unfit for intensive chemotherapy (int-ch). Fit patients are started on high-intensity therapy (e.g., 3+7, CPX-351, FLA(G)-IDA, etc.) and, if indicated, allogeneic hematopoietic stem cell transplantation (alloHSCT).We present here an analysis of the patient cohort with AML treated at our center between 2020 and april 2026. Specifically, we analyzed overall survival (OS) data for patients who underwent intensive chemotherapy (int-ch) versus those who underwent non-intensive, hypomethylating-agent-based (HMA) therapy. Patients who underwent alloHSCT were excluded to eliminate bias related to peri- and intra-transplant mortality. The total sample consisted of 53 patients, 24 (45,3%) who received int-ch and 29 (54,7%) who received HMA. In accordance with ELN 2022 guidelines, patients undergoing int-ch were classified as high-risk in 33,3%, intermediate-risk in 33,3%, and low-risk in 33,3%, compared to 51,7%, 31,1%, and 17,2% in the HMA group. The OS of the int-ch group is 12,9 months versus 15,9 months for the HMA group. In the HMA group, a higher proportion of patients were classified as high-risk and intermediate-risk compared to the int-ch group (82,8% vs. 66,6%).In our real-world cohort, the OS of patients treated with int-ch versus HMA was lower; however, the p-value was not statistically significant. This study appears to confirm that there is no clear difference between the two therapeutic approaches; it should be emphasized, however, that this is a real-world observational study with significant limitations, such as the potential for selection bias and the lack of sample selection or randomization. Furthermore, the sample size may not have sufficient statistical power to detect a difference. Further, more robust experimental studies will be needed to investigate and validate these results, such as the one by Fathi et al. (67th ASH 2025, Abstract 617): if this were the case, it would change the standard of care for AML treatment, in which HMA would represent a new therapeutic option for fit and unfit patients, resulting in lower hematologic and systemic toxicity, improved quality of life, and better treatment adherence.



Acute myeloid leukemia

DIFFERENT EXTRAMEDULLARY EFFICACY OF REVUMENIB IN A CASE OF RELAPSED/REFRACTORY KMT2A-REARRANGED ACUTE MYELOID LEUKEMIA: HEPATIC RESPONSE AND CENTRAL NERVOUS SYSTEM ESCAPE

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Background. Revumenib, a first-in-class menin inhibitor, demonstrated significant activity in relapsed/refractory (R/R) acute leukemia with KMT2A rearrangements (KMT2Ar) or NPM1 mutations, inducing complete remission (CR) and measurable residual disease (MRD) negativity. Its efficacy in extramedullary sites has been reported, but central nervous system (CNS) activity remains poorly defined.
Case Report. A 36-year-old man was diagnosed with AML harboring t(11;17) and KMT2Ar (Figure 1). He received induction chemotherapy with "3+7" regimen achieving CR and he underwent allogeneic stem cell transplant (HSCT) from an HLA-matched sibling donor. Relapse occurred three months post-HSCT with persistent KMT2Ar. Salvage therapy with venetoclax plus azacitidine was performed for two cycles without response during which CNS prophylaxis was administered.In March 2025 thanks to the presence of a molecular target, compassionate use of revumenib was requested. At that time, liver transaminases were out of range. Therefore, abdominal ultrasound was performed, showing multiple hepatic lesions. A liver biopsy confirmed myeloid leukemic infiltration. Following resolution of a concomitant infection, revumenib was initiated. After two cycles of therapy at the FDA approved dosage, the patient achieved CR with MRD negativity by multiparameter flow cytometry, along with normalization of liver enzymes and complete disapperance of hepatic lesions. No drug-related toxicity was observed. Given the remission and improved clinical conditions, the patient was referred for a second HSCT from a haploidentical donor, with revumenib used as a bridge approach. However, in July 2025, the onset of severe headache prompted CNS evaluation; the morphology analysis revealed the presence of myeloid blasts. Two intrathecal therapy was administered reducing the blast count and HSCT was performed. At engraftment, CR with full donor chimerism was documented. Unfortunately, two months post-HSCT, the patient showed progression disease and ultimately died due to sepsis.
Conclusions. This case confirms that revumenib can induce deep response in medullary and extramedullary compartments also in heavily pretreated KMT2A-r AML and could be an effective bridge to HSCT. However, CNS disease control may be limited, emphasizing the need for continued intrathecal prophylaxis during the treatment with this novel class of drugs.

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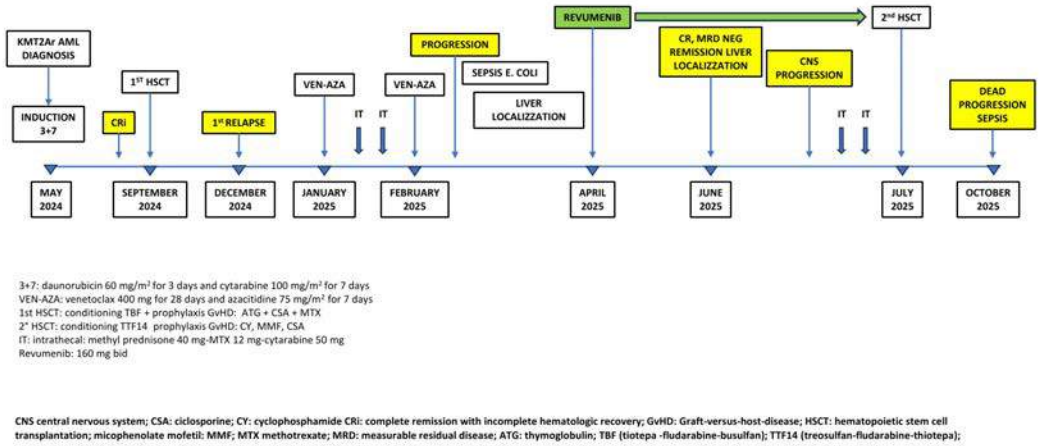

3+7: daunorubicin 60 mg/m² for 3 days and cytarabine 100 mg/m² for 7 days
VEN-AZA: venetoclax 400 mg for 28 days and azacitidine 75 mg/m² for 7 days
1st HSCT: conditioning TBF + prophylaxis GvHD: ATG + CSA + MTX
2° HSCT: conditioning TTF14 prophylaxis GvHD: CY, MMF, CSA
IT: intrathecal: methyl prednisone 40 mg-MTX 12 mg-cytarabine 50 mg
Revumenib: 160 mg bid

CNS central nervous system; CSA: ciclosporine; CY: cyclophosphamide CRi: complete remission with incomplete hematologic recovery; GvHD: Graft-versus-host-disease; HSCT: hematopoietic stem cell transplantation; micophenolate mofetil: MMF; MTX methotrexate; MRD: measurable residual disease; ATG: thymoglobulin; TBF (tiotepa -fludarabine-busulfan); TTF14 (treosulfan-fludarabine-thiotepa);

Acute myeloid leukemia

LATE-ONSET CARDIOTOXICITY IN AN AML PATIENT TREATED LONG-TERM WITH AZACITIDINE–VENETOCLAX: A CASE REPORT AND LITERATURE REVIEW

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Background. Azacitidine (AZA) plus Venetoclax (VEN) is the standard regimen for elderly/unfit patients with newly diagnosed acute myeloid leukemia (AML). Clinical series and pharmacovigilance data have reported an increased incidence of major cardiac events (MCEs) in about 7-20% of patients, including cardiomyopathy, acute coronary syndromes, pericarditis and atrial arrhythmias. Preclinical models show VEN-induced myocardial injury with oxidative stress, inflammation and apoptosis, supporting a potential cardiotoxicity mediated by oxidative stress and NF κB/BCL 2 related pathways.Materials and MethodsWe describe a 77-year-old man with IDH2 and SRSF2 mutated AML, without known structural heart disease, who received 24 cycles of AZA–VEN, achieving durable complete remission (CR) from cycle 6 and developed cardiac complications.

Results. After the 24th AZA–VEN cycle, with ongoing CR and mild chronic anemia, the patient developed pericarditis, intermediate coronary syndrome and multivessel coronary artery disease, requiring percutaneous coronary intervention with drug-eluting stents, and new-onset atrial fibrillation, in the absence of prior clinically evident cardiomyopathy.DiscussionReal world cohorts of AML patients treated with (hypomethylating agents) HMA and VEN have consistently reported clinically relevant cardiac toxicity, most frequently during initial cycles, with a cumulative one year incidence of MCEs of approximately 18–19%. In some series, these rates are comparable to those observed in anthracycline treated controls, underlining that VEN based regimens cannot be considered cardiologically safe from complications. Cardio oncology studies and pharmacovigilance reports indicate that cardiac events may also occur after several months of continuous therapy, suggesting a spectrum of toxicity that ranges from early, possibly susceptibility driven events, to later manifestations related to cumulative myocardial injury, in accordance to preclinical models of VEN induced oxidative, inflammatory and apoptotic cardiac damage.

Conclusions. This case of late-onset cardiotoxicity adds to growing evidence that cardiac events are a clinically relevant and likely under-recognized complication of HMA–VEN therapy. Our observations support systematic baseline cardiologic assessment, early and serial echocardiographic and electrocardiographic monitoring and high suspicion for pericardial and ischemic syndromes throughout VEN-based treatment.

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Acute myeloid leukemia

SHARED GERMLINE VARIANTS BETWEEN DONOR AND RECIPIENT IN SECONDARY AML AFTER HSCT

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Background. Secondary acute myeloid leukemia (AML) after hematopoietic stem cell transplantation (HSCT) is rare and biologically complex. Integrated somatic and germline next-generation sequencing (NGS) may uncover mechanisms of clonal evolution and inherited susceptibility.

Case presentation. We report a 49-year-old male diagnosed with intermediate-risk AML harboring variants in NPM1, FLT3, KRAS, TET2, and GATA2. The patient underwent haploidentical HSCT from a related donor (sister), achieving full donor chimerism maintained for four years. He subsequently developed AML relapse with a different immunophenotypic profile, suggestive of secondary AML. Somatic NGS analysis on bone marrow at relapse identified variants in RUNX1 and PHF6, while only the TET2 variant of uncertain significance (p.Gln138Leu) was shared with the initial mutational profile. Extended analysis using a custom NGS panel for myeloid predisposition confirmed the TET2 variant and revealed a variant of uncertain significance in PALB2 (p.Ser1165Leu). This variant was detected in pre-transplant peripheral blood T lymphocytes and in the donor sample (>97% purity), indicating a shared germline origin. Co-occurrence of germline variants in TET2 and PALB2 suggests multifactorial predisposition with incomplete penetrance. TET2 regulates DNA demethylation and hematopoietic stem cell self-renewal and is linked to clonal hematopoiesis. PALB2, involved in homologous recombination repair, may contribute to genomic instability in myeloid malignancies; similar variants have been reported in pancreatic and hereditary breast cancer and are predicted to be pathogenic by in silico tools. The combination of germline and somatic alterations affecting distinct cellular pathways may create a permissive environment for clonal expansion under selective pressure. Post-transplant bone marrow remodeling and inflammatory signals may further promote expansion of pre-existing clones with proliferative advantage.

Conclusions. This case highlights the complexity of hereditary myeloid neoplasms and the value of integrated somatic and germline NGS analysis. The identification of shared germline variants in both recipient and donor has relevant biological and clinical implications, supporting the need for comprehensive genetic assessment in HSCT candidates.

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CONCOMITANT SOLID CANCERS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA AND TREATED WITH ORAL DECITABINE AND CEDAZURIDINE A SINGLE CENTRE EXPERIENCE

V. Carluccio, T. M. Santeramo, C. Buquicchio, L. Strippoli, G. De Santis, R. M. Miccolis, M. Leo, C. G. Germano, S. Mallano, E. Arcuti, V. Strafella, A. Perfetto, D. Loconte, G. Tarantini

Hematology, POMDimiccoli

Background Multiple primary cancer (MPC) refers to the presence of two or more tumors in the same or different organs, differs from tumor recurrence and metastasis, and can be classified into synchronous or metachronous. There are many cases of MPCs, instead involvement of a solid and an hematological malignancy is rare and different from secondary leukemia after CHT and RT, which represents a well-defined nosological entity.

Aims. we report 3 cases of acute myeloid leukemia (AML) and concomitant pancreatic, prostatic and bowel cancer. A 68-year-old man presented on February 2025 with neutropenia and thrombocytopenia in pancreatic cancer. Bone marrow biopsy confirmed AML, molecular biology is negative, NGS proved IDH2 and BCOR mutations, Cytogenetic was 46 XX [10]. Concomitant treatment with Capecitabine and oral Decitabine/Cedazuridine was started; after 6 cycles he achieved complete remission but he died on February 2026 for pancreatic cancer progression.On October 2025 a 74-year-old man presented with leukocytosis and anemia in metastatic prostate cancer treated with Triptorelin and Apalutamide. Bone marrow aspirate showed 90% of myeloid blasts, treatment was started with Decitabine/cedazuridine and he achieved transfusion independence with complete recovery of platelet count after 2 cycles, but he died in March 2026 for progression disease. A 78-year-old woman presented in February 2026 with anemia and thrombocytopenia in bowel cancer treated with surgery. Bone marrow aspirate showed AML; she started oral Decitabine/cedazuridine but she died in April 2026 due to infectious complications.

Methods. in patients with solid tumors and unexplained blood changes the presence of an hematological malignancy should be evaluated with bone marrow biopsy, cytogenetics, molecular biology, flow cytometry, IIC and NGS.Results:The risk of developing MPC is associated with age, history of previous cancer, the type of the first tumor, environmental and genetic factors. The prognosis of these patients depends on both the malignancy and stage of the solid tumor and the patient's age and comorbidities.

Conclusions. Early diagnosis and interdisciplinary cooperation are essential; in clinical practice, given the rapid progression of leukemia, it's reasonable to start treatment for AML or administer combination chemotherapy. In our case series the use of oral Decitabine/ cedazuridine is well tollerated and can lead from transfusion independence to AML complete remission

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Acute myeloid leukemia

EARLY MOLECULAR REMISSION AND RESOLUTION OF LEUKEMIA CUTIS AFTER FIRST-CYCLE DECITABINE/CEDAZURIDINE IN A FRAIL PATIENT WITH NPM1-MUTATED AML

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Background. NPM1-mutated acute myeloid leukemia (AML) is a distinct biological entity frequently associated with monocytic differentiation and extramedullary involvement. In elderly or unfit patients, hypomethylating agents are widely used; however, data on the kinetics and depth of molecular response, particularly early measurable residual disease (MRD) clearance, remain limited.

Methods. We report the case of an 80-year-old woman diagnosed with AML harboring an NPM1 mutation (type J). At presentation, bone marrow evaluation showed 78% blasts with monocytic features, along with concomitant leukemia cutis. Significant comorbidities, including dilated cardiomyopathy with bundle branch block and sepsis at diagnosis, precluded intensive chemotherapy. Treatment with oral decitabine/cedazuridine was initiated. Molecular monitoring of NPM1 was performed by quantitative PCR on peripheral blood.

Results. After the first treatment cycle, complete clinical resolution of cutaneous lesions was observed. Molecular assessment showed undetectable NPM1 transcripts in peripheral blood, consistent with early molecular remission. Treatment was well tolerated, with no unexpected toxicities reported during the first cycle.

Conclusions. This case highlights the potential of decitabine/cedazuridine to induce rapid and deep responses, including early MRD negativity, even in frail elderly patients with aggressive and extramedullary AML presentation. Early clearance of NPM1 may carry favorable prognostic implications and supports the role of molecular monitoring in this setting. Further studies are warranted to better define the predictive value of early molecular response during hypomethylating therapy.

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Chronic myeloid leukemia

CEREBRAL AMYLOID ANGIOPATHY-RELATED INFLAMMATION AFTER NILOTINIB THERAPY IN A PATIENT WITH CHRONIC MYELOID LEUKEMIA

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Introduction Nilotinib is a second-generation tyrosine kinase inhibitor (TKI) approved for chronic myeloid leukemia (CML) treatment. Some studies have linked TKI treatment with neurological adverse events. This report describes the case of a patient with CML treated with nilotinib who developed cerebral amyloid angiopathy-related inflammation (CAA-ri), which entirely resolved after TKI discontinuation.

Case description. In May 2009, a 71-year-old man received a diagnosis of CML in chronic phase. He started imatinib in May 2009 (400 mg once daily), achieving a major molecular response (MMR) after 3 months. In January 2013, the patient stopped imatinib due to toxicity (mild anemia and peripheral edema). The Bcr-Abl transcript level remained stable without therapy, until May 2014, when we observed loss of MMR. The patient hence started treatment with nilotinib (300 mg twice daily), with a deep molecular response (MR5) after 3 months.After about 1 year of therapy, the patient presented repeated episodes of pre-syncope. In March 2017, the patient presented a state of confusion, with psychomotor retardation. The computed tomography (CT) scan of the brain showed “large areas of hypodensity in the right frontal and left temporal center”, suspected of CAA-ri. The brain MRI was not performed because of a cochlear implant. Further investigations ruled out the presence of any vascular abnormalities in the carotid arteries, or any cardiac structural or functional alterations. Neurodegenerative diseases were excluded by cerebrospinal fluid analysis. A biopsy of the right frontal lesion was performed and the radiological suspicion of CAA-ri was confirmed (positivity on brain parenchyma fragments of Congo red histochemical staining for amyloid substance). The patient was treated with corticosteroids and nilotinib was discontinued. Follow-up CT scans showed reduction of the cerebral lesions (Fig. 1 C, D, E and F), with progressive clinical improvement. A MR5 was periodically confirmed, even at the last follow-up in January 2026.

Conclusions. We report a case of CAA-ri in a patient with CML treated with nilotinib, which is known to be associated in the animal model of Alzheimer's disease with increased clearance of amyloid, a mechanism that underlies iatrogenic forms of CAA-ri in humans. The possible association between nilotinib and the neurologic complication is supported by the resolution of both clinical and radiological signs of CAA-ri after treatment discontinuation.

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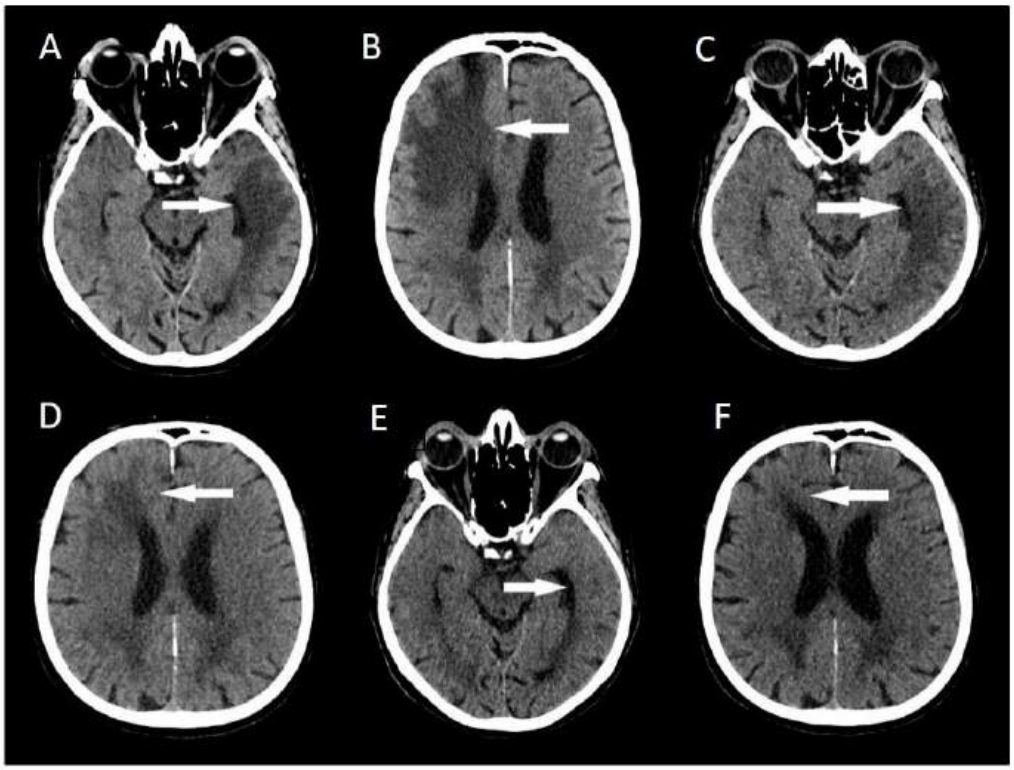

Fig.1 - Axial brain CT images showing large areas of hypodensity in the left temporal (A) and right frontal area (B). Initial reduction of hypodensity areas in the white matter of the left temporal (C) and the right frontal area (D) 1 month after nilotinib withdrawal. Further reduction of hypodensity areas in the white matter of the left temporal (E) and the right frontal area (F) 3 months after nilotinib withdrawal.

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Chronic myeloid leukemia

FISH-NEGATIVE BCR-ABL1 POSITIVE B2A2 CHRONIC MYELOID LEUKEMIA: A CASE REPORT

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Chronic myeloid leukemia (CML) is a malignant clonal disorder of the hematopoietic stem cells characterized by the aberrant production and uncontrolled proliferation of mature granulocytes with normal cell differentiation. At diagnosis, up to 85–90% of CML cases have a t(9;22)(q34;q11) on conventional cytogenetic analysis. In 1-5% of cases there is a cryptic BCR-ABL1 fusion gene without any cytogenetically-visible involvement of chromosomes 9 or 22. The presence and location of BCR-ABL1 fusion gene generate by variant translocations or cryptic rearrangements is identified by fluorescence in situ hybridization (FISH) or reverse transcription PCR (RT-PCR). FISH negative, BCR-ABL1 positive patients are extremely rare. We report a case of 65-years old male admitted to the Hematology Department for worsening fatigue. The peripheral blood count showed hyperleucocytosis (WBC 310 × 10^9/L), anemia (hemoglobin 9.5 g/dl) and mild thrombocytopenia (107 × 10^9/L). Peripheral blood smear showed 4% myelocytes, 9% metamyelocytes, 1% promyelocytes, 74% neutrophils, 1% lymphocytes, 3% monocytes, 2% eosinophils, and 3% basophils with 3% blasts. Bone marrow biopsy showed extremely active proliferation, with a markedly increased granulocyte lineage. Abdominal ultrasound revealed splenomegaly (16 cm). RT-PCR detected a classical b2a2 fusion transcript. But unexpectedly, conventional cytogenetic analysis showed a normal male karyotype in all metaphases examined (46,XX[20]) and FISH for BCR-ABL1 analysis was negative. The patient was diagnosed with chronic phase CML. The Sokal and ELTS scores indicated high risk. Patient started therapy with imatinib 400 mg QD. After two months of treatment the patient presented WBC 6 ×10^9/L, hemoglobin 11 g/dl, platelet 147 × 10^9/L. Although a longer follow-up is necessary to evaluate effectiveness of TKIs in CML with this particular variant translocation.

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Hodgkin's Lymphoma

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: A 10-YEAR SINGLE-CENTER RETROSPECTIVE ANALYSIS OF CLINICAL CHARACTERISTICS AND OUTCOMES

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma with generally favorable outcomes, but a non-negligible risk of relapse and histological transformation. Given its biological and clinical similarities with B-cell non-Hodgkin lymphomas, the optimal therapeutic approach remains uncertain. We analyzed 32 consecutive patients (pts) diagnosed with NLPHL between 2015 and 2025, evaluating clinical characteristics, treatment, and outcomes. In line with other previously published studies, histological patterns were grouped into two categories (typical/nodular pattern A-B (NP) vs variant/diffuse pattern C-F (DP)) for analysis. Progression-free survival (PFS) was estimated using the Kaplan–Meier method. Outcomes were also compared between pts treated with R-ABVD and those receiving R-CHOP or similar regimens. A total of 32 pts were included, with a median age of 48 years (range 18–81) and a male predominance (71.9%). Most pts presented with early-stage disease (AAS I–II: 65.6%), while 34.4% had advanced-stage (AAS III-IV) disease. NP and DP growth patterns were equally represented (50% each). DP was significantly associated with advanced-stage disease (8 vs 1 cases; p=0.01) and older age (62 vs 29 years, p=0.002). After a median follow-up of 57 months, median OS was not reached, and the 5-year PFS was 78.8%. R-CHOP was more frequently administered in pts with DP (70%, n=7), whereas R-ABVD was more commonly used in NP (58.3%, n=7 p 0.184). Among 23 pts treated with R-CHOP (n=10) or R-ABVD (n=13), no significant difference in PFS was observed (HR 0.31; p=0.29), although 5-year PFS was higher with R-CHOP (88.9% vs 59.9%). When analyzing PFS within treatment groups, no differences were observed between DP and NP in pts treated with R-ABVD (p=0.95) or R-CHOP (p=0.48). Consolidative radiotherapy was administered in 11 pts with a lower risk of progression (HR 5.39; 95% CI 0.59–48.99; p=0.135) and higher 5-year PFS (87.5% vs 54.5%). Transformation to diffuse large B-cell lymphoma occurred in 7.1% of cases, without significant association with histological pattern. No significant differences were observed between treatment groups in terms of cardiac toxicity or secondary malignancies. In our experience, NLPHL confirmed a favorable overall prognosis. DP was associated with inferior PFS, without differences in OS. No significant differences emerged between R-CHOP and R-ABVD, likely reflecting treatment selection based on disease characteristics

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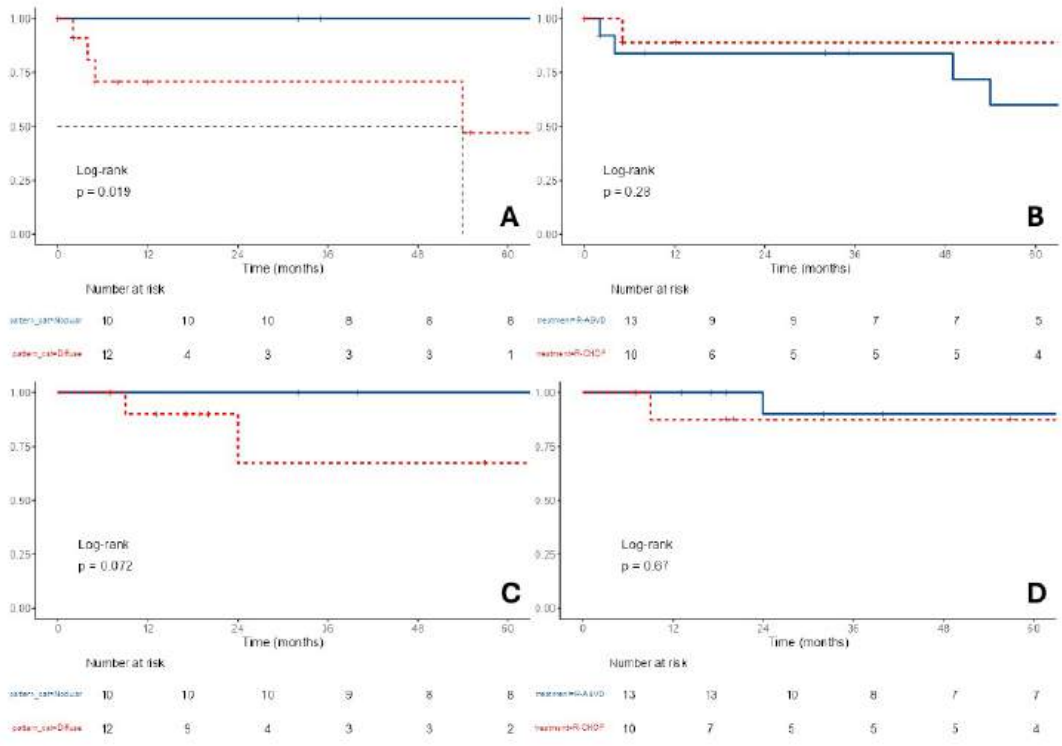
Figure 1: Comparison between NP vs DP (OS e PFS A and C) and treatment between R-CHOP/COMP vs R-ABVD (OS e PFS B and D)



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Hodgkin's Lymphoma

NEUTROPHIL-TO-LYMPHOCYTE RATIO AS A POTENTIAL PREDICTOR OF THROMBOSIS IN CLASSICAL HODGKIN LYMPHOMA: AN EXPLORATORY ANALYSIS

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Aims. Neutrophil-to-lymphocyte ratio (NLR) is a simple inflammatory biomarker associated with cancer-associated thrombosis (CAT). We aimed to evaluate NLR as a predictor of CAT in classic Hodgkin lymphoma (cHL).

Methods. Consecutive patients diagnosed with cHL from 2017 to 2020 at our institution were included. Exclusion criterium was anticoagulation for any indication. Thrombotic event(TE)-free survival (t-EFS) was defined as the time from diagnosis to the occurrence of a TE or last follow-up. Associations between NLR, established clinical risk scores and TEs were assessed using Pearson's χ^2 test. Time-to-event analyses were performed using Cox proportional hazards regression. A multivariable Cox model was used to assess the independent predictive value of NLR beyond clinical scores. Statistical significance was set at $p<0.05$.

Results. Ninety patients were included (48 males, 42 females). Median age was 42 years (18-85). Disease stage was early favorable in 11.1%, early unfavorable in 38.9%, and advanced in 50%. Median NLR at diagnosis was 4 (0.4–21.2). Khorana score was intermediate in 82.2% and high in 15.6% (2.2% not assessable, NA). Throly score was low in 15.6%, intermediate in 62.2%, and high in 21.1% (1.1% NA). Thro-HL score was low in 44.4%, intermediate in 33.3%, and high in 21.1% (1.1% NA). Eighteen patients (20%) experienced venous TEs, no arterial events occurred. Median t-EFS was 22.2 months (range 0.1-49.2). Median follow up was 28.3 months (1.3-50.3). All patients were alive at last follow up. ROC analysis identified NLR >3.9 as the optimal cut-off for predicting TE (AUC 0.633; sensitivity 72.2%; specificity 54.3%). At χ^2 analysis, NLR >3.9 (p=0.045), Khorana score (p=0.046), Throly score (p=0.01), and Thro-HL score (p=0.008) were all significantly associated with TE.In univariate Cox regression, the Khorana high-risk group (HR 2.99, 95% CI 1.03–8.62, p=0.043) and the Thro-HL high risk-group (HR 7.33, 95% CI 1.94–27.67, p=0.003) were significantly associated with TEs occurrence. NLR >3.9 (HR 2.62, 95% CI 0.93–7.35, p=0.067) and the Throly high-risk group (HR 6.96, 95% CI 0.87–55.69, p=0.067) showed a trend toward statistical significance. In multivariable analysis, only the Thro-HL score emerged as independent predictor of TEs.

Conclusions. NLR showed a trend toward association with CAT in cHL, but it did not result as an independent predictor. Whether NLR may complement existing clinical scores remains to be determined.

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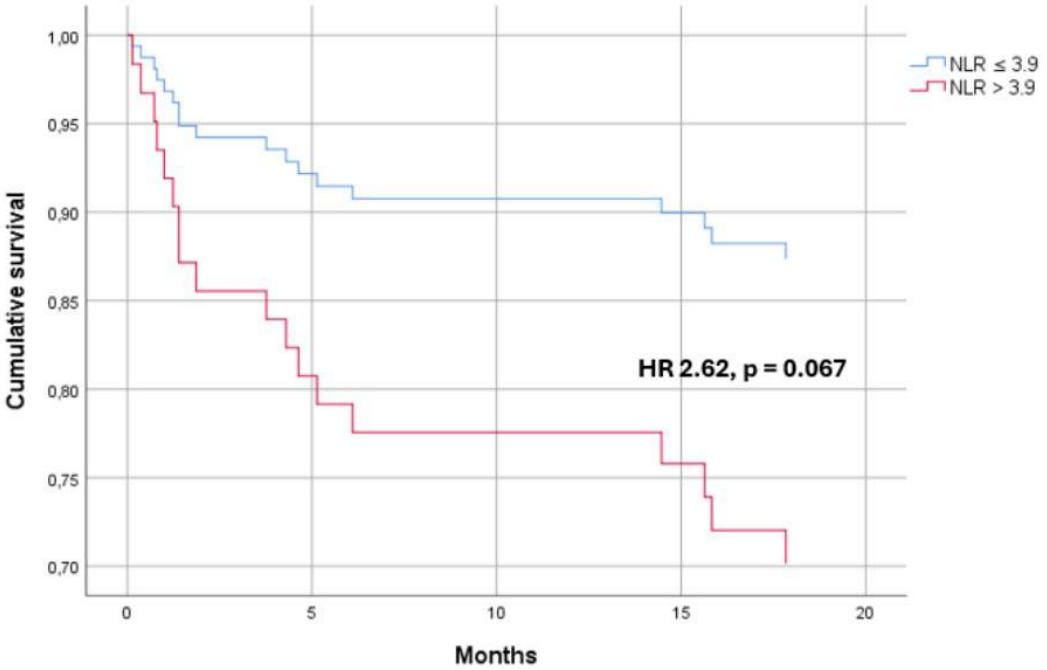

Figure 1. Kaplan–Meier curves for thrombotic events according to NLR categories (cut-off 3.9). Patients with NLR > 3.9 showed a higher incidence of thrombotic events compared to those with NLR ≤ 3.9. In univariable Cox regression analysis, NLR > 3.9 was associated with a non-significant trend toward increased thrombotic risk (HR 2.62, 95% CI 0.93–7.35, p = 0.067).

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Hodgkin's Lymphoma

CLINICAL JUDGMENT ENHANCES INTERIM PET INTERPRETATION IN HODGKIN LYMPHOMA: A REAL-WORLD MONOCENTRIC EXPERIENCE

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Background. Interim PET after 2 cycles of ABVD (PET2) is a well-established prognostic tool in Hodgkin lymphoma (H-L), yet its role in guiding treatment decisions is still debated. Real-world data on how PET2 results impact therapeutic choices are scarce.

Methods. We retrospectively analyzed consecutive classical HL patients treated with ABVD between January 2010 and December 2023 at the University Hospital of Udine. PET2 was evaluated using a semiquantitative Deauville Score (D-S): DS>=4 was defined as positive when SUVmax of the hottest residual lesion exceeded the hepatic SUV reference. For PET2-positive (PET2+) patients, the institutional protocol recommended a switch to high-dose salvage chemotherapy (IGEV or BeGEV) plus autologous stem cell transplantation; however, the treating clinician was allowed to continue ABVD based on an overall clinical assessment integrating residual uptake, response trajectory and patient fitness.

Results. Of 378 evaluable patients, 51 (14%) were PET2+ (DS=4 in 88%, DS=5 in 12%) and constituted the study population. Median age was 38 years (range 16-74), 64% males; advanced stage in 79%, B symptoms in 55%, bulky disease in 33%. Twenty-eight patients (55%) underwent treatment intensification, while 23 (45%) continued ABVD. Paradoxically, the subsequent PET (PETpost) showed complete metabolic response (CMR, DS<=3) more frequently in patients who continued ABVD than in those switched to salvage (65% vs 36%; p=0.036). We used univariate logistic regression to identify which variables affected decision-making, driving clinicians to therapy switch: decreasing age (OR 1.08 per year, p=0.023) and higher delta-SUV between the lesion and the hepatic reference (OR 1.73, p=0.057) were associated with the choice to intensify therapy. The same choice to intensify treatment was significantly associated with persistent PET positivity at PETpost (OR 5.0, 95%CI 1.04-24.0; p=0.045).

Conclusions. In a real-world setting, clinicians appear to integrate clinical and PET-derived information beyond the binary Deauville Score to identify patients at higher risk of treatment failure. This clinical judgment, acting as a heuristic filter, effectively discriminated truly chemorefractory cases from those with borderline PET2 positivity still responding to ABVD. Our findings highlight the added value of clinical expertise in interim PET interpretation and urge caution when implementing algorithmic PET-driven strategies in HL without clinical integration.

Hodgkin's Lymphoma

REAL-WORLD OUTCOMES OF NIVOLUMAB-AVD IN ELDERLY PATIENTS WITH ADVANCED CLASSICAL HODGKIN LYMPHOMA: UPDATED SINGLE-CENTRE EXPERIENCE

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Background Nivolumab plus AVD (N-AVD) demonstrated superior efficacy and tolerability versus brentuximab vedotin-AVD in older patients with advanced classical Hodgkin lymphoma (cHL) in the phase III S1826 trial. However, real-world data in elderly patients remain limited. We report an updated single-centre experience, representing the largest real-life Italian cohort of elderly patients with cHL treated with N-AVD.

Methods. We retrospectively analyzed consecutive elderly patients (age >60 years) with advanced cHL treated with N-AVD. Treatment consisted of nivolumab (240 mg, days 1 and 15) combined with AVD every 28 days for six cycles, with dose attenuation at physician discretion. Responses were assessed by PET-CT. Overall response rate (ORR; complete and partial response [CR, PR]) was assessed at end-of-treatment (EOT). Progression-free survival (PFS) was defined from treatment start to disease progression or death from any cause, with censoring at last follow-up. Adverse events were graded according to CTCAE ver. 5.0.

Results. Eleven patients were included (median age 71 year, range 65-85; 8 male), all with stage III-IV disease. Median IPS was 3 (range 2-5), with 64% high-risk disease (IPS ≥3). AVD dose attenuation was applied in 5/11 patients (4 at 50% and 1 at 75% of standard dose), while nivolumab was given at full dose in all patients. Interim PET showed CR in 6/11 (54%) and PR in 4/11 (36%), with one progressive disease (PD). At EOT, ORR was 70% (CR 60%, PR 10%); three patients had PD and one patient was pending response evaluation. PD occurred in both dose-attenuated and full-dose groups. With a median follow-up of 18 months (range 5-23), estimated 18-month PFS was 53% (Figure 1). Most progression events occurred within the first 10 months of follow-up. One death due to PD occurred beyond 18 months. Treatment was mainly associated with hematologic toxicity, including grade ≥3 neutropenia in 7/11 patients (64%). Infections included pneumonia (2/11) and urinary tract infection (1/11). Immune-related adverse events occurred in two patients (hypothyroidism and interstitial pneumonitis).

Conclusions. In this real-world cohort of elderly patients with advanced cHL, N-AVD achieved high response rates despite dose attenuation; however, early progression events were frequent, likely reflecting a frailer population underrepresented in clinical trials, as a substantial proportion of our patient cohort would not have met S1826 eligibility criteria.

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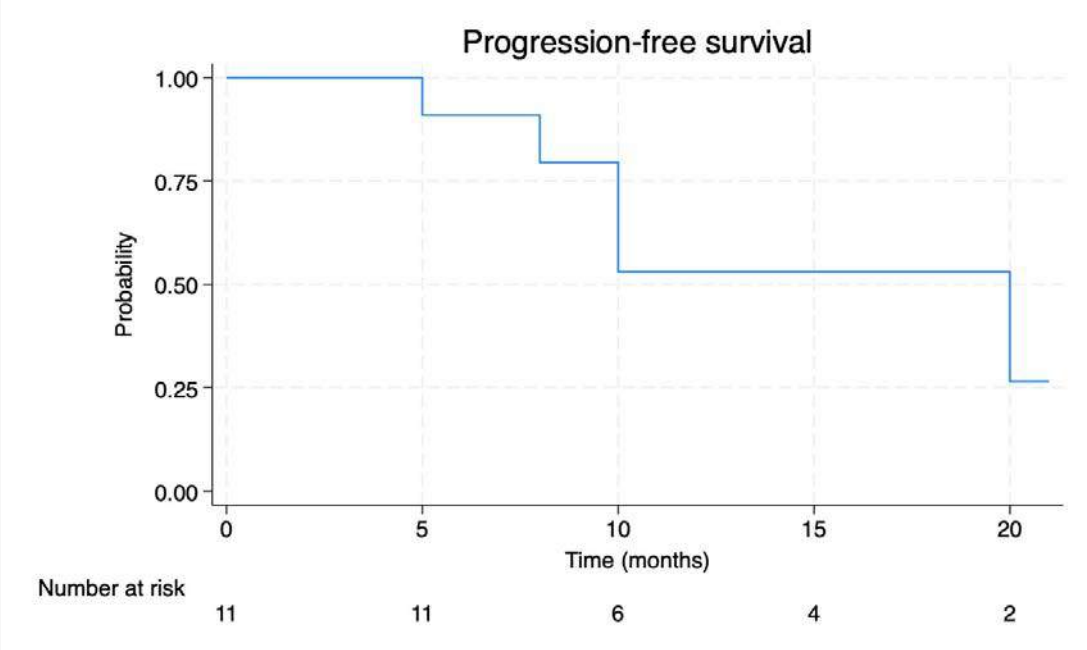
Progression-free survival
1.00
0.75
0.50
0.25
0.00
Probability
0
5
10
15
20
Time (months)
Number at risk
11
11
6
4
2

Non-Hodgkin's Lymphoma

HD-MTX IN AGGRESSIVE LYMPHOMAS: REAL-WORLD DATA ON NEPHROTOXICITY AND GLUCARPIDASE USE

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Introduction. High-dose methotrexate (HD-MTX) is mainly renally cleared; nephrotoxicity, though uncommon, can be severe. Acute kidney injury (AKI) reduces MTX clearance, increasing systemic toxicity, particularly mucositis and myelosuppression. Despite standard prophylaxis (hyperhydration, urine alkalinization, leucovorin), interpatient variability remains significant, and delayed clearance increases the risk of life-threatening exposure. Glucarpidase rapidly degrades extracellular MTX and is recommended within 48–60h in patients with MTX levels >2 standard deviations (SDs) above the mean excretion curve (www.MTXPK.org). However, real-world data are limited, and patient selection who would benefit from glucarpidase remains challenging. Herein, we report incidence, management, and outcomes of HD-MTX–related AKI and glucarpidase use in routine clinical practice at a single center.

Methods. Adults with aggressive lymphomas and normal renal function (CrCl ≥50 ml/min) treated with MTX ≥2 g/m² (Dec 2023–Jan 2026) were analyzed. MTX was given as a 3h infusion with a 500 mg/m² loading dose over 15 minutes. Plasma levels at 24 and 48h were measured by enzyme immunoassay; clearance was estimated via MTXPK. Leucovorin rescue followed guidelines. All patients received standard supportive care with strict urine output and pH monitoring. AKI was graded per CTCAE v5.0, considering grade ≥2 events.

Results. 38 patients (21F/17M; median age 58, 18–77) received 102 HD-MTX courses. Most had DLBCL with primary or secondary CNS involvement or high CNS risk; others had HGBCL or T-cell lymphomas. MTX was used for therapy (polychemotherapy; 92) or CNS prophylaxis (monotherapy; 10), with a delivered dose of 3–3.5 g/m² in 95%. MTX levels at 24 h exceeded +2 SD in 15 courses (15%). AKI occurred in 4 courses (3 grade 2; 1 grade 3), including 2/15 with elevated 24h MTX level vs 2/87 others (13% vs 2%; p=0.102). All AKI resolved, only one patient required glucarpidase. Three patients completed planned MTX courses without dose changes or AKI recurrence.

Conclusions. Despite its retrospective design, this study shows a low AKI incidence in patients treated with short-infusion MTX with adequate supportive measures, even in those with elevated 24h MTX levels. This finding should not alone guide glucarpidase use. Rising creatinine at 24–36h, extrarenal toxicity, and MTX >0.5 mmol/L at 48h should guide decisions. HD-MTX can be safely resumed after reversible AKI.

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Non-Hodgkin's Lymphoma

EXTRACELLULAR VESICLES PROFILE PREDICTS ENHANCED ANTI-TUMOR RESPONSE IN CAR T-CELL–TREATED LYMPHOPROLIFERATIVE NEOPLASMS

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Background. CAR T-cells are a groundbreaking therapy for patients with non Hodgkin lymphoma (nHL). Despite impressive results, some patients fail to respond or relapse. Early biomarkers of response are valuable for optimizing management of high-risk patients. The aim of this study is to investigate the role of extracellular vesicles (EVs), small membrane-bound particles released by various cell types, as predictive biomarkers of response following CAR-T.

Methods. EVs were characterized using a multiparametric flow cytometry (MFC) antibody panel (Phalloidin; LCD; CD41a; CD31; CD45 and CD146) to count EVs originating from leukocyte (LK-EVs, CD45+), endothelial cells (EC-EVs, CD45-/CD31+/CD41a-), and platelet (CD45-/CD31+/CD41a+). In addition, CD146 was used to identify EVs from activated EC and LK. The BD Trucount was used for absolute EVs counts.

Results. Between Oct-2023 and Feb-2026, 33 adult patients with nHL received commercial CAR-T at our unit. The most common diagnosis was diffuse large B cell lymphoma (n=22). The main infused product was axi cel (n=21); tisa cel was used in 7, and brexu cel in 3 patients with mantle cell lymphoma. After a median follow up of 12 months, OS was 71% and PFS was 58%. Twenty two patients achieved complete remission (CR); the 12 month the cumulative incidence (CI) of relapse was 21%. The 12 month CI of TRM was 10.4%. Patients who achieved CR had significantly lower total EVs and CD146+ EVs on day +14 post infusion (p=0.022 and p=0.038, respectively), likely reflecting a lower inflammatory burden. On day +10, the ratio of CD146+ LK EVs to total LK EVs was significantly higher in responding patients (p=0.002), as a marker of enrichment in activated leukocytes involved in leukocyte–endothelial interaction. These biomarkers had strong predictive performance by ROC analysis (AUCs: 0.783, 0.757, and 0.848, respectively). In multivariable analysis for PFS, a high CD146+ LK EV ratio on day +10 remained an independent predictor of response (HR 0.023, p=0.039).

Conclusions. Lower levels of total EVs and CD146+ EVs at day +14 may reflect reduced systemic inflammation following CAR-T, while an elevated CD146+ LK EV/total LK EV ratio at day +10 indicates early activation of leukocytes involved in leukocyte–endothelial interactions. Together, these patterns suggest that early, targeted leukocyte–endothelial activation coupled with a lower inflammatory milieu might be associated with effective anti tumor response and improved PFS.

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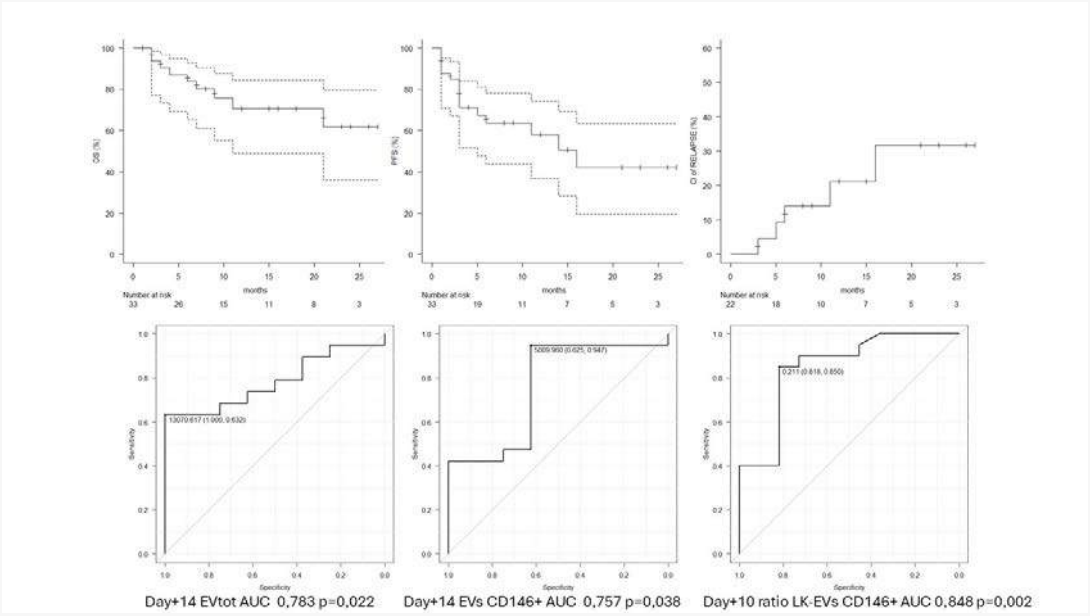
Day+14 EVtot AUC 0,783 p=0,022
Day+14 EVs CD146+ AUC 0,757 p=0,038
Day+10 ratio LK-EVs CD146+ AUC 0,848 p=0,002

Non-Hodgkin's Lymphoma

PROGNOSTIC IMPACT OF POD24 ACROSS DIFFERENT TREATMENT SETTINGS IN WALDENSTRÖM MACROGLOBULINEMIA TREATED WITH BENDAMUSTINE-RITUXIMAB, DEXAMETHASONE-RITUXIMAB-CYCLOPHOSPHAMIDE AND BTK INHIBITORS

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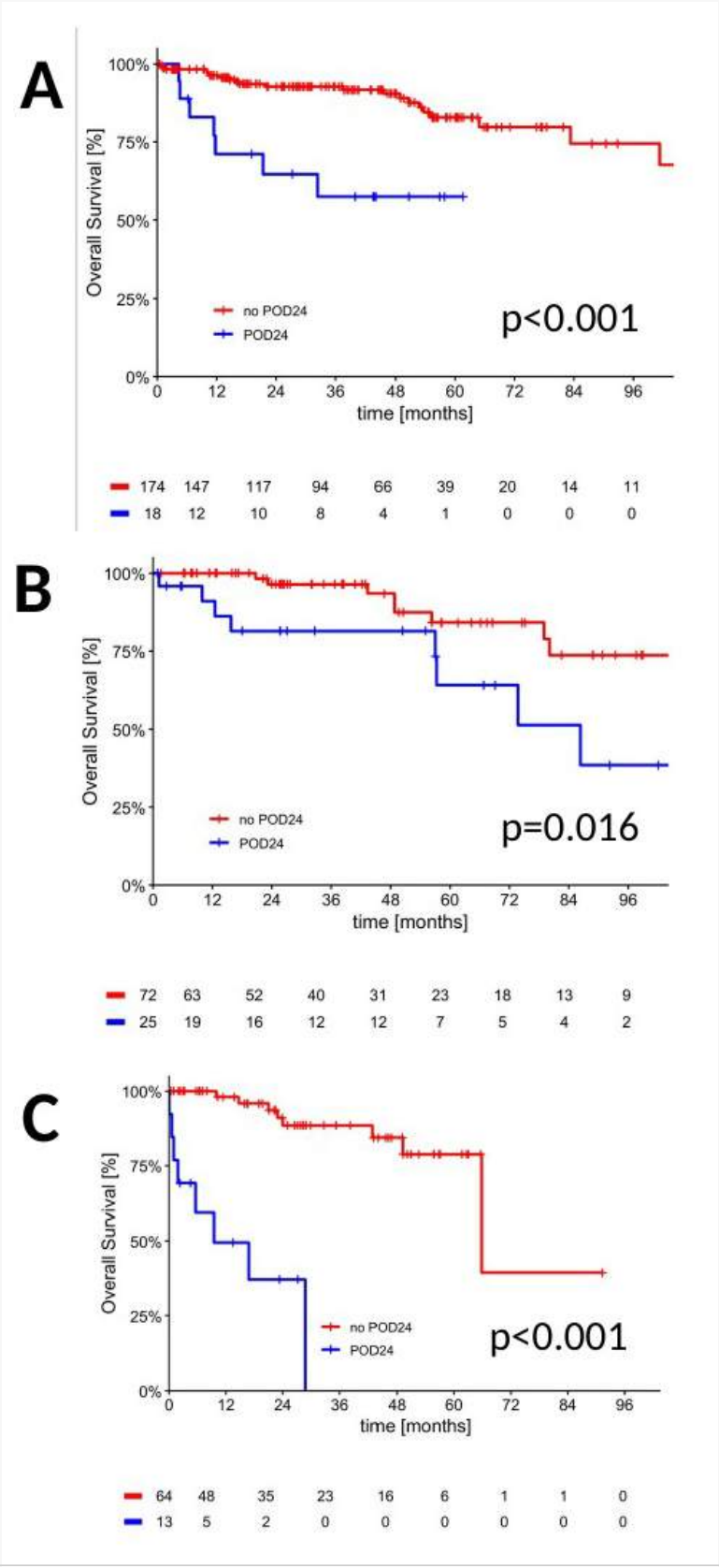
Progression of disease within 24 months (POD24) is a validated dynamic prognostic marker in indolent lymphomas, but its role in Waldenström Macroglobulinemia (WM) remains incompletely defined across treatment settings and in relation to baseline risk factors and molecular features.Our aim was to evaluate the prognostic impact of POD24 in WM and to compare its discriminatory value with IPSSWM and mutational status.We conducted a multicenter retrospective FIL study including WM patients treated with frontline bendamustine-rituximab (BR, n=244), frontline dexamethasone-rituximab-cyclophosphamide (DRC, n=116), and BTK inhibitors (BTKi) in relapsed disease (n=102: 71 ibrutinib, 31 zanubrutinib). Survival was estimated by Kaplan–Meier and compared by log-rank test, with a 24-month landmark analysis. Standardized mortality ratios (SMR) were calculated using matched general population data. Median follow-up was 54, 59, and 44 months for BR, DRC, and BTKi, respectively.POD24 incidence was 9.4% in BR, 25.8% in DRC, and 16.9% in BTKi. Across all cohorts, POD24 was associated with inferior overall survival (OS): BR (5-year OS 57% vs 83%, HR 4.6 (95% CI: 1.9-11.0), p<0.001; figure 1A), DRC (64% vs 84%, HR 3.1 (95% CI: 1.2-8.4), p=0.016; figure 1B), and BTKi although based on limited sample size (0% vs 79%, HR 15.7 (95% CI: 5.0-49.6), p<0.001; figure 1C). In BR, SMR was 4.8 for POD24 vs 2.3 for non-POD24; in DRC, 5.1 vs 1.9; and in BTKi, 22.2 vs 3.5.CXCR4 mutations were associated with inferior outcomes, particularly in BTKi-treated patients, whereas MYD88L265P status did not significantly impact OS. Among BTKi patients in the landmark analysis, 13 experienced POD24: 10 treated with ibrutinib and 3 with zanubrutinib. MYD88 was wild-type in 23%, mutated in 61%, and unknown in 15%; CXCR4 was wild-type in 15%, mutated in 23%, and unknown in 61%. Prior therapies included BR (31%), DRC (61%), and R-chemotherapy (8%).No correlation was observed between POD24 and high IPSS-WM. POD24 appeared to provide stronger prognostic discrimination than IPSSWM in BR-treated patients, whereas IPSSWM retained greater prognostic value in the DRC cohort.In conclusion, POD24 is a robust and clinically meaningful prognostic marker in WM, confirming prior evidence in BR-treated patients and extending its relevance across multiple therapeutic settings. Early recognition of patients at risk for POD24 remains essential for upfront risk stratification and treatment tailoring.

Stampa pp. 561-562



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Non-Hodgkin's Lymphoma

FGF/FGFR INHIBITORS HAMPER THE GROWTH OF C-MYC-DRIVEN AGGRESSIVE B-CELL NON-HODGKIN LYMPHOMA

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Background. B-cell non-Hodgkin lymphomas (B-NHL) are a heterogeneous group of malignancies arising from peripheral B lymphocytes. A subset of diffuse large B-cell lymphomas (DLBCL) and all Burkitt's lymphomas (BL) are aggressive c-MYC-driven B-NHL. Although current treatments often provide complete remission, about half of patients relapse. We recently demonstrated that fibroblast growth factor (FGF) signaling contributes to c-MYC protein stabilization, while FGF or FGF receptor (FGFR) inhibition induces its proteasomal degradation, suggesting a promising therapeutic strategy.

Aims. To investigate the effects of FGF signaling inhibition in c-MYC-driven aggressive B-NHL using two approaches: (i) extracellular FGF trapping and (ii) FGFR TK inhibition approach.

Methods. FGF and FGFR expression were assessed by qPCR. FGFR activation and c-MYC protein levels were analyzed by Western blot and immunohistochemistry. Drug effects were evaluated by viable cell counting, TMRE, Mitosox, Annexin-V/PI staining, and flow cytometry. In vivo experiments were performed in NOD/SCID mice.

Results. c-MYC positive DLBCL and BL patient samples showed high levels of activated/phosphorylated (p)FGFR, whereas c-MYC-negative DLBCL lacked FGFR activation, indicating a strong correlation between FGFR activation and c-MYC protein expression. To assess the role of the FGF/FGFR system in c-MYC-driven B-NHL, we tested the effect on lymphoma fitness of the FGF trap molecule NSC12 and the FDA-approved FGFR TK inhibitor Erdafitinib in c-MYC positive DLBCL (RI-1, U2932, SU-DHL-6 and SU-DHL-10) and BL (RAJI, DAUDI) cell lines. All cell lines express several FGFRs and FGF ligands and high levels of pFGFR in the absence of exogenous stimuli, indicating the presence of an autocrine FGF stimulation. In vitro NSC12 or Erdafitinib treatments strongly inhibited FGFR activation and induced the rapid proteasomal degradation of c-MYC protein, confirmed by MG132 co-treatment. c-MYC reduction was associated with decreased tumor cell proliferation and increased ROS-mediated apoptosis in all cell lines tested. To note, NSC12 or Erdafitinib showed synergistic effects with the standard therapy R-CHOP. In vivo treatment with NSC12 or Erdafitinib significantly reduced the growth of both DLBCL and BL tumor xenografts.

Conclusions. These findings demonstrate that the FGF/FGFR system sustains growth and survival of DLBCL and BL cells and open new therapeutic hints for the treatment of c-MYC-driven aggressive B-NHL.

Stampa p. 563

Non-Hodgkin's Lymphoma

THE IMPACT OF MYC ALTERATIONS IN LARGE B-CELL LYMPHOMAS TRANSFORMED FROM FOLLICULAR LYMPHOMA: A SINGLE CENTRE EXPERIENCE

S. Maifredi[1], C. Pagani[2], A. Passi[2], R. Daffini[2], G. V. Facchetti[2], A. Anastasia[2], M. Motta[2], E. Lovato[2], C. Cattaneo[2], A. Re[3], L. Lorenzi[4], S. Ferrari[2], N. Bianchetti[2], C. Bottelli[2], C. Aquilina[2], A. Pantaleo[2], A. Tucci[2]

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Follicular lymphoma (FL) is an indolent malignancy with a heterogeneous clinical course. Despite improved survival with immunochemotherapy, some patients (pts) develop histological transformation into aggressive disease which is associated with poor outcomes.This study aimed to value outcomes of pts with transformed large B cell lymphoma (t-LBCL) from FL.We retrospectively analyzed all consecutive pts aged ≥18 years (y) with tLBCL treated at our center between 2011 and 2025. Pts were classified according to the classification proposed by C. Rusconi (Br J Haematol. 2019;185(4):713-717).A total of 190 pts was included, with a median age of 66y (range 32-89) and a male/female ratio 106/84. According to Rusconi classification: 97 pts (51,1%) were classified as group 1 (transformation at diagnosis), 19 (10,0%) as 2A (treatment-naïve at transformation), 58 (30,5%) as 2B (one prior line of therapy), and 16 (8,4%) as 2C (≥2 prior lines). Histology showed diffuse LBCL in 147 cases and high-grade BCL in 43. FISH analysis was performed in 156 pts, of whom 60 (38,5%) harbored MYC rearrangements (translocations, increased copy number >4 and amplifications) and 24,4% were double hit (DH). IPI score was 3-5 in 103 pts (54,2%).For survival analysis we evaluated 172 pts who underwent therapy with curative intent.With a median follow-up of 41 months (range 1-144) 5y-PFS and OS were 48,7% (fig. 1a) and 53,9% respectively (fig. 1b).No significant clinical differences were observed among groups 1, 2A, 2B and 2C.Rusconi classification identified groups of pts with significant worse 5y-PFS (group 1: 56,6% vs 2A: 54,2% vs 2B: 34,9% vs 2C: 44,9%; p=0.009; fig. 1c) and 5y-OS (group 1: 65,1% vs 2A: 51,4% vs 2B: 39,2% vs 2C: 43,5%; p=0.027; fig. 1d).Pts with MYC rearrangement showed inferior 5-y PFS (MYC-unmutated: 65,9% vs MYC--mutated: 37,9%; p=0.002; fig. 1e) and 5y-OS (MYC-unmut: 71,0% vs MYC-mut: 40,1%; p=0.007; fig. 1f).In univariate analysis, advanced stage, IPI 3-5, MYC rearrangement and DH lymphomas are associated with a worse prognosis. In multivariate analysis, only the IPI has an impact on OS and PFS.In this real-world cohort of tLBCL, outcomes remain heterogeneous but overall poor. The Rusconi classification provides useful prognostic stratification while MYC rearrangements are associated with inferior survival. These findings support integrated clinical and biological risk assessment to improve patient stratification and guide future therapeutic strategies.

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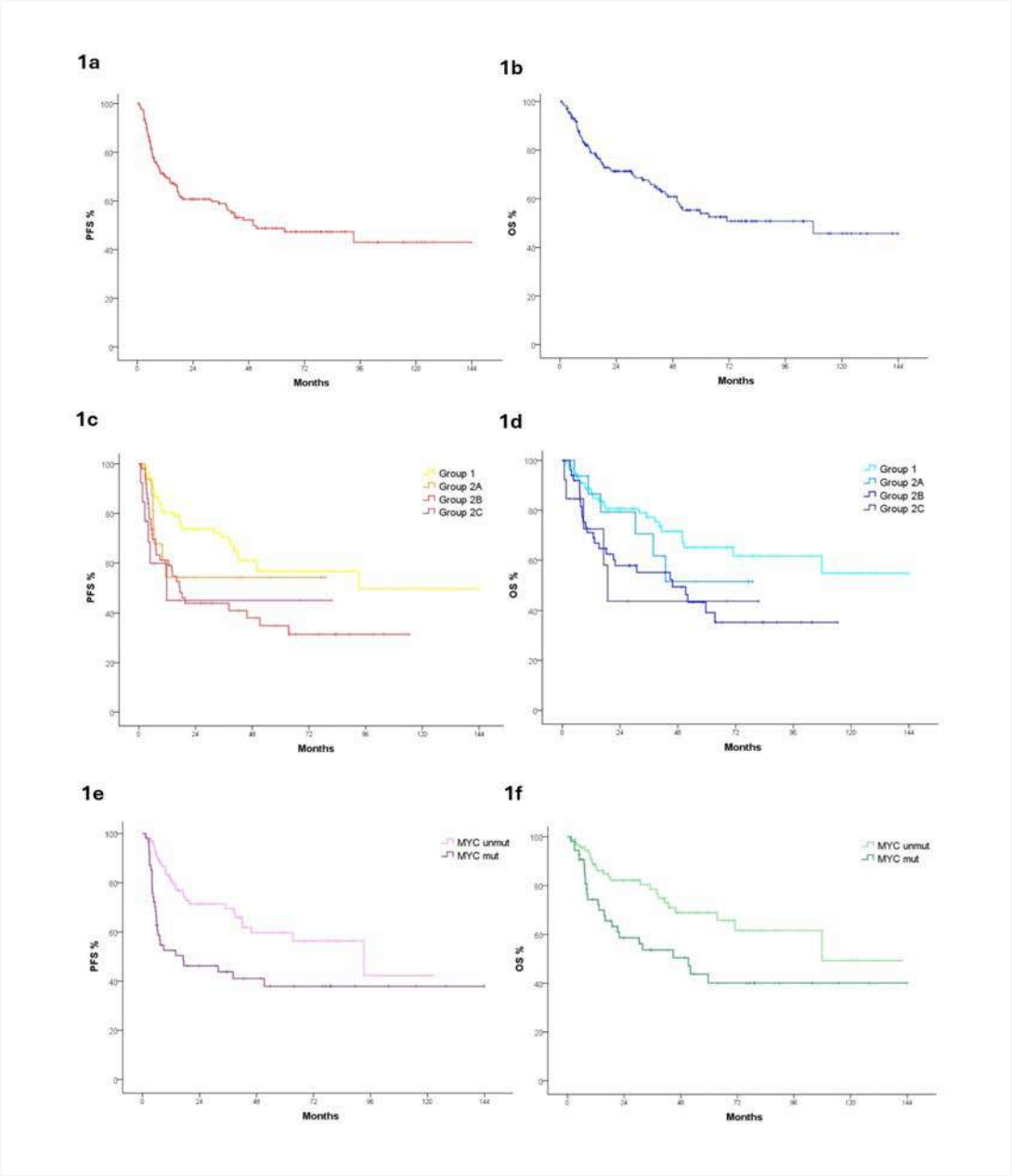
1a
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Non-Hodgkin's Lymphoma

PROGNOSTIC VALUE OF PET-DERIVED PARAMETERS (SUVMAX AND ΔSUV) IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA PATIENTS TREATED WITH CAR-T CELL THERAPY: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Background. Nearly 60% R/R LBCL patients treated with CAR-T cell therapy relapse or fail to respond, highlighting the need for improved prognostic tools. FDG PET/CT at 1 and 3 months provides widely accessible biomarkers such as SUVmax and ΔSUV. This retrospective study evaluates their prognostic value.

Methods. Data from 53 LBCL patients treated with axi-cel or tisa-cel at Sapienza University Center (Nov 2019–Nov 2024) were analyzed. SUVmax before infusion (PET0), and SUVmax and ΔSUV at 1 and 3 months (PET1, PET3) were evaluated. Cutoffs for SUVmax and ΔSUV were set at 4 and 70%, according to the literature. OS and PFS were estimated by Kaplan–Meier and compared with the log-rank test; Cox models were used for uni- and multivariable analyses, reporting HRs with 95% CIs, with p<0.05 considered significant.

Results. In this cohort, 42 (79%) patients had DLBCL and 11 (21%) PMBCL; 31 (58.5%) received axi-cel and 22 (41.5%) tisa-cel. Median age was 52 and 47% had advanced disease, with a median of two prior therapies. Median SUVmax at PET0 was 12.8 (range: 0-43.3). At 13 months median follow-up, 1-year OS and PFS were 76.9% and 61%. One month after CAR-T infusion, 26 (49%) patients achieved CR, 18 (34%) PR, 4 (8%) SD, and 5 (9%) PD. Among patients with 1-month PR, 56% converted to CR. At PET1, SUVmax>4 and ΔSUV<70% did not correlate with significantly shorter OS and PFS. Conversely, at PET3, the 1-year OS was 95% for SUVmax<4 vs 63.7% for SUVmax>4 (p=0.00072), and 100% for ΔSUV>70% vs 65.9% for ΔSUV<70% (p=0.01). The 1-year PFS was 86.5% for SUVmax<4 vs 60% for SUVmax>4 (p=0.0016), and 92.3% for ΔSUV>70% vs 59.6% for ΔSUV<70% (p=0.0087). In separate multivariable analyses, ΔSUV<70% was associated with an unfavorable impact on PFS (HR = 7.10; 95% CI: 1.19-42.21, p = 0.031) and OS (HR = 10.84; 95% CI: 1.11-106.21, p = 0.041) and SUVmax>4 was associated with an unfavorable impact on OS (HR = 25.4; 95% CI: 2.42–266.48, p = 0.007), while showed a trend toward worse PFS, although no consistent independent association was observed across models.

Conclusions. PET response at 3 months improves prognostic discrimination. In our study, SUVmax>4 and ΔSUV<70% at 3 months post-CAR-T correlate significantly with OS and PFS, providing a dynamic assessment of tumor metabolism and an additional tool to support clinical decision-making.ReferencesFarolfi et al. JNuclMed.2025;66(8):1183-1191Ceriani et al. J Nucl Med.2025;66(2):209-214Itti et al. JNuclMed.2023;64(11):1706-1711

Stampa pp. 566-567

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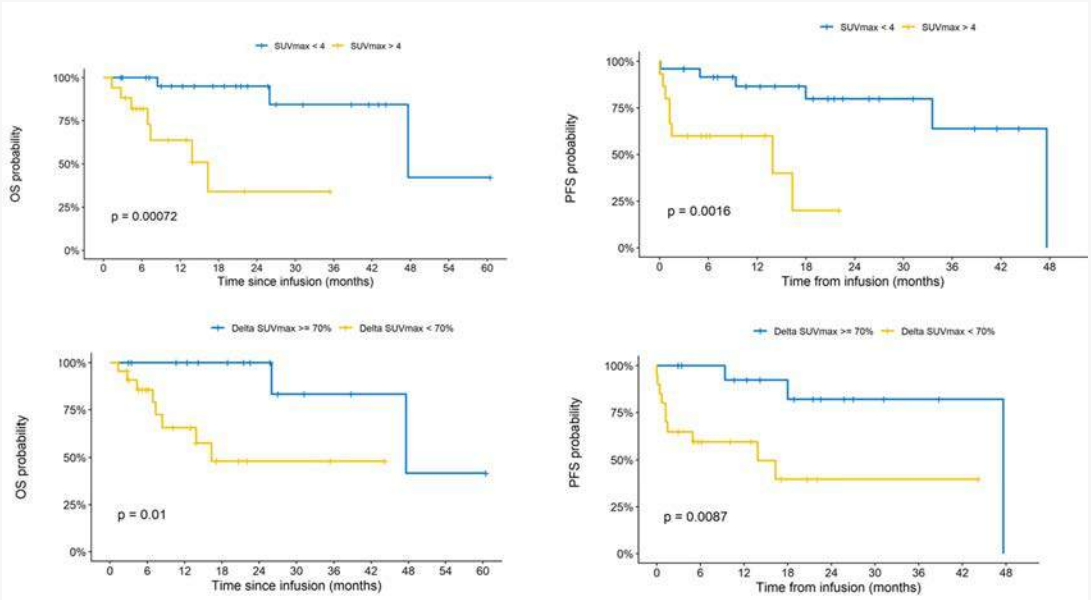

PET IMAGING PARAMETERS				
PET 3 months	1-year OS	p value	1-year PFS	p value
SUVmax <4 SUVmax >4	95% (IC:85.9-100%) 63.7% (IC:42-96.6%)	0.00072	86.5% (IC:73.4-100%) 60% (IC:39.7-90.7%)	0.0016
ΔSUV >70% ΔSUV <70%	100% 65.9% (IC:46.6-93.1%)	0.01	92.3% (IC:78.9-100%) 59.6% (IC:41.4-85.7%)	0.0087

Non-Hodgkin's Lymphoma

ALLO-HSCT IN ADVANCED MYCOSIS FUNGOIDES AND SÉZARY SYNDROME: A REAL-WORLD ITALIAN MULTICENTER EXPERIENCE

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Sézary syndrome (SS) and advanced-stage mycosis fungoides (MF) represent a significant unmet medical need, characterized by poor prognosis and a limited, highly heterogeneous, treatment algorithm. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative strategy in eligible patients, its use is limited by relapse risk, treatment-related morbidity, and the challenge of adequate disease control prior to transplantation. Optimal patient selection and treatment sequencing are critical priorities.We retrospectively analyzed therapeutic pathways, pre-transplant disease control, and post-transplant outcomes (according to Olsen et al., Blood 2022) in eight patients with advanced MF (n=6) or SS (n=2) treated across multiple Italian centers between 2021 and 2025 and considered eligible for allo-HSCT.Median age at diagnosis was 46 years; median time to first systemic therapy was 28 months. Patients received a median of 2 systemic lines (range 1–4). First-line intravenous therapy, following topical and oral treatments, was mogamulizumab in five patients and cytotoxic regimens in three. Five patients required second-line therapy, receiving brentuximab vedotin (BV, n=3), mogamulizumab (n=1), or alemtuzumab (n=1). Two patients received third-line with CHOEP and BV. Seven patients underwent total skin electron beam irradiation (TSEB, 24 Gy) to achieve better disease control before transplantation.-Four patients proceeded to transplantation (median time from diagnosis: 62 months). Prior to transplant, three were in partial response (PR) and one in very good partial response (VGPR). Best post-transplant response was complete response (CR) in three patients and PR in one. Two patients relapsed within three months (one from CR, one from PR), while two remain in sustained CR at one year. No treatment- or disease-related mortality was observed. Among patients awaiting transplantation, three are currently in VGPR; one patient is receiving fourth-line therapy for progressive disease with pegylated liposomal doxorubicin.Despite the small sample size inherent to this rare disease, these real-world data highlight the feasibility of allo-HSCT in refractory MF/SS and suggest TSEB as an effective bridging strategy. Durable post-transplant remissions were observed in patients achieving the deepest pre-transplant disease response, supporting allo-HSCT as the primary therapeutic goal as soon as optimal disease control is achieved.

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Non-Hodgkin's Lymphoma

THE CONTRIBUTION OF FLOW CYTOMETRY TO THE IDENTIFICATION OF CD5+ DIFFUSE LARGE B CELL LYMPHOMA (CD5+ DLBCL)

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Aberrant CD5 expression is observed in about 10% of diffuse large B cell lymphoma (DLBCL) and is associated with aggressive clinical features and high rate of systemic and central nervous system (CNS) relapse. This study aims to evaluate CD5 expression on pathological B cells using flow cytometry (FC) and to compare diagnostic performance of FC with immunohistochemistry (IHC) in order to improve identification of this high-risk group that may benefit from novel therapies. We analyzed 66 cases of CD5+ DLBCL (58 at diagnosis, 5 at relapse and 3 transformed from indolent lymphomas) collected between Jan 2012 and Jan 2026. Samples were obtained from lymph nodes (LN), bone marrow (BM), pleural effusion and cerebrospinal fluid (CSF). CD5 expression was identified by IHC (CD5 IHC+) and/or FC (CD5 FC+). Clinical characteristics confirmed a high prevalence of adverse prognostic factors: median age was 71 years (range 20-88), 76% presented with advanced stage, 67% had elevated LDH and 66% had an International Prognostic Index ≥3. Extranodal involvement was observed in 82%, including bone/BM (31%) and peripheral blood (24%). Among 39 pts with available immunoelectrophoresis data, 24 (61.5%) had a monoclonal component which was of IgM class and sharing the same clonality of pathological B cells in 12 (31%). IHC data was available in all cases except one primary effusion LBCL and CD5 positivity was observed in 51/65 cases. FC was available in 45 cases and with both IHC results in 44. FC initially failed to detect CD5 in 3 IHC+ cases, however CD5 was subsequently identified in all CSF at time of CNS progression. Conversely in 13 of 44 cases (29.5%) CD5 expression was detected only by FC despite a high median percentage of expression (90%, range 20-99%). These findings correspond to an estimated sensitivity of 70% for IHC and 93% for FC in detecting aberrant CD5 expression. Overall 44 clinical events were recorded, including 9 events among the 13 pts identified as CD5 FC+ only. CNS progression was frequent (15%) and CSF samples were consistently CD5 FC+. Median event-free survival was 20 months (range 9-72) in pts treated with curative intent (mainly R-CHOP) and 6 months (range 1-9) in those treated with R-miniCOMP. Our findings highlight the value of FC as a complementary tool for identifying CD5+ DLBCL at higher risk of progression. Furthermore, FC may improve diagnostic sensitivity particularly in the detection of rare events such as occult CNS involvement.

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Non-Hodgkin's Lymphoma

CYTOTOXIC T-CELL ACTIVATION AND SST2 ELEVATION CHARACTERIZE LYMPHOMA-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Lymphoma-associated hemophagocytic lymphohistiocytosis (LA-HLH) is a rare, life-threatening hyperinflammatory syndrome with high mortality, particularly in adults with aggressive lymphomas. Scoring systems, including the H-score and the simplified Optimized HLH Inflammatory (OHI index), based on elevated ferritin and sCD25 levels, have been proposed to facilitate identification of LA-HLH, based on clinical and laboratory parameters.We prospectively enrolled 109 consecutive patients with newly diagnosed lymphomas at risk for LA-HLH (72 aggressive B-cell, 8 T-cell, and 29 Hodgkin lymphomas), to evaluate novel biomarkers. Specifically, we assessed the presence of activated cytotoxic T cells in peripheral blood and serum levels of soluble ST2 (sST2), a marker of tissue injury and inflammation.Using the OHI-Index and an H-Score threshold > 169, the incidence of LA-HLH was 11.9% and 4.5%, respectively. Positive scores were associated with inferior median overall survival: 10 months for patients with a positive OHI-index, and < 2 months for those with H-Score ≥169.Immunophenotypic analysis identified an expanded population of recently activated cytotoxic T lymphocytes ($CD8^+$/HLA-DR^+/$CD38^{++}$) strongly expressing the activation marker PD-1 in peripheral blood from patients with LA-HLH. A threshold of > 9% was observed in 28 patients significantly associated with LA-HLH, as defined by OHI -Index (p=0.0013). Serum sST2 levels above the normal range (35 ng/ml) were detected in 25/109 (23%) patients. ROC curve analysis demonstrated that an sST2 threshold >44 ng/mL predicted a positive OHI-index with a sensitivity of 76.9% and a specificity of 87.5% corresponding to an AUC of 0.90 (p < 0.0001). Elevated sST2 levels were strongly associated with adverse prognosis (p=0.0012). In multivariable analysis, both $CD8^+$/HLA-DR^+/$CD38^{++}$ >9% and elevated sST2 levels independently predicted HLH.These findings suggest that expansion of recently activated cytotoxic T cells may represent an early immunopathogenetic event in LA-HLH, potentially preceding overt tissue injury reflected by increased levels of sST2. Incorporation of these biomarkers into current diagnostic algorithms may enable earlier recognition of LA-HLH and facilitate timely therapeutic intervention. Prospective validation of these parameters in larger cohorts is warranted.

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Non-Hodgkin's Lymphoma

A REAL-WORLD ANALYSIS OF AXICABTAGENE CILOLEUCEL AS SECOND LINE TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMAS: A REPORT FROM RETE EMATOLOGICA PUGLIESE

C. Mancino[1], C. Ingrosso[2], M. Delia[3], A. Spina[4], G. Dell'Olio[1], D. Salvatore[1], R. Presicci[2], T. Perrone[3], G. Quintana[4], L. Ciuffreda[5], V. Fesce[5], G. De Santis[6], R. Miccolis[6], G. Lerario[7], L. Tonialini[7], C. Contento[8], V. Federico[8], R. De Francesco[9], G. Greco[9], L. Melillo[5], G. Loseto[7], N. Di Renzo[8], A. Mele[9], D. Pastore[4], G. Tarantini[6], P. Musto[10], A. Maggi[2], A. Carella[1]

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Background. Axicabtagene ciloleucel (Axi-cel) is approved in Italy as second-line treatment for patients with early-relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL). Real-world data are needed to confirm feasibility, effectiveness and safety outside clinical trials. We report outcomes from a consecutive cohort treated within the Rete Ematologica Pugliese (REP) CAR-T programme.

Methods. We retrospectively analysed 41 R/R DLBCL patients who underwent leukapheresis and were infused with second-line Axi-cel from December 2023 to November 2025. Data were available for 36 patients. Median follow-up from apheresis was 9.6 months (range 1.6-23.1). Responses were assessed by FDG-PET at predefined timepoints: PET1 (3 months), PET2 (6 months) and PET12 (1 year). PFS and OS were calculated from apheresis; toxicities were graded according to ASTCT criteria.

Results. Median age was 50.5 years (range 26-74). Bridging therapy was given to 29/36 patients, mainly polatuzumab-based regimens (52%), platinum/ARA-C combinations (38%) or radiotherapy (10%). Disease status after bridging was available in 17/36 patients and showed CR 6%, PR 18%, PD 18% and SD 58%. Median time from apheresis to infusion was 38 days (range 16-118). At PET1 (n=36), 17 patients (47.2%) achieved CR and 8 (22.2%) PR, with ORR 69.4%; 13.9% progressed. At PET2, 12 patients (33.3%) were in CR, 13.9% in PR and 25.0% in progression. At PET12 (n=16), 7 patients were in CR; 50% of PET1 CRs remained in CR at PET12 (5/10). CRS occurred in 61.1% (grade ≥3: 16.7%) and ICANS in 22.2% (grade ≥3: 8.4%). Late events included prolonged cytopenias (19.4%), hypogammaglobulinemia >3 months (11.1%) and infections (11.1%). Median PFS was 13.9 months, with 12-month PFS 68.6%; median OS was not reached and 12-month OS was 72.4%. There were 12 deaths (33%), primarily due to progression (66%) or treatment-related events (34%; 2 fatal sepsis, 1 sudden death, 1 macrophage activation syndrome). A total of 27.8% required post-CAR-T therapy, mainly bispecific antibodies or radiotherapy.

Conclusions. In this real-world cohort, second-line Axi-cel in R/R DLBCL demonstrated high early response rates, manageable toxicity and survival outcomes comparable to pivotal trials. Our experience supports Axi-cel effectiveness in routine practice and highlights the importance of integrated post-CAR-T therapeutic strategies, including bispecific antibodies, in the modern management of refractory DLBCL.

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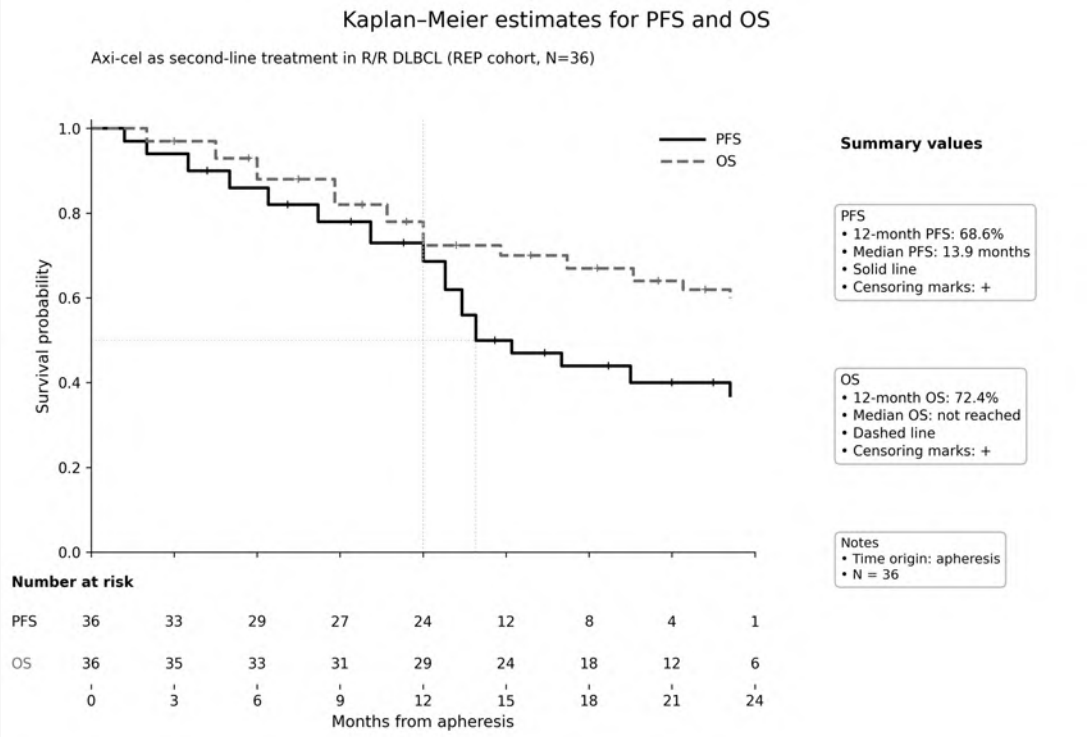
Kaplan–Meier estimates for PFS and OS
Axi-cel as second-line treatment in R/R DLBCL (REP cohort, N=36)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
PFS
OS
Summary values
PFS
• 12-month PFS: 68.6%
• Median PFS: 13.9 months
• Solid line
• Censoring marks: +
OS
• 12-month OS: 72.4%
• Median OS: not reached
• Dashed line
• Censoring marks: +
Notes
• Time origin: apheresis
• N = 36
Number at risk
PFS 36 33 29 27 24 12 8 4 1
OS 36 35 33 31 29 24 18 12 6
0 3 6 9 12 15 18 21 24
Months from apheresis

Non-Hodgkin's Lymphoma

PROGNOSTIC VALUE OF SEMI-QUANTITATIVE METABOLIC PARAMETERS ON [18F]FDG PET/CT IN PATIENTS WITH FOLLICULAR LYMPHOMA AT DIAGNOSIS

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Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin lymphoma (NHL) subtype. The early identification of high-risk patients at diagnosis is still identified as an unsolved problem. Recent studies showed that semiquantitative volume parameters on pre-treatment 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) could represent variables with prognostic significance. Among these PET-derived measures, baseline total metabolic tumor volume (TMTV) was reported as a promising tool in various NHL subtypes. However, only few real-life studies are available for FL with discordant findings.We aimed to determine the prognostic impact of these metabolic parameters in patients with FL receiving first-line therapy.We have retrospectively analyzed a cohort of 47 consecutive patients, treated between 2016 and 2022. Diagnosis was made according to WHO 2016 classification. PET/CT scan was performed according to the 2014 European Association of Nuclear Medicine and Molecular Imaging guidelines version 2.0. Semiquantitative metabolic parameters, assessed by LIFEx (www.lifexsoft.org), included TMTV, total lesion glycolysis (TLG), Dmax and DmaxVox. TMTV was calculated using the fixed threshold of SUV4.All cases received treatment regimens with curative intent, including R-CHOP/CHOP-like (3/47), bendamustine plus rituximab (24/47) or obinutuzumab (5/47), rituximab single-agent (6/47) or in association with radiation therapy (9/47).Out of 47 patients, CR was achieved in 42/47 (89.3%) and 4/47 achieved a PR with an ORR of 97.8%; 6/47 (12.7%) relapsed after achieving a CR/PR. For the entire cohort, median PFS was 60 months and 5-y OS was 67%.In univariate analysis, FLIIPI 2 score and TMTV (with best cut-off value assessed by ROC curve), were associated with reduced PFS (HR 4.0747, 95%CI 1.5191-10.9298, p=0.02 and HR 3.29, 95%CI 1.13-9.57, p=0.02, respectively) and OS (HR 2.4357, 95%CI 0.5801-10.2279, p=0.0001 and HR 3.1706, 95%CI 1.0627-9.4592, p=0.03 respectively).At last follow-up, 32/47 patients were alive, causes of death included progressive disease (2 cases), death while in CR (3 patients, aged >80 years), hepatic cirrhosis (2 cases), COVID-19 disease (7 cases) and secondary acute myeloid leukemia (1 case).In conclusion, the semi-quantitative metabolic parameters of PET/CT at diagnosis are proposed as innovative elements capable of interpreting the burden and dissemination of FL and predicting survival.

Non-Hodgkin's Lymphoma

LONGITUDINAL CHANGES IN TRYPTOPHAN METABOLISM AND CYTOKINE PROFILE IN LYMPHOMA PATIENTS TREATED WITH CAR-T: ASSOCIATION WITH ICANS

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Background. Tryptophan (TRP) metabolism through the indoleamine 2,3-dioxygenase 1 (IDO1)–kynurenine (KYN) pathway plays a key role in immune regulation and systemic inflammation. Chimeric antigen receptor T-cell (CAR-T) therapy induces intense immune activation and cytokine release, potentially affecting TRP catabolism. However, real-world longitudinal data on TRP metabolism in lymphoma patients receiving CAR-T remain limited. This study aims to characterize temporal changes in TRP metabolism and cytokine profiles after CAR-T infusion and to explore their association with immune-mediated toxicities.

Methods. This multicenter exploratory study analyzes longitudinal plasma samples from lymphoma patients undergoing CAR-T therapy. Samples were collected at predefined time points (day 0, +1, +3, +7, +10, +14). Plasma TRP and KYN concentrations were measured by high-performance liquid chromatography, while 45 cytokines and chemokines were quantified using multiplex ELISA assays. Statistical analyses were descriptive and longitudinal, focusing on temporal patterns and interindividual variability. Preliminary data were obtained from 20 patients with diffuse large B-cell lymphoma treated with CAR-T.

Results. Preliminary findings showed a progressive decrease in plasma TRP levels after CAR-T infusion, with lowest values at day +7. In parallel, plasma KYN concentrations increased, leading to a marked rise in the KYN/TRP ratio at day +7, followed by a return toward baseline by day +14. Plasma interferon-gamma and interleukin-6 increased, peaking at day +7. A significant increase in interleukin-10 was also observed, together with a decrease in chemokines CCL2, CCL3, CCL4 and CCL5. A trend toward correlation between increased KYN production, TRP depletion and development of immune effector cell-associated neurotoxicity syndrome (ICANS) was observed, suggesting activation of the IDO1-mediated TRP pathway during early immune responses.

Conclusions. Longitudinal monitoring of TRP metabolism and cytokine profiles reveals dynamic immunometabolic changes following CAR-T therapy. The KYN/TRP ratio may represent a promising early biomarker of immune activation and neurotoxicity risk. Ongoing analyses in a larger cohort may define immunometabolic signatures associated with clinical outcomes and treatment-related toxicities.

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Non-Hodgkin's Lymphoma

REAL WORLD EFFECTIVENESS AND SAFETY OF ZANUBRUTINIB IN RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA PATIENTS: A LOCAL MULTI-CENTER REAL LIFE EXPERIENCE (ABRUZZO)

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Introduction. standard treatment of relapsed/refractory (R/R) marginal zone (MZL) lymphoma is not yet established. Zanubrutinib is approved according to the results of MAGNOLIA trial, which demostrated high overall response rate (ORR) and safe toxicity profile. Real world evidence is limited to studies including 78 and 118 MZL patients (pts), confirming the remarkably response and safety. Also an italian study showed efficacy in pts treated under the named pts program.AIM: the purpose is to evaluate the efficacy and the tolerability of zanubrutinib in R/R MZL in a real life setting.

Methods. This retrospective study included R/R MZL pts receiving zanubrutinib and previously treated with anti CD20 regimen. All subtypes were included: splenic (SMZL), nodal (NMZL), and extranodal (EMZL). Baseline characteristics, prior lines of treatment, response rates, survival, adverse events (AEs) were analyzed. A total of 25 patients were included. Median age at zanubrutinib start was 75 years (range 46-91) with 36% of patients ≥80 years. According to MZL subtypes: 48% were SMZL, 36% NMZL, 16% were EMZL. Compared to MAGNOLIA trial where the median number of previous therapy was 2, in our study 72% of patients had only one previous treatment. Five pts were refractory to the prior therapy and 41% POD24. Stage IV and Ie were respectively 84% and 16%, 50% presented ECOG 2. MYD88 L265P status was available in 6 pts, mutated in one case. Comorbities were frequent: 72% presented with ≥2 comorbities and 64% had at least one cardiovascular risk factors. Only 12% of pts started with reduced dose (80mg BID), due to comorbities or older age.

Results. With a median follow up of 22 months overall response rate (ORR) was 88%, with 20% of complete response (CR). At 15 months estimated PFS was 92% (95% CI 81.4-100) with median PFS and OS not reached (NR). At last update 84% remained on treatment, with median duration of 12 months. No difference according to MZL subtype, POD24 status or the number of previous treatment were noticed.Adverse events (AE) were reported in 50% of pts, all of grade 1-2. Most common AE were: bleeding (=6), AST/ALT increasing (=2), infections (=2), diarrhea (=1). Only one pts discontinued therapy, due to diarrhea g2, and dose reduction occurred in only 8% of pts related to adverse events.

Conclusions. this real world of zanubrutinib in R/R MZL confirm favourable efficacy and tolerability, supporting the use in second line, even in elderly pts.

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Table. PATIENT'S CHARACTERISTICS

	MZL pts (25)
Median age, range	75 (46-91)
≥80 years	36%
Male	56%
ECOG	
0-1	50%
2	50%
POD24	41%
REFRACTORY disease	20%
MZL subtypes	
Splenic	48%
Nodal	36%
extranodal	16%
Prior lines of systemic therapies	
1	72%
2	17%
3	11%
Previous therapy	
RITUXIMAB	40%
RITUXIMAB+/- RADIOTHERAPY	8%
RITUXIMAB-BENDAMUSTINE	40%
R-CHOP	8%
R-CHLORAMBUCILE	4%

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Non-Hodgkin's Lymphoma

IDENTIFICATION OF THE BLASTOID VARIANT OF MANTLE CELL LYMPHOMA BY FLOW CYTOMETRY PARAMETERS OF LYMPH NODE BIOPSIES: A PILOT STUDY

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Introduction. The blastoid variant represents an aggressive subset of mantle cell lymphoma (MCL) still lacking an established standard of care. Recent incorporation of targeted small molecules into first-line therapy may improve outcome. We evaluated whether flow cytometry analysis on lymph node biopsies can contribute to the rapid identification of the blastoid variant of MCL.

Methods. Cell suspensions were generated from lymph node biopsies of 31 consecutive pts with MCL diagnosed at our center between October 2021 and March 2026. A pathological B cell population suggestive for MCL was identified by gating on CD19+/CD5+/light-chain-restricted events. We analyzed forward scatter (FSC) and side scatter (SSC) of the pathological B cell population and normalized these parameters to those of CD3+ reactive T cells in the samples, generating FSC ratio and SSC ratio. The morphological/immunohistochemical analysis on the same biopsy confirmed the diagnosis of MCL in all cases and identified the blastoid variant according to WHO criteria.

Results. The cohort of 31 MCL cases included 9 blastoid variants. As expected, the median percentage of Ki-67+ cells was higher in the 9 blastoid cases (80%, 30–95% vs 35%, 5–90%; p<0.01).A median of 25,038 (2,897–612,746) leukocyte events per sample was acquired.The median FSC ratio was 1.00 (0.80–1.61) and the median SSC ratio was 1.34 (0.69–2.70).Using a ROC analysis, the FSC ratio showed an excellent power to identify the blastoid MCL variant (AUC 1.00; p<0.001), with a cut-off at 1.26 yielding 100% sensitivity and 100% specificity. The SSC ratio also demonstrated a high capacity to identify the blastoid variant (AUC 0.88; p<0.001), with a cut-off >1.46 providing 88.9% sensitivity and 86.4% specificity.In addition, both the SSC ratio and FSC ratio correlated with Ki-67 staining results (Spearman r=0.73, 95% CI 0.49–0.87; p<0.0001, and r=0.55, 95% CI 0.22–0.77; p=0.002, respectively). In particular, Ki-67 ≥50% was associated with a higher FSC ratio (1.29 vs 0.98; p=0.002) and SSC ratio (1.51 vs 1.14; p<0.001).

Conclusions. The short turn-around time of flow cytometry analysis allowed the rapid identification of blastoid variant of MCL using normalized FSC and SSC ratios between the pathological B cell population characterized by CD19+/CD5+/light-chain-restriction and normal T cells. . Validation on larger cohorts and comparison of these parameters to sample obtained frombone marrow or peripheral blood samples are needed.

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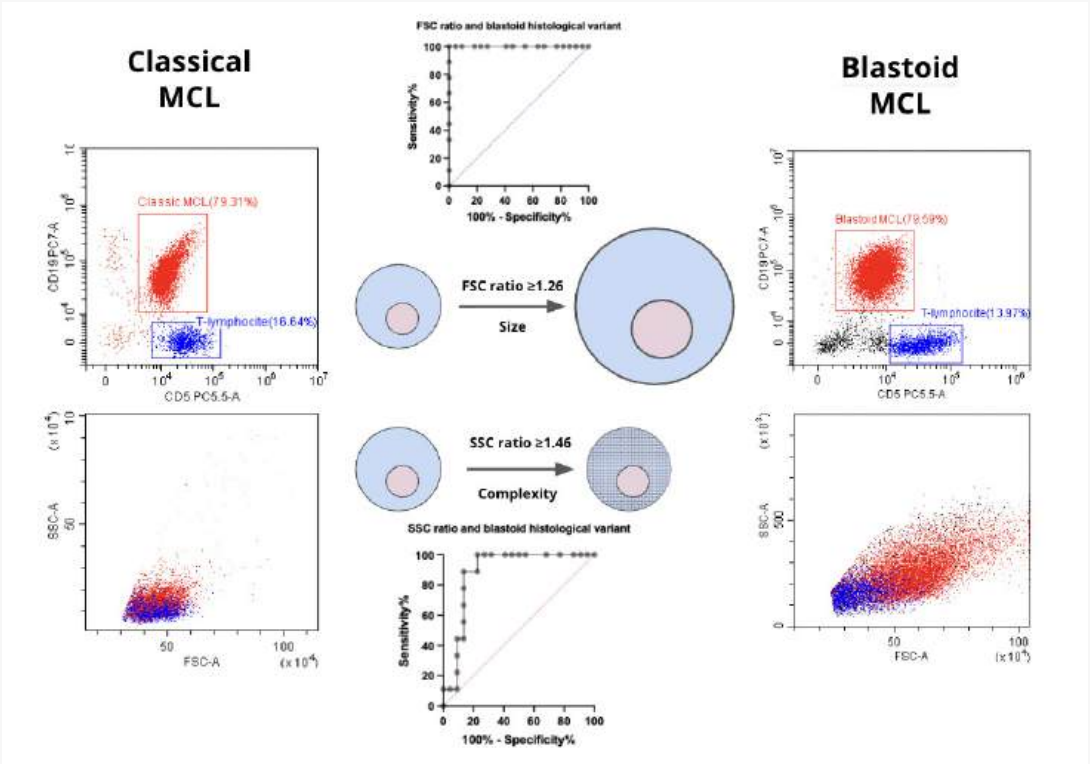
Non-Hodgkin's Lymphoma



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Non-Hodgkin's Lymphoma

PEGYLATED INTERFERON-A-2A IN MYCOSIS FUNGOIDES/SÉZARY SYNDROME: A SINGLE-CENTRE RETROSPECTIVE EXPERIENCE IN 17 PATIENTS

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IFN-α is a guideline-endorsed cornerstone of MF/SS therapy, acting through Th1 polarization, cytotoxic T-/NK-cell activation, and direct antiproliferative effects. Pegylated IFN-α-2a (peg-IFN) offers sustained plasma exposure and once-weekly dosing, with real-world ORRs of 53–55%. We retrospectively analysed 17 consecutive MF/SS patients treated at our centre with subcutaneous peg-IFN. Disease staging followed the TNMB classification, responses were assessed according to ISCL/EORTC/USCLC consensus criteria, and adverse events (AEs) were graded per CTCAE v5.0. The cohort comprised 9 men (53%), with MF in 16 patients (94%) and SS in 1 (6%); median age at diagnosis was 53 years (range 27–70). Disease stages were distributed as follows: IB in 6 patients (35%), IIB in 7 (41%), III in 3 (18%), and IVA in 1 (6%). The population was heavily pretreated, with a median of 6 prior lines of therapy (range 1–12), including brentuximab vedotin and radiotherapy in 10 patients each (59%). Peg-IFN was administered as relapsed/refractory (R/R) therapy in 9 patients (52%), as post-chemotherapy maintenance in 4 (24%), and as post-allogeneic transplant maintenance in 4 (24%); it was used as monotherapy (8 patients, 47%) or in combination regimens (9 patients, 53%). The starting dose was 90 µg/week in all patients, with a median treatment duration of 16 weeks (range 0–145); dose reductions were required in 3 patients (18%) and treatment interruptions in 3 (18%). Best responses were complete response in 5 patients (29%), partial response in 5 (29%), progressive disease in 3 (18%), and not evaluable in 4 (24%), yielding an ORR of 58%. Median time to response was 6 weeks (range 3–95). All 17 patients were alive at last follow-up (median 3.9 months, range 0–33.4). AEs were exclusively grade 1–2 and included neutropenia in 4 patients (24%), hepatic toxicity in 3 (18%), and flu-like syndrome, fatigue, and lymphopenia in 2 patients each (12%); AE-driven dose reduction was required in 3 patients (18%) and permanent discontinuation in 1 (6%), with 1 serious AE (SAE) reported overall (6%). In this heavily pretreated, predominantly R/R MF/SS cohort, weekly peg-IFN achieved an ORR of 58% with a favourable, exclusively grade ≤2 safety profile, supporting its role as a viable, well-tolerated therapeutic option in CTCL. Limitations include the retrospective single-centre design, small sample, heterogeneous combination regimens, and short follow-up.

Non-Hodgkin's Lymphoma

OUTCOMES OF EPCORITAMAB IN HEAVILY PRETREATED AND CAR-T–EXPOSED PATIENTS WITH AGGRESSIVE B-CELL LYMPHOMAS: A MULTICENTER ITALIAN REAL-WORLD STUDY

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Background. Patients with relapsed or refractory aggressive B-cell lymphomas who progress after multiple lines of therapy, including CAR-T cell treatment, represent a population with limited therapeutic options and poor prognosis. Epcoritamab, a subcutaneous CD3xCD20 bispecific antibody, has demonstrated efficacy in clinical trials, but real-world data in heavily pretreated patients remain limited.

Methods. We retrospectively analyzed adult patients with aggressive B-cell lymphomas treated with epcoritamab at three Italian hematology centers between July 2023 and July 2025. Baseline clinical characteristics, prior therapies, and outcomes were collected. Treatment response was assessed by PET/CT according to Lugano criteria. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Safety data were obtained from electronic medical records.

Results. Nineteen patients were included in the analysis. The median age was 58 years, and most patients presented with advanced disease and extranodal involvement. The median number of prior lines of therapy was 3, with more than half of patients receiving three or more previous treatments. Seven patients (37%) had been treated with prior CAR-T cell therapy. Epcoritamab achieved an overall response rate of 42%, including complete responses in 26% of patients. After a median follow-up of 9.2 months, median PFS was 10.0 months and median OS was 20.4 months. Treatment was generally well tolerated. Cytokine release syndrome occurred in 47% of patients and immune effector cell-associated neurotoxicity syndrome in 26%, all events being grade 1–2. No unexpected toxicities were observed.

Conclusions. In this real-world multicenter italian cohort of heavily pretreated and CAR-T–exposed patients with aggressive B-cell lymphomas, epcoritamab demonstrated meaningful clinical activity with durable survival outcomes and a manageable safety profile. These findings support the use of epcoritamab as a valuable therapeutic option in late-line settings where effective alternatives are limited.

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Non-Hodgkin's Lymphoma

PERIPHERAL T CELL REMODELING DURING EPCORITAMAB TREATMENT IN AGGRESSIVE B CELL LYMPHOMAS

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Epcoritamab is a CD3×CD20 bispecific antibody that induces tumor cell killing through T cell recruitment and activation. The peripheral T cell compartment represents a readily accessible biomarker to explore early immune dynamics associated with treatment and may provide relevant information in real world clinical practice.Methods:We conducted a retrospective multicenter real world study including 19 consecutive patients with aggressive B cell lymphomas treated with epcoritamab according to standard step up dosing. Median age was 58 years; 84% had Ann Arbor stage IV disease, 95% extranodal involvement, and patients were heavily pretreated (median 3 prior lines), including CAR T therapy in 37%. Peripheral blood immunophenotyping by flow cytometry was performed at baseline and during early treatment, evaluating CD3+ T cells, CD4+, CD8+ subsets and CD4/CD8 ratio. When available, CD19+ B cells, NK cells (CD3−CD56+) and activated T cells (CD3+CD56+) were also assessed. Treatment response was evaluated by PET/CT according to routine clinical practice.Results:At baseline, patients showed a preserved peripheral CD3+ T cell compartment. During the initial phases of epcoritamab therapy, a consistent immunophenotypic remodeling was observed in a subset of patients, characterized by an increase in CD8+ T cells and a reduction of the CD4/CD8 ratio, suggesting an early cytotoxic polarization. Additional analyses documented profound depletion of peripheral CD19+ B cells, frequent reduction of NK cells, and emergence of activated CD3+CD56+ T cells, supporting early immune activation. At final PET assessment, the overall response rate was 42%, with complete response in 26% of patients.Conclusions:In a real world multicenter cohort, epcoritamab treatment is associated with early and clinically relevant peripheral T cell remodeling, marked by CD8+ predominance and evidence of immune activation. Standard peripheral immunophenotyping represents a simple, reproducible tool to monitor immune dynamics in patients receiving T cell engaging bispecific antibodies.

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Non-Hodgkin's Lymphoma

BRIDGING THERAPY BEFORE CHIMERIC ANTIGEN RECEPTOR T-CELL IN B-CELL NON-HODGKIN LYMPHOMAS: IMPACT ON EARLY TOXICITY AND OVERALL RESPONSE RATE

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Bridging therapy is commonly administered to reduce disease burden before CAR-T therapy.We retrospectively analyzed 60 patients with B-cell non-Hodgkin lymphomas treated with CAR-T between 2024 and 2025 at Hematology and Transplant Unit, "La Maddalena", Palermo, Italy. Histologies included Diffuse large B-cell lymphoma (n=40), Follicular Lymphoma (n=16), Primary mediastinal B-cell lymphoma (n=3) and High-Grade B-Cell Lymphoma (n=1). Patients were classified as no bridging therapy (n=19), radiotherapy (n=5), radiotherapy+chemotherapy (n=1), polatuzumab-based regimens (n=22) or other systemic bridging therapies (n=13). Bridging response was categorized as responder (CR/PR) or non-responder (SD/PD). Comparisons with CRS and ICANS, grade ≥3 neutropenia, thrombocytopenia ≥3 and ORR at day+90 were performed using Fisher's test.Bridging therapy was administered to 41/60 patients (68.3%) and 16/41 (39%) achieved CR/PR; bridge response rates did not differ significantly across radiotherapy, radiotherapy + chemotherapy, polatuzumab-based and other systemic groups (40%, 0%, 40.9% and 38.5%, respectively; p=1.000). Among 35 bridged patients evaluable for both bridge response and day+90 ORR, bridge responders showed no significant advantage over non-responders in day+90 ORR (85.7% vs 81.0%; p=1.000). ORR (day+90) was 77.8% with no bridge, 100% with radiotherapy, 0% with radiotherapy plus chemotherapy, 88.9% with polatuzumab-based bridging and 72.7% with other systemic therapy (p=0.26). There were no significant variations between the five groups for adverse events, including any-grade ICANS (p=0.746), grade ≥3 neutropenia (p=0.301), or thrombocytopenia (p=0.177). The only endpoint that showed a significant correlation with the bridging strategy was the incidence of any-grade CRS (p=0.008), which occurred in 88.9%, 100%, 100%, 100%, and 58.3% of patients across the respective group (no bridge, radiotherapy, radiotherapy+chemotherapy, polatuzumab-based bridging and other systemic therapy).In this real-life cohort, neither the choice of bridging strategy nor the achievement of a clinical response to such therapy proved to be a predictor of reduced CAR-T-related toxicities or superior ORR at day +90. It is important to note that these data suggest that clinical response to bridging therapy is not a valid surrogate marker for post-infusion outcomes; therefore, a lack of response should not prevent eligible patients from receiving CAR-T cell therapy.

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Non-Hodgkin's Lymphoma

FLOW CYTOMETRY IMMUNOPHENOTYPING ON TISSUE BIOPSIES IN NON-HODGKIN'S LYMPHOMA DIAGNOSIS: A SINGLE CENTER EXPERIENCE

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Introduction. Flow Cytometry (FC) immunophenotyping on tissue biopsies can provide complementary data to immunohistochemistry (IHC), that is considered the gold standard for the diagnosis of lymphoma.

Materials and Methods. Between January 2021 and May 2024, a total of 208 tissue biopsies (181 lymph nodes and 27 extranodal lesions) clinically suggestive of lymphoma were processed in our FC laboratory and compared with histologic findings. The cellularity and viability with 7-Aminoactinomycin D (7-AAD) were assessed for each sample. First, we performed a lymphoid screening panel (CD3, CD4, CD8, CD5, CD56, CD19, CD20, lambda, kappa, CD45) to detect the presence of pathological population. If evidence of B cells monoclonality or B/T aberrant immunophenotype was detected, an additional panel followed to narrow the different diagnosis according to B/T cell lineage. Data acquisition was performed on FACSCanto II (BD Biosciences) using FACSDiva software.

Results. One hundred fifty-one cases of lymphoma were evidenced by IHC (73%):123(59%) were B cell Non-Hodgkin's Lymphoma (B-NHL), 8 (4%) were T cell Non-Hodgkin's Lymphoma (T-NHL) and 20 cases (10%) were Hodgkin's Lymphoma (HL). In 57 cases (27%), IHC was negative for B/T-NHL and HL. FC analysis resulted positive for NHL in 120 cases (58%):114 (55%) were B-NHL and 6 cases (3%) T-NHL. In 84 cases (40%), FC analysis was negative for NHL and inconclusive in 4 cases (2%) Table1. Considered the NHL diagnosis, the FC sensitivity was 94% and the FC specificity was greater than 97%. The concordance between FC and IHC for lymphoma diagnosis was 86.3%. The concordance increased to 95.7% excluding cases of HL, for which FC analysis cannot be clearly diagnostic due to problems about Reed-Sternberg cells identification.

Conclusions. In agreement with the literature, our study confirms that FC routinely performed on tissue samples suspected of lymphoma results applicable for the diagnosis and classification of B/T-NHL. FC analyses shows good sensitivity and high specificity, as well as high concordance with IHC. FC is able to provide results on very small samples and on viable cells, within few hours, allowing information for haematologist especially in clinically critical patients for which early treatment needed.Our data suggests that an integrated approach between immunohistochemistry and flow cytometry is possible and useful in patients with Non-Hodgkin's Lymphoma.

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Table 1: Comparison between immunohistochemistry and flow cytometry of all 208 samples evaluated in the study

	IHC		FC		
	+	-	+	-	**inconclusive**
B-NHL	123	0	114	6	3
T-NHL	8	0	6	2	0
HL	20	0	0	20	0
Negative	0	57	0	56	1
Total	151	57	120	84	4
	208		208		

Legend: IHC, immunohistochemistry; FC, flow cytometry; +, positive; -, negative

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Non-Hodgkin's Lymphoma

FOLLICULAR LYMPHOMA IN THE IMMUNOTHERAPY ERA: ANALYSIS OF A LARGE SINGLE-CENTER COHORT (2010–2023)

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Follicular lymphoma (FL) represents the second most common histological subtype among non-Hodgkin lymphomas, accounting for approximately one-fifth of all diagnoses. Despite the availability of effective therapeutic options, complete disease eradication remains a clinical challenge.We conducted a retrospective, single-center analysis on 327 FL patients (pts; excluding grade 3B histology, WHO 2016 classification) diagnosed between January 1, 2010, and December 31, 2023, and followed at the Hematology Unit of the A.O.U. "Città della Salute e della Scienza di Torino".Median age at diagnosis was 62 years (range 52–71). B symptoms were present in 12% of pts, 64% had advanced-stage III–IV disease, 36% bulky disease, and 16% extranodal involvement. Prognostic indices (FLIPI and FLIPI2) were available for 149 pts: 32% and 17% low-risk, 30% and 63% intermediate-risk, 38% and 20% high-risk according to FLIPI e FLIPI2, respectively.Among the 327 pts, 70 (21%) were managed with a watch-and-wait (WW) strategy; of these, 35 (50%) were still in WW at the data cut-off (March 31, 2026). Out of 292 pts (89%) who required treatment, 66% received one line of therapy, 18% two lines, and 16% three or more lines.With a median follow-up (mFU) of 8.2 years, the 5-year progression-free survival (5y-PFS) and 5-year overall survival (5y-OS) for the entire cohort were 68% and 88%, respectively. Stratified by treatment approach according to GELF criteria and ESMO guidelines, 5y-PFS and 5y-OS were 80% and 91% for WW, 71% and 95% for radiotherapy alone, and 63% and 84% for curative-intent chemoimmunotherapy.Among the 191 pts treated with systemic chemoimmunotherapy at diagnosis, the overall response rate (ORR) was 97%, with a complete remission (CR) rate of 89%. Although a trend toward higher ORR was observed for R-CHOP compared with R-bendamustine (99% vs. 90%; RR 1.1, 95% CI 1.00–1.21), statistical significance was not seen (p = 0.051). Of these, 160/191 initiated maintenance with monoclonal antibody, and 97 (61%) completed it.Disease progression or histological transformation within 24 months from first-line therapy occurred in 15% of pts.The incidence of second malignancies at 10 years was 9.2%. Specific causes of mortality at 10 years were: 8.0% due to disease, 3.8% due to treatment-related toxicity, 4.3% due to second malignancies; 5.3% and 5.1% due to unrelated and unknown causes, respectively.Further analyses (TTNT, toxicity, COVID impact, POD24, etc.) are ongoing.

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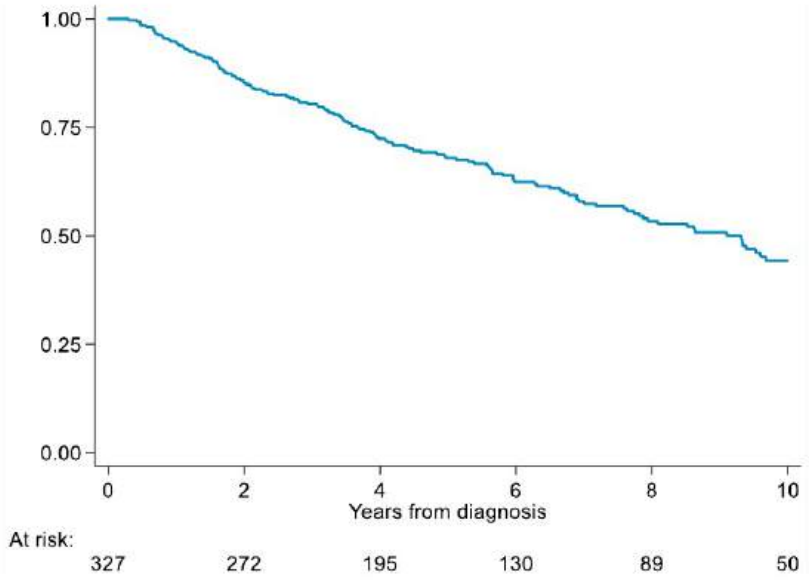
Figure 1: PFS from diagnosis for the whole cohort (mFU: 8.21 years; IQR 4.77–11.21).



Time	Survivor Function	Std. Error	[95% Conf.	Int.]
3	0.8042	0.0222	0.7564	0.8436
5	0.6795	0.0272	0.6228	0.7295
10	0.4432	0.0361	0.3716	0.5123

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Non-Hodgkin's Lymphoma

MITIGATION STRATEGIES TO REDUCE CAR-T-CELL–RELATED TOXICITIES IN PATIENTS WITH B-CELL LYMPHOPROLIFERATIVE NEOPLASMS TREATED WITH AXI-CEL OR BREXU-CEL: A SINGLE-CENTER OBSERVATIONAL STUDY

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Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are potentially life-threatening complications of CD19-directed CAR T-cell therapy, occurring more frequently in patients with high disease burden or suboptimal responses to bridging therapy. Prophylactic corticosteroids before infusion have been proposed to mitigate these events, based on ZUMA-1 (cohort 6), with limited real-world validation. Early use of anti–interleukin-1 receptor (IL1R) antagonists to treat grade (G)1 ICANS has also been associated with improved outcomes.From August 2023 to December 2025, 21 consecutive adults received prophylactic steroids on days 0 to +2 of CD19-directed CAR T-cell therapy (axi-cel or brexu-cel) in the presence of incomplete bridging response or bulky disease. An IL1R antagonist was administered in case of G≥1 ICANS per institutional policy. Data were collected prospectively and analyzed retrospectively.According to approved indications, 21 patients (median age 51 years, range 24–70) received lymphodepletion with fludarabine and cyclophosphamide followed by autologous CD19-directed CAR T-cell infusion. 12 patients (57.1%) presented with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL), 2 (9.5%) with r/r primary mediastinal large B-cell lymphoma (PMBCL), 3 (14.3%) with r/r follicular lymphoma (FL), 3 (14.3%) with r/r mantle cell lymphoma (MCL), and 1 (4.8%) with r/r B-cell acute lymphoblastic leukemia (B-ALL). 17 (81%) received axi-cel and 4 (19%) brexu-cel; 15 (71.4%) received CAR-T as ≥3rd line. All patients underwent bridging therapy.All patients received dexamethasone 10 mg daily on days 0, +1, and +2. CRS occurred in 20 patients (95.2%) after a median of 4 days (range 1–6), all G≤2. Tocilizumab was required in 19 patients (90%); 13 patients (61.9%) also required dexamethasone for refractory symptoms. ICANS G1 occurred in 2 patients (9.5%) and only one required dexamethasone plus anakinra administration. All patients were discharged without recurrence and none required intensive care unit admission. At a median follow-up of 12.3 months, complete remission was documented in 13 patients (61.9%).Prophylactic dexamethasone and early IL1R antagonist use may attenuate severe CRS and ICANS manifestations following CAR T-cell infusion without compromising clinical benefit. Additional studies are needed to further validate these findings.

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Non-Hodgkin's Lymphoma

AUTOLOGOUS STEM CELL BOOST FOR PROLONGED CYTOPENIA AFTER CAR-T CELL TREATMENT: A SINGLE INSTITUTION EXPERIENCE

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Prolonged cytopenia is a complication of CAR-T potentially exposing to severe infections or death after successful anti-tumor treatment. The etiology is unknown: bone marrow failure, therapy-related myelodysplasia (t-MDS), immunological pathways alterations have been suggested. Autologous stem cells (ASC) rescue is advised in EBMT recommendations. We present three cases treated at our center (details in Table).Patient 1: 67-year-old man with DLBCL who received CAR-T in 4th line. He experienced prolonged grade 3 cytopenia with transient response to G-CSF and seldom transfusion needs. After 7 months the cytopenia worsened with weekly transfusion needs, prompting diagnosis of t-MDS and treatment with 5-AZA, complicated by fungal pneumonia refractory to antimicrobials. He was infused with ASC in t-MDS remission, quickly obtaining normal blood counts, transfusion independence and pneumonia recovery, allowing allogeneic transplantation for his t-MDS.Patient 2: 51-year-old woman with DLBCL who received CAR-T in 3rd line. She previously suffered lasting cytopenia after bridging therapy, yet fully recovered. She then developed grade 4 cytopenia after CAR-T, with weekly transfusion needs. At +44 a severely hypoplastic marrow environment with normal molecular genetics was documented. She suffered several infections with life-threatening sepsis. She received an ASC boost at +76, achieving normal blood counts and is infection-free after 16 months.Patient 3: 61-year-old woman with DLBCL. She had a complex journey due to 2 long COVID that delayed treatment. She received a first out-of-specification CAR-T product, with no response, and developed persistent grade 3 neutropenia and grade 2 anemia and thrombocytopenia. The bone marrow analysis showed dysplastic notes with normal genetics. She attained a partial blood count recovery after 9 months, and was given a second CAR-T during a 4 months COVID infection. She obtained remission, but suffered grade 4 cytopenia and recurrent superinfections. The bone marrow was hypoplastic with dysmegakaryopoiesis. She received an ASC boost at +101, securing a partial blood counts recovery and transfusion independence. **Conclusions.** ASC boost for prolonged cytopenia after CAR-T, although not always leading to complete hematological recovery, is a safe strategy to improve the survival and the quality of life of patients, lowering the risk of severe infections, allowing transfusion independence and access to further treatment.

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Table 1: Patients and cytopenia characteristics

	Diagnosis	CAR-T	Acute complications	Response at +30	Long term cytopenia*	Bone marrow analysis	Cytopenia complications	ASC infusion	Outcome
Patient 1	DLBCL (transformed from FL)	Tisacel	CRS G1	CR	G3 neutropenia +7 months: onset of trilinear G4 pancytopenia	+218 MDS NGS: DNMT3A and TET2 mutations	Fungal pneumonia	+310 4.56x10^6 CD34+ cells/kg	Partial blood count recovery with grade 2 thrombocytopenia, transfusion independence and recovery from fungal pneumonia
Patient 2	DLBCL, NOS	Axicel	CRS G1 (dexamethasone required)	CR	G4 trilinear cytopenia	+44 Severe hypoplasia KT wild type NGS wild type	Recurrent infections including *Influenza A, K. pneumoniae* sepsis and CMV reactivation	+76 2,4x10^6 CD34+ cells/kg	Complete blood count recovery
Patient 3	DLBCL, NOS	1: Tisacel (OOS) 2: Axicel	1. CRS G1 2. CRS G1	1. PD 2. CR	G4 trilinear cytopenia	+148 (from Tisacel) Dysplastic notes KT wild type NGS wild type +46 (from Axicel) Dysplastic notes KT wild type NGS wild type +67 (from Axicel) Dysmegakariop. 1% blasts +99 (from Axicel) Dysmegakariop. KT wild type NGS wild type	Recurrent infections including long SARS -CoV-2 and *Bacteroides* colitis	+101 3.5x10^6 CD34+ cells/kg	Partial blood count recovery, with G2 trilinear cytopenia, transfusion independence.

Abbreviations: Axicel: axicabtagene ciloleucel; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B cell lymphoma; dysmegakariop.: dysmegakaryopoiesis; FL: Follicular lymphoma, G1: grade 1; G2: grade 2; G3: grade 3; G4: grade 4; KT: karyotype; MDS: myelodysplastic syndrome; NGS: next generation sequencing; NOS: not otherwise specified; OOS: out of specification; PD: progressive disease; Tisacel: tisagenlecleucel.
*Considered persisting beyond 30 days after CAR-T infusion

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Non-Hodgkin's Lymphoma

DEVELOPMENT OF AN ARTIFICIAL INTELLIGENCE–BASED SYSTEM FOR EARLY PREDICTION OF CYTOKINE RELEASE SYNDROME IN LYMPHOMA PATIENTS TREATED WITH BISPECIFIC ANTIBODIES

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CD3-engaging bispecific antibodies (BsAbs) have significantly improved outcomes in relapsed or refractory B-cell lymphomas. However, their clinical implementation is challenged by early immune-related toxicities, particularly cytokine release syndrome (CRS), which mainly occurs during the first treatment cycles and requires prompt recognition and standardized management. Reliable early predictors of CRS severity are currently lacking.To develop and describe a clinically applicable artificial intelligence (AI)–based framework for early prediction of clinically relevant CRS (grade ≥2) in patients with lymphoma treated with bispecific antibodies, integrating clinical, laboratory, and treatment-related variables within routine hospital workflows.A knowledge-driven dataset was constructed using structured real-world variables routinely available in clinical practice, including patient characteristics, disease burden indicators, laboratory parameters, treatment scheduling (step-up dosing), and premedication strategies. An interpretable machine learning model based on penalized logistic regression was implemented to estimate the individual risk of CRS ≥2 within the first treatment cycles. The model was developed within an integrated digital architecture connected to electronic health records, hospital pharmacy systems, and pharmacovigilance workflows, enabling traceability, explainability, and regulatory compliance. Unlike previous simulation-based approaches, this framework focuses on real-world clinical integration and operational implementationThe proposed framework demonstrated the feasibility of dynamic CRS risk stratification using routinely collected clinical data. The integration of AI-driven risk estimation with predefined operational thresholds allowed the identification of patients requiring intensified monitoring, proactive supportive measures, or tailored organizational pathways. The system is designed to complement clinical judgment, facilitating early interventions and standardized management during high-risk treatment phases.This AI-enabled framework represents a scalable and clinically oriented approach to support early CRS risk assessment in lymphoma patients receiving bispecific antibodies. By embedding predictive models into routine clinical and organizational processes, the proposed system may improve patient safety, optimize resource utilization, and enhance the governance of innovative immunotherapies. Prospective real-world validation is ongoing.

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Non-Hodgkin's Lymphoma

EFFICACY AND SAFETY OF LONCASTUXIMAB TESIRINE IN PATIENTS WITH RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: A REAL-LIFE EXPERIENCE

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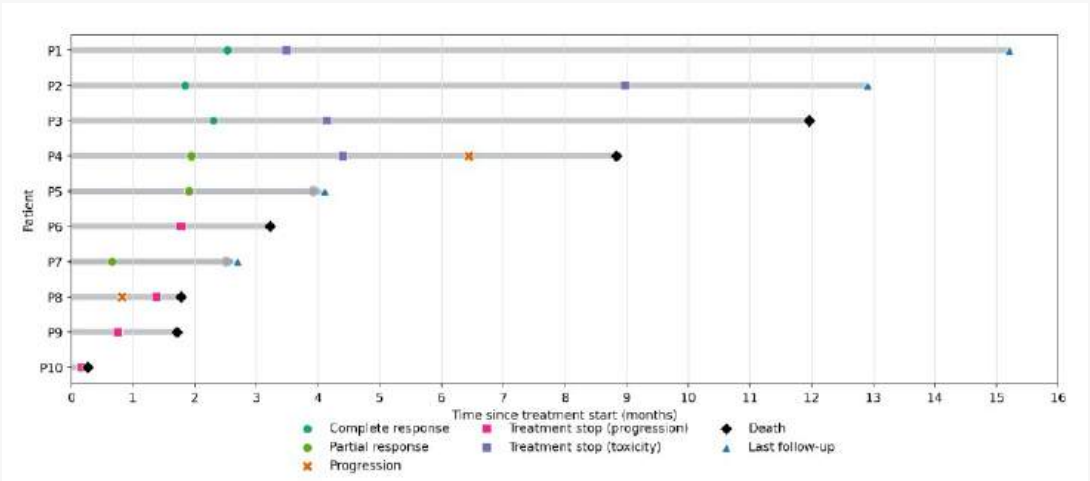
Background. Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have a poor prognosis. Loncastuximab tesirine (lonca), an anti-CD19 antibody–drug conjugate, in the phase II LOTIS-2 trial showed promising efficacy in patients with R/R DLBCL after ≥2 prior lines of therapy. We report real-world data on its use.

Results. We retrospectively analyzed 10 patients treated at three hematology centers in Campania from December 2023 to March 2026. Nine had de novo DLBCL and one transformed lymphoma. Five patients had non–germinal center B-cell subtype, and six were double-expressor. At baseline, seven patients had Ann Arbor stage III–IV and five had an International Prognostic Index >3; seven were refractory or relapsed within 12 months of first-line therapy. Median age at lonca initiation was 74 years (range, 54–88), six were male. Lonca was given as third-, fourth-, and fifth-line therapy in 3, 6 and 1 patients, respectively (median prior lines: 4). One patient had received prior CAR T-cell therapy and four had prior bispecific antibodies; six were refractory to the last treatment.The overall response rate was 60% (6/10), including three complete (CR, 30%) and three partial responses (PR, 30%). Median progression-free and overall survival was 6.44 and 8.84 months, respectively.Infections occurred in three patients (two causind delay). GGT elevation was observed in three (all grade <2, rapidly resolving). Edema/effusions were reported in four patients (one requiring pleural drainage). Cutaneous toxicity occurred in four patients. Hematologic toxicity (anemia, neutropenia, thrombocytopenia) was the most common adverse event (7/10) and represented the main cause of dose delay. Four patients discontinued lonca due to toxicity.At data cutoff, four patients were alive: two on treatment and two in CR at 12 and 4 months after lonca discontinuation due to toxicity (pancytopenia and effusions in one case; effusions and cutaneous toxicity in the other). Of the deaths, five were due to progression and one occurred in CR.

Conclusions. Despite the small sample size, our real-world experience supports the efficacy of lonca observed in LOTIS-2. Careful monitoring of treatment-related toxicities is warranted, as these may lead to discontinuation, particularly after multiple cycles (median 7 in our cohort). Notably, durable remissions were observed even after treatment discontinuation in a subset of patients.



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Non-Hodgkin's Lymphoma

BISPECIFIC ANTIBODIES AS A BRIDGE TO ALLOGENEIC HSC TRANSPLANTATION FOLLOWING CAR-T FAILURE: A SINGLE-CENTER REAL-WORLD EXPERIENCE IN DLBCL AND FL

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Background. Relapsed/refractory DLBCL and FL remain a major therapeutic challenge despite CAR-T therapy, which achieves high response rates and durable remissions in a subset of patients. However, 30–60% ultimately progress, representing a population with poor prognosis and limited options. Bispecific antibodies (BsAb, CD20×CD3) have shown clinical activity in heavily pretreated patients and may serve as a bridge to allogeneic stem cell transplantation (allo-SCT).

Methods. We retrospectively analyzed 9 consecutive patients (6M, 3F; born 1960–1982) with DLBCL (n=7) or FL (n=2) progressing after CAR-T therapy, subsequently treated with epcoritamab (n=4), glofitamab (n=4), or mosunetuzumab (n=1). Median interval CAR-T → BsAb was 4 months (range 3–10). Clinical data included response to BsAb, timing, subsequent allo-SCT, and treatment-related toxicities. Response was assessed according to standard criteria.

Results. Overall response rate to BsAb was 75%, including 3 complete responses (CR) and 3 partial responses (PR). Four patients successfully proceeded to allo-SCT after BsAb treatment. Most responses occurred within 3–4 months from CAR-T relapse. Treatment was generally well tolerated: CRS grade 1–2 occurred in approximately 50% of patients, with no grade ≥3 events. One patient progressed and subsequently underwent allo-SCT.

Conclusions. In this real-world cohort, BsAb demonstrate meaningful clinical activity and a favorable safety profile in post-CAR-T DLBCL and FL. They may effectively bridge selected patients to allo-SCT, supporting the CAR-T → BsAb → allo-SCT sequence as a feasible and potentially curative strategy in younger, fit patients. Prospective studies are warranted to refine patient selection and optimize sequencing of these therapies.

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Table 1. Patient characteristics, treatment sequencing, and outcomes

Patient	Sex	Birth Year	Diagnosis	BsAb	Time CAR-T → BsAb (months)	Response	Bridged to allo-SCT
1	M	1982	DLBCL	Epcoritamab	4	CR	Yes
2	F	1966	DLBCL	Glofitamab	10	PR	Yes
3	M	1969	DLBCL	Glofitamab	9	CR	No
4	M	1969	DLBCL	Glofitamab	4	PD	Yes
5	F	1960	DLBCL	Epcoritamab	3	PR	Yes
6	M	1963	DLBCL	Glofitamab	4	Not evaluable	No
7	M	1979	FL	Epcoritamab	3	PR	Planned
8	F	1970	FL	Mosunetuzumab	5	Not evaluable	No
9	M	1976	FL	Epcoritamab	4	CR	No

Abbreviations:
DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; BsAb: bispecific antibody; CR: complete response; PR: partial response; PD: progressive disease; allo-SCT: allogeneic stem cell transplantation; CRS: cytokine release syndrome.

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Non-Hodgkin's Lymphoma

SHORT COURSE OF PEMBROLIZUMAB FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION AND PEMBROLIZUMAB MAINTENANCE, IS EFFECTIVE IN HEAVILY PRE-TREATED REFRACTORY GRAY ZONE LYMPHOMA

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Mediastinal Gray-zone lymphoma (MGZL) is a B cell neoplasm that lies on the biological spectrum between primary mediastinal (thymic) large B-cell lymphoma (PMBCL) and nodular sclerosis classical Hodgkin lymphoma (NS-cHL), with overlapping clinical, histological, molecular and epigenetic features.Conventional CHOP-based chemotherapy regimens (R-CHOP or R-EPOCH) in first line and a salvage treatment including chemotherapy plus autologous stem cell transplantation (ASCT) in refractory/relapsed disease, often produce unsatisfactory results. The evidence of CD30 expression in MGZL, supported the use of Brentuximab Vedotin, an anti-CD30 antibody drug conjugate, in the treatment of the disease with encouraging results. Moreover, both cHL and PMBCL frequently show a PD-L1 overexpression, suggesting the use of Pembrolizumab into the treatment strategy.We report two cases of young women diagnosed with MGZL by lymph node biopsy. Neoplastic cells were positive for CD20, CD79a, PAX5, MUM1, BCL2, CD30, and PDL-1, but negative for CD15, CD10, BCL6, ALK, EMA, BOB1, OCT-2, and EBER. Lymph node biopsy also revealed focal CD23 expression and an eosinophil-rich inflammatory microenvironment. Patients were refractory to both first line and salvage immune-chemotherapy by R-EPOCH and R-DHAP, respectively. One of them included also Brentuximab Vedotin in DHAP regimen without any effectiveness. Because neoplastic tissues showed the PDL-1 expression, both patients were enrolled in a third line therapeutic strategy including 4 courses of Pembrolizumab induction therapy followed by ASCT and subsequent 8 cycles of Pembrolizumab maintenance. Interim PET was scheduled after induction, ASCT and at the end of treatment. Both patients obtained a complete metabolic response (for the first time in their disease story) after the induction and completed the planned therapeutic program. The patients are still in continuous complete metabolic response after 36 and 21 months, respectively.Our data, although limited to two individual cases, demonstrated that pembrolizumab is effective even in heavily pretreated or refractory patients with MGZL and may represent a valuable bridge to stem cell transplantation. Future efforts should focus on refining diagnostic criteria for MGZL through advanced molecular and immunophenotypic profiling to ensure accurate diagnosis and improved treatment, and on early optimization of pembrolizumab-based strategies, including combination approaches.

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Non-Hodgkin's Lymphoma

CLINICO-BIOLOGICAL CHARACTERIZATION, THERAPEUTIC MANAGEMENT, AND OUTCOMES OF EXTRANODAL DIFFUSE LARGE B-CELL LYMPHOMA OF THE HEAD AND NECK: A REAL-WORLD MONOCENTRIC COHORT ANALYSIS

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Introduction. Lymphomas account for approximately 5% of head and neck malignancies, with DLBCL representing over 40% of cases, making it the most frequent and aggressive subtype. This study analyzes a real-world cohort of 30 patients with **exclusively extranodal (EN) localizations** treated between 2021 and 2025. The aim is to evaluate the impact of high-risk biological profiles and treatment efficacy in a population with a high median age of 72 years.
Methods. Staging, biology, and risk scores (IPI, CNS-IPI) were retrospectively evaluated. c-MYC, BCL2, and BCL6 expression was determined via immunohistochemistry (IHC), and the Cell of Origin (COO) subtype was defined using the Hans algorithm. Overall survival (OS) and progression-free survival (PFS) were calculated from diagnosis to last follow-up. Statistical analysis included Pearson correlation for biomarkers and Fisher's Exact Test for age stratification.
Results. The cohort exhibited a markedly aggressive biological profile: 80% non-GCB, 63.3% Ki-67 ≥ 80%, and 50% Double/Triple Expressors. Primary sites included Waldeyer's ring/Pharynx (33.3%), Thyroid (16.7%), and Salivary Glands (13.3%). Among molecular markers, BCL6 expression showed the strongest negative association with survival (r = -0.30). While global OS was 80% and the Complete Response (CR) rate reached 70%, the PFS was notably low at 13.3% (median 14.5 months), reflecting a high rate of early events. Age > 65 years was a critical unfavorable prognostic factor (p = 0.023): this subgroup (n=17) showed a lower OS (64.7%) and a therapy failure rate (RR) of 88.2%. Regarding treatments, R-CHOP and R-miniCHOP yielded excellent results (CR/OS 84.6% and 80%, respectively), whereas R-DA-EPOCH was limited by toxicity (CR/OS 50%). 73% of patients had a CNS-IPI ≥ 2. CNS prophylaxis (administered to 45% of cases; 11 LP, 7 HD-MTX) followed a risk-adapted strategy (100% of CNS-IPI 5 and 80% of CNS-IPI 4 received treatment), restricting neuraxial relapses to 3.3%. However, survival for relapsed patients was 0%.
Conclusions. EN head and neck DLBCL carries significant biological and neurological risks, with BCL6 expression as a critical marker of poor outcome. While CNS prophylaxis is effective and standard/adapted regimens offer good initial outcomes, the low PFS and dismal prognosis for RR patients highlight that primary chemo-resistance remains the main challenge. Early integration of innovative immunotherapies is essential for this fragile population

Non-Hodgkin's Lymphoma

CHEMO-FREE FIRST-LINE THERAPY IN FRAIL PATIENTS WHIT MARGINAL AND MANTLE CELLS NON-HODGKIN LYMPHOMA THIS IS THE FUTURE? OUR EXPERIENCE

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University of Medicine Hematology

BKT inhibitors(iBKT)in the treatment of some non-Hodgkin's lymphomas are shifting the balance in the therapeutic approach of these diseases,increasingly moving towards chemotherapy-free(f-CHT) treatment.The lymphomas that already have approval for the use of iBKT are mantle cell lymphoma(mNHL) and marginal lymphoma(MNHL)with good results but used only as monotherapy and from second line.An unmet medical need is how to treat frail elderly pts in the first line with iBTK and without cht.The aim of our study is to treat frail pts diagnosed with mNHL or MNHL with a single dose of bendamustine 70mg/m2immediately discontinued, followed by one weekly cycle of rituximab375mg/m2,after which iBKT (zanubrutinib for MNHL and acalabrutinib for mNHL)was added concurrently with immunotherapy (Rituxmab375mg/m2,one dose every 28days for 4administrations).Subsequently, they were revaluated and,if in response,the program includes iBTK and rituximab375mg/m2every 2m for 2years or until unacceptable toxicity or disease recurrence.In our Division,from September2023 to Avril2026, we treated 24pts(8mNHL and 16MNHL).10F and14M had a median age of79y(range:61-88)and a median performance status of2(range:1-3).17pts(71%)were evaluable after 6m of treatment. 3pts died: 2 due to infection (1fungal infection and 1sepsis,+1 and+16m from the start respectively) and 1 for complications unrelated to treatment at+3m.Of the 17 evaluable pts,the ORR at 6m was100%:5CR(30%);6VgPR(30%)and6PR(40%).At 12m, 15pts were evaluable, with a confirmed ORR of100%,with improved outcome:11CR(75%);4RP(25%).No pts experienced grade>2 cardiac adverse events;3/24pts(14%)experienced grade >2 bleeding events that led to iBKT discontinuation with subsequent resumption at a50% reduced dose;no pts experienced >2 hematological toxicity; no pts experienced CMV reactivation;3pts(12%)developed serious infection (2 fungal,maxillary sinus mucormycosis with death and pulmonary aspergilloma treated with isavuconazole, and 1 bacterial sepsis).5/24pts (20%) discontinued treatment: 3 due to death and 2 due to the development of a second neoplasm(1 breast carcinoma and 1 intestinal carcinoma).No disease progression has been documented and the projected 30-months OS is 87%(whit a median follow-up of 15m).In conclusion, even if small cohort and with a short follow-up, the first-line f-CHT treatment in frail pts with marginal and mantle cell lymphoma has proven to be very active with good compliance and an excellent quality of life.

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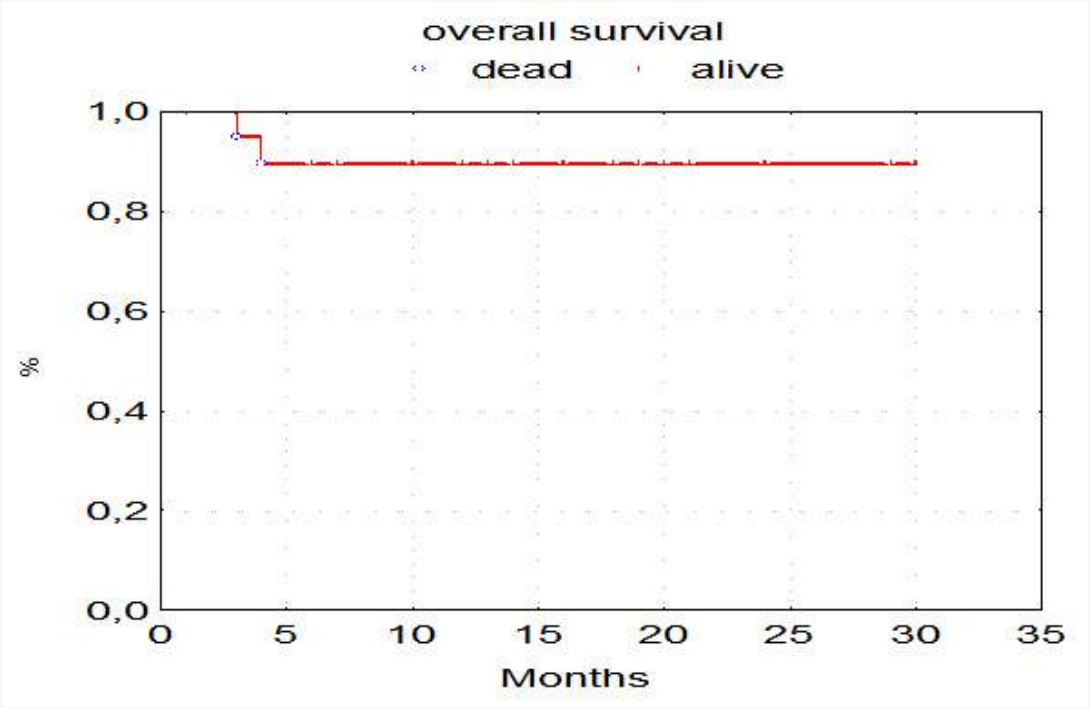
overall survival
dead
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1,0
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25
30
35
Months

Non-Hodgkin's Lymphoma

BEYOND FETAL SCREENING: NIPT REVEALING A MATERNAL LYMPHOPROLIFERATIVE DISEASE

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Non-invasive prenatal testing (NIPT) is becoming a first approach to fetal screening, as it focuses on the research of fetal aneuploidy through the analysis of cell-free DNA on maternal blood. However, atypical results may unveil maternal conditions. Here, we describe a case in which NIPT findings prompted the diagnosis of an underlying maternal haematological disorder.IG a 35 years old woman subjected to NIPT test at around 10 weeks of pregnancy. Results showed multiple aneuploidies: trisomy of 3, 7 and 18, monosomy of 9 chromosomes, fetal sex XY. She then underwent an amniocentesis test some weeks later which did not reflect the NIPT findings. She was then referred to our center by the geneticist as the NIPT findings could be linked to a maternal hematological malignancy.On her first hematological visit, she did not show any signs nor symptoms with normal blood tests. A full work-up was performed: an immunophenotype (IP) on peripheral blood and a chest magnetic resonance imaging (MRI). IP showed only an abnormal polyclonal expression of IgK. The MRI was negative. She had a delivery at week 36 (+6 days) of pregnancy.Five months later, she made a new contact with our Center, as she recently self-assessed some enlarged cervical lymph nodes, with fever and headaches. The spleen was enlarged up to 4 cm below the costal arch and multiple enlarged lymph nodes were palpable on laterocervical areas. Blood tests confirmed an IgM monoclonal component (MC) rapidly increasing in the next few days up to a dosage of 6062 mg/dL of IgM. An ultrasound of deep lymph nodes stations was performed, highlighting multiple adenomegalies stretching up to 2 cm.Subsequently a bone marrow and inguinal lymph node biopsies were performed, revealing a diagnosis of diffuse large B-cell lymphoma (DLBCL) with a secretory IgM MC. A session of plasmapheresis was carried out in order to lower MC, allowing to start treatment with R-CHOP.After 4 cycles of R--CHOP, the patient showed good clinical response with an interim PET-scan showing no uptake. CT and PET-scan will be planned at the end of treatment.The association of abnormal NIPT findings and occult maternal disease has been previously reported in the literature, with haematological malignancies representing the most commonly identified underlying pathology. Our case further supports the importance of starting promptly a diagnostic work-up, whenever NIPT findings might be suggestive for a maternal occult oncological disease.

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Non-Hodgkin's Lymphoma

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AFTER ANTI-CD20 MONOCLONAL ANTIBODIES: A CASE-BASED NARRATIVE REVIEW

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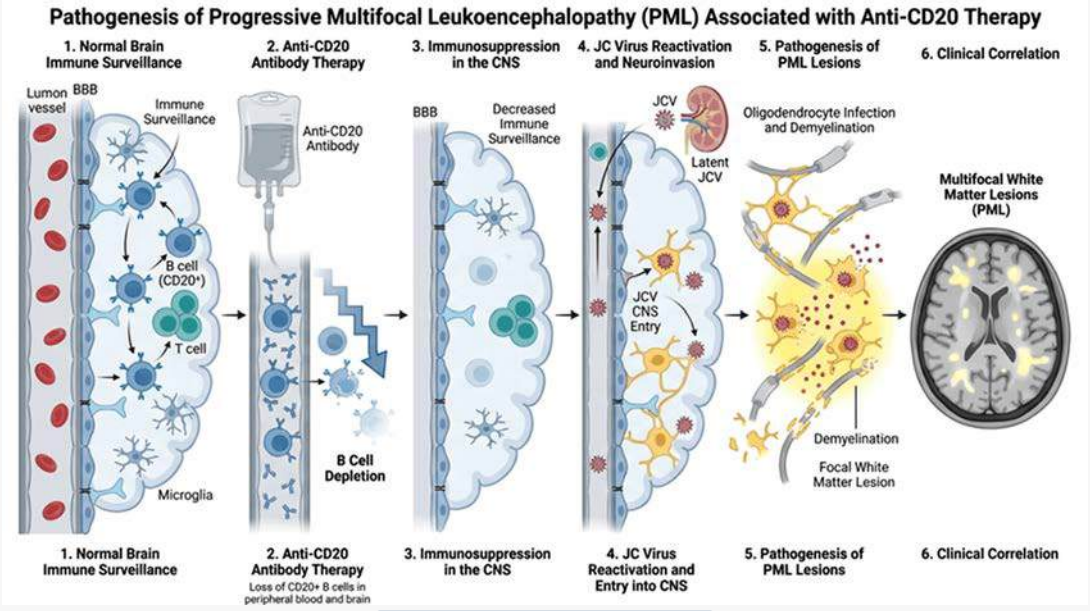
Background. Progressive multifocal leukoencephalopathy (PML) is a severe JC polyomavirus (JCPyV)-driven demyelinating infection of the central nervous system occurring with impaired immune surveillance. Anti-CD20 monoclonal antibodies are increasingly relevant in hematology, especially when combined with bendamustine, maintenance therapy, corticosteroids, hypogammaglobulinemia and delayed T-cell recovery.

Methods. We performed a case-based narrative review of anti-CD20-associated PML, focusing on pathogenesis, risk factors, diagnosis and emerging immune-based treatments. The case was interpreted in light of evidence on rituximab- and obinutuzumab-associated PML, checkpoint inhibitors and virus-specific T-cell therapy.

Results. A 61-year-old woman with stage IVA follicular lymphoma received obinutuzumab plus bendamustine, followed by maintenance obinutuzumab. During maintenance she developed dysarthria, blurred vision and gait disequilibrium. MRI showed a non-enhancing left parietal white matter lesion compatible with PML, while the first CSF test detected very low JCPyV DNA. Repeat CSF testing and serial MRI documented rising viral load, worsening aphasia, progressive right-sided motor impairment and bilateral white matter extension. The immune profile showed profound B-cell depletion and marked T-cell disequilibrium. Corticosteroids produced only transient benefit. Because PML progressed despite anti-CD20 withdrawal and spontaneous immune recovery was unlikely, the patient received partially HLA--matched third-party donor-derived JCV-specific T lymphocytes. Infusion was well tolerated and followed by early subjective improvement; however, the patient died due to PML progression and neurologic deterioration.

Conclusions. Anti-CD20-associated PML should be viewed as layered immune failure rather than isolated drug toxicity. Diagnosis requires early MRI, repeat CSF JCPyV PCR when suspicion persists, and integrated clinical, virologic and radiologic assessment. Treatment depends on immune restoration, since empiric antivirals have no consistent efficacy. Checkpoint inhibitors may help selected patients with residual virus-specific immunity, whereas adoptive virus-specific T-cell therapy is a promising rescue strategy for profoundly immunocompromised hosts. This case emphasizes that timing is prognostically crucial: referral and lymphocyte administration must be early and timely, before irreversible lesion burden and neurologic decline limit stabilization.



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Non-Hodgkin's Lymphoma

LATE SEROCONVERSION AND BTKI-INDUCED FLARE IN CRYOGLOBULINEMIC WALDENSTRÖM MACROGLOBULINEMIA: A CASE REPORT

M. Draisci, S. Franceschetti, R. Marcolin, S. Marinoni, A. Corso

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Background. Waldenström Macroglobulinemia (WM) can manifest as a severe "protein-driven" disease where organ damage often precedes the biochemical detection of cryoglobulins. Type I cryoglobulinemia is a rare complication, occurring in less than 5-10% of WM patients, and often presents significant diagnostic challenges. We present a case illustrated by late seroconversion and a paradoxical response to Bruton's Tyrosine Kinase inhibitor (BTKi) therapy.

Case Report. A 68-year-old HCV-negative male presented with painful, necrotic bilateral plantar ulcers since 2022, initially refractory to dermatological treatments and skin grafts. In July 2025, a diagnosis of *MYD88*$^{\{L265P\}}$ mutated WM revealed the systemic etiology; however, the serum cryocrit was absent and TP53 molecular analysis was negative A partial and transient response, both clinical and serological, was achieved with first-line R-CD. After 6 months (January 2026), the disease progressed with a rare seroconversion (appearance of Type I IgM Kappa cryocrit). Re-evaluation confirmed persistent negativity for TP53 gene mutations, describing a phenotypically aggressive but genetically stable clone. At this stage, the previously healed ulcers remained stable. In March 2026, Zanubrutinib (320 mg daily) was initiated.

Results and Discussion. Within one month, a prompt biohumoral response occurred (IgM decreased from 32.08 to 22.52 g/L). Paradoxically, this biochemical improvement was accompanied by a violent inflammatory "flare" of the cutaneous ulcers, which had previously been stable. This phenomenon, documented in BTKi literature, is linked to rapid shifts in plasma viscosity and the mobilization of tissue-bound cryoglobulins. To consolidate the response, the future treatment plan includes the addition of Rituximab to Zanubrutinib (iNNOVATE-like regimen) to target the CD20+ clone and prevent further flares.

Conclusions. This case highlights how laboratory findings in WM can lag behind clinical signs by years. The phenomenon of late seroconversion and the BTKi-induced flare of stable ulcers in a TP53-negative patient underscore the complexity of managing cryoglobulinemic WM. The transition to Zanubrutinib and the planned integration of Rituximab represent a necessary paradigm shift to overcome the "flare paradox" and ensure definitive tissue healing.

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Non-Hodgkin's Lymphoma

SUCCESSFUL USE OF EPCORITAMAB IN REFRACTORY RICHTER SYNDROME AFTER FAILURE OF ALLOGENEIC STEM CELL TRANSPLANT: A CASE REPORT

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Cardinale G Panico Hospital, Hematology and Bone Marrow Transplant

Background. Richter Syndrome (RS) is an aggressive transformation of chronic lymphocytic leukemia (CLL), with poor prognosis. No standard treatment for RS has been established. Epcoritamab may show antitumour activity in this setting and offer clinical benefit.

Methods. An 59-year-old man was diagnosed with high risk CLL (TP53mutation with 17p13 deletion, IGHV unmutated) in 2021, without comorbidities at disease onset,. The patient remained untreated for nearly 3 years. In January 2024, a lymph node biopsy showed a development in GCB DLBCL-RS. Bone marrow biopsy revealed a diffuse proliferation of small CD19 CD5 CD23 lymphoid cells positive. DA-EPOCH-R as first line treatment resulted in a transient lymph nodes reduction. Zanubrutinib was used as bridging therapy to aploidentical allogeneic transplant (allo HSCT). At day+100 after alloHSCT the patient showed a rapid progression of disease. Epcoritamab was started as third line therapy in July 2025.

Results, Four weeks after starting Epcoritamab the LDH levels decreased, fever desappeared and the patient showing a better quality of life. Grade 1 CRS was observed during step up dosing. CMV reactivation was observed after the third cycle. ICANS was not observed. Intravenously immunoglobulin replacement was administered due to hypogammaglobulinemia. Whole body CT (WBCT) after 3 cycles showed a partial response. After eighth cycle of therapy, WBCT revealed a VGPR with a further decrease of lymphadenopathy (>75%).

Conclusions. This case is an example of Epcoritamab's potential effectiveness and safety in refractory high risk DLBCL- Richter syndrome.

Non-Hodgkin's Lymphoma

OFF-LABEL GLOFITAMAB INDUCES RAPID REVERSAL OF BONE MARROW FAILURE IN MANTLE CELL LYMPHOMA REFRACTORY TO BOTH COVALENT AND NON-COVALENT BTK INHIBITORS

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Mantle cell lymphoma (MCL) progressing after both covalent and non-covalent BTK inhibitors represents a critical unmet clinical need with extremely limited therapeutic options and poor outcomes. We report a 76-year-old female with high-risk MCL (stage IV with bone marrow involvement, MIPI high risk) diagnosed in 2010. The patient underwent multiple lines of therapy: R-CHOP (CR), RB (PR), R-BAC (CR, ASCT declined), Ibrutinib (72 cycle, subsequent progression) and pirtobrutinib (refractory disease). Notably, the disease followed a clinically indolent course for nearly two decade before evolving into a refractory phase. At the time of new treatment indication, the patient presented with severe pancytopenia and was transfusion-dependent consistent with advanced marrow infiltration and exhausted standard therapy options, with no access to CAR-T or clinical trial due to advanced age (78 years at treatment initiation) and frailty. TP53 mutation was not detected. Off-label glofitamab was initiated as fifth-line therapy. After 12 complete cycles, glofitamab induced a clinically meaningful hematologic recovery, with complete resolution of pancytopenia and restoration of peripheral blood counts with achievement of transfusion independence, consistent with complete hematologic remission, and improved functional status. This translated into a rapid clinical benefit, with improved functional status and reduced supportive care requirements. The depth and rapidity of response strongly suggest effective disease control within the bone marrow compartment. Treatment was well tolerated, with only grade 1 cytokine release syndrome during initial administration. Intravenous immunoglobulins were administered as prophylaxis. This case, although based on a single.patient experience, provides clinically relevant evidence supporting glofitamab as a highly active therapeutic option in ultra-refractory MCL, even after failure of both covalent and non-covalent BTK inhibitors. The rapid reversal of bone marrow failure highlights a potent anti-lymphoma effect in a setting with otherwise dismal prognosis. Off-label glofitamab may represent a critical rescue strategy for patients lacking alternative options and may redefine therapeutic expectations in this otherwise unmet clinical setting.

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Non-Hodgkin's Lymphoma

LONCASTUXIMAB TESIRINE: A NEW THERAPEUTICAL OPTION IN A HEAVILY PRETREATED ELDERLY PATIENT

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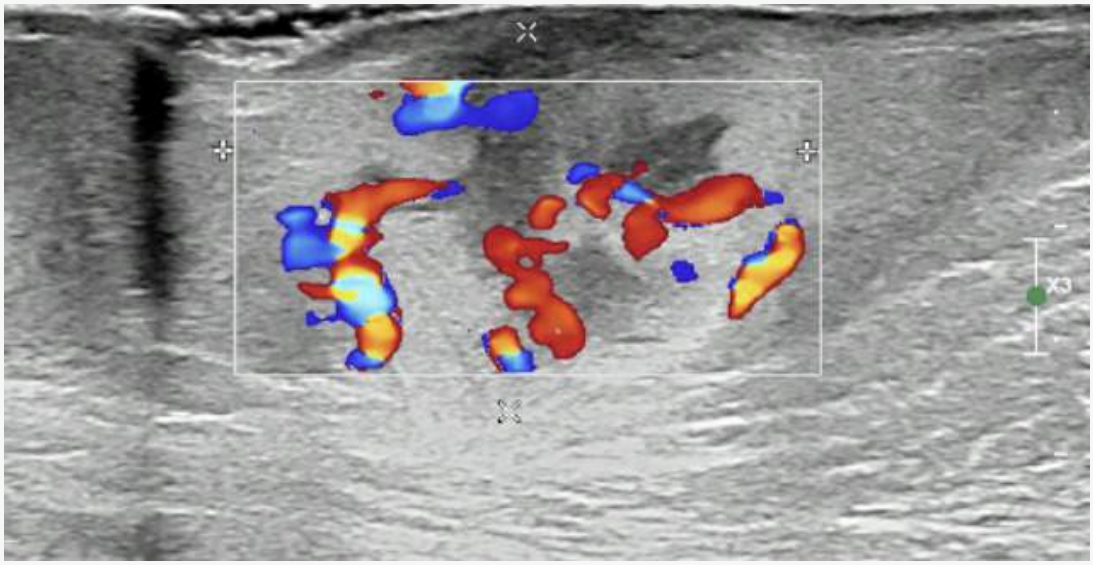
Background. In the last few years new therapeutical options (like CAR-T cells and bispecific monoclonal antibodies) for treating DLBCL have completely changed the outcomes for relapsed and refractory disease. Elderly patients may not be fit for these treatments, but might subtain lower toxicity treatments. For these patients the new antibodies targeting CD-19 may represent an alternative treatment.
Case Report. an 83 year-old male patient, with diabetes and a previous cardiological history of coronary disease with multiple PTCAs, atrial fibrillation and PMK implant had a nucal skin involvement and nucal lymphadenomegalies, which upon biopsy revealed the diagnosis of Diffuse Large B-Cell Lymphoma leg-type. The positron emission tomography (PET), total body scan and bone marrow staging showed involvement of all the laterocervical nodes but none in the bone marrow.The patient was treated with R-mini-COMP and local radiotherapy as a first line therapy. The response was poor, so he switched to a second line treatment with tafasitamab and lenalidomide (due to age and comorbidities). He had a complete response after 6 cycles, but after 15 cycles he hada new relapse, involving the laterocervical lymph nodes and the bladder, with acute renal failure that required surgery, during which a biopsy wasperformed. The biopsy confirmed the CD-19 expression, so loncastuximab tesirine was chosen as third line treatment, due to the manageable toxicity profile. After two cycles the patient showed complete response at the total body scan, but he experienced both a skin rash and urosepsis, which required hospitalization and led to the post-ponement of cycle 3. After eight cycles the patient had suspected relapse, a skin lesion of 2 cm (Fig. 1), but showed a spontaneous regression so he resumed treatment. After ten cycles the patient had a new myocardial infarction, treated with PTCA. After the hospital discharge the patient showed a new relapse on inguinal lymph nodes of 6 cm. The treatment was definitively discontinued. The patient passed away a month later.
Conclusions. The patient, even with the complications, was able to complete 10 cycles of loncastuximab tesirine, with a good quality of life and a PFS of 8.9 months (PFS of registration study was 4,9 months). The case shows that the treatment with loncastuximab tesirine may represent a feasible option in elderly patients relapsed patients and shows different adverse effects that can come with the treatment.



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Myeloma and other monoclonal gammopathies

AL AMYLOIDOSIS: CLINICAL CHARACTERISTICS AND OUTCOMES IN A SINGLE-CENTER EXPERIENCE

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Background. AL amyloidosis is a rare multisystem disorder with significant impact on prognosis and healthcare resources. Advances in diagnostics, staging, and therapy have reshaped its clinical management. We analyzed our institutional dynamic evolution that led during time to a modification of clinical evaluations, treatment patterns, and outcomes.

Methods. This retrospective monocentric study included 39 consecutive patients diagnosed between 1999 and 2025. Baseline clinical and laboratory data were collected. A total of 63 treatment lines were analyzed, corresponding to multiple lines per patient. Hematologic and organ responses were assessed according to consensus criteria.

Results. The median age was 70 years (range 47–94) with a slight female predominance (52%). Median dFLC was 1641.85 mg/L and the predominant light chain isotype was lambda (87%). Multiple myeloma was the most frequent underlying condition (64%), followed by monoclonal gammopathy of clinical significance (31%) and Waldenström macroglobulinemia (5%). FISH analysis identified amp1q (n=6), t(11;14) (n=4), hyperdiploidy (n=3). The number of diagnoses increased over time: 10 before 2020, 19 between 2021–2024, and 10 in 2025. At diagnosis, cardiac involvement was observed in 64% of patients (mainly Mayo Stages II-III), renal involvement in 59% (mostly stage II) and multi-organ involvement in 46%. Thirty-six patients received frontline therapy (3 patients were excluded: 2 treated elsewhere, 1 unfit). Subsequent second, third, fourth and fifth lines were administered to 13, 9, 4 and 1 patients, respectively. Median time to partial hematologic response was 33 days. Hematologic and organ responses by treatment line and regimen are summarized in Table 1. The median follow-up was 21 months (range 0-157) and the overall survival (OS) was 80,5%. 7 patients (19%) died within 24 months from diagnosis, including 6 that had advanced cardiac involvement (Mayo Stage III). Figure 1 shows worse OS in patients with cardiac involvement and advanced stages, although not statistically significant (Figure 1A: p = 0.561; Figure 1B: p = 0.153).

Conclusions. The increasing number of diagnoses over time reflects improved disease awareness and diagnostic strategies. In this real-world cohort, OS compares well with historical data and cardiac involvement confirmed its key prognostic role, particularly in advanced stages.

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Myeloma and other monoclonal gammopathies

Table 1.

	HEMATOLOGIC RESPONSE					CARDIAC RESPONSE					RENAL RESPONSE				
1° line	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR
RCP	1				1	0					1				1
VelDex	2	2				2	1			1*	2	1			1
VCD	9	4	1	3	1	5	1	1		3	5	1	1	2	1
BMDex	3	2			1	2			1	1	1	1			
VTD	1				1*	0					1				1*
Dara-VCD	15	9	3	2	1*	11	1	2	1	6 + 1*	9		4	2	3
Dara-Len-Dex	3		1	1	1*	2			2		2				2*
R-VD	2	1			1	1				1	1				1*
Total:	36	18	5	6	4 + 3*	23	3	3	4	11+2*	22	3	5	4	6 + 4*
2° line	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR
VelDex	1			1		1			1		1				1*
VCD	2			2		1			1		1			1	
Dara-Len-Dex	5	2		2	1	2				2	3		1		1+1*
Len-Dex	2				2	2		1		1	2			1	1*
Pom-Dex	1				1	1				1	0				
R-Benda	1			1		1				1	1				1*
Teclistamab	1	1				1			1		1				1
Total:	13	3	0	6	4	9	0	1	3	5	9	0	1	2	6
3° line	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR
VCD	2			2		1				1	2				1+1*
Dara-VCD	1			1		1				1	1				1*
Len-Dex	2			1	1	2				2	0				
Pom-Dex	2				2	2		1		1	1		1		
Daratumumab	1			1		1				1	1				1
PVD	1				1	0					1				1*
Total:	9	0	0	5	4	7	0	1	0	6	6	0	1	0	2+3*
4° line	n.	CR	VGPR	PR	NR		CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR
Pom-Dex	1				1	1				1*	1				1*
Daratumumab	1	1				1		1			1		1		
Teclistamab	2	2				2				2	1				1*
Total:	4	3	0	0	1	4	0	1	0	2	3	0	1	0	2*
5° line	n.	CR	VGPR	PR	NR		CR	VGPR	PR	NR	n.	CR	VGPR	PR	NR
Teclistamab	1	1				1				1	1	1			
Total:	1	1	0	0	0	1	0	0	0	1	1	1	0	0	0

Legend to table: n.: total number of patients per line; (*) not evaluable; CR:Complete Response; VGPR: Very Good Partial Response; PR: Partial Response, NR: No Response; RCP: Rituximab+Cyclophosphamide+Prednisone; VelDex: Bortezomib+Dexamethasone; VCD: Bortezomib+Cyclophosphamide+Dexamethasone; BMDex: Bortezomib+Melphalan+Dexamethasone; VTD: Bortezomib+Thalidomide+Dexamethasone; Dara-Len-Dex: Daratumumab+Lenalidomide+Dexamethasone; R-VD: Rituximab+Bortezomib+Dexamethasone; Pom-Dex: Pomalidomide+Dexamethasone; R-Benda: Rituximab+Bendamustine; PVD: Pomalidomide+Bortezomib+Dexamethasone.

Figure 1.

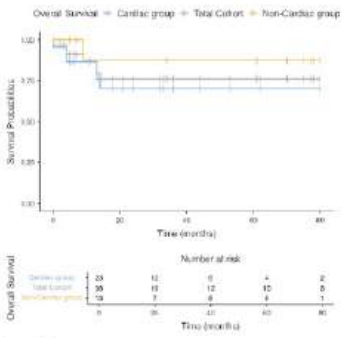

Figure 1A

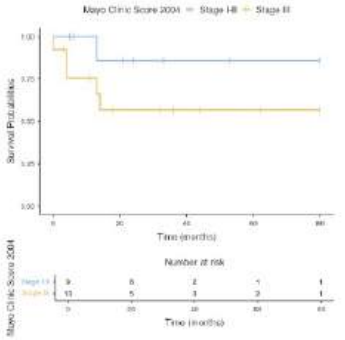

Figure 1B

Myeloma and other monoclonal gammopathies

ISATUXIMAB SUBCUTANEOUS VIA AN ON-BODY INJECTOR PLUS POMALIDOMIDE-DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: SUBGROUP ANALYSIS BY PRIOR LINES OF THERAPY FROM THE PHASE 3 IRAKLIA TRIAL

C. Cerchione[1], S. Ailawadhi[2], A. Oriol[3], S. Ling[4], F. Schjesvold[5], C. Li[6], Ma. Dimopoulos[7|8], P. Rajnics[9|10], Sk. Beşışık[11], V. Hungria[12], G. Parmar[13], X. Leleu[14], C. Gomez[15], T. Ishida[16], Tt. Buck[17], F. Suzan[18], M. Stefanova-Urena[19], R. Zhang[19], I. Špička[20]

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Introduction. The international, non-inferiority, open-label IRAKLIA trial (NCT05405166) of isatuximab (Isa) subcutaneous (SC) vs intravenous (IV) + pomalidomide-dexamethasone (Pd) is the first Phase 3 trial of an innovative on-body injector (OBI) in relapsed/refractory multiple myeloma (RRMM) patients (pts), who have been previously exposed to lenalidomide (LEN) and a proteasome inhibitor; pts with 1 prior line of therapy (LOT) had to be LEN-refractory. This post-hoc subgroup analysis of IRAKLIA evaluates outcomes by 1 or >1 prior LOT after Isa SC OBI vs IV administration + Pd.

Methods. RRMM pts ≥18 years (y) were randomized 1:1 to Isa SC OBI (1400 mg; n=263) or IV (10 mg/kg; n=268) weekly in Cycle 1, then every 2 weeks with Pd. Overall response rate (ORR) was a co-primary endpoint (stratification factors included number of prior LOT [1-2 vs ≥3]).

Results. Baseline characteristics were balanced across prior LOT subgroups for Isa SC OBI vs IV: median age was 66-67 y for 1 prior LOT and 66 y for >1 LOT. The >1 LOT group had a median of 3 prior LOT. Isa-Pd demonstrated efficacy regardless of the number of LOT; ORRs for Isa SC OBI vs IV were 74% vs 76% (1 prior LOT) and 70% vs 68% (>1 prior LOT). Among 1 prior LOT pts, 95% (Isa SC OBI) and 90% (Isa IV) were LEN-refractory; among >1 prior LOT pts, 59% (Isa SC OBI) and 52% (Isa IV) of pts were LEN-refractory at last regimen. For pts who were LEN-refractory at last regimen, ORRs for Isa SC OBI vs IV were 72% vs 74% (1 LOT) and 68% vs 62% (>1 LOT); for 1 prior LOT, rates of ≥ very good partial response (≥VGPR) and ≥ complete response (≥CR) for Isa SC OBI vs IV were 42% vs 51% and 15% vs 17%, respectively; for >1 prior LOT, rates were 40% vs 45% (≥VGPR), and 17% vs 20% (≥CR). Among all pts being assessed according to prior LOT, Grade ≥3 treatment-emergent adverse events (TEAE) for Isa SC OBI vs IV were 74% vs 68% (1 LOT) and 85% vs 80% (>1 LOT), with rates of treatment discontinuation due to TEAE of 7% vs 5% (1 LOT) and 9% vs 10% (>1 LOT).

Conclusions. In IRAKLIA, comparable results were observed between the Isa SC OBI + Pd and Isa IV + Pd arms regardless of the number of prior LOT, demonstrating efficacy of Isa-Pd in the ≥1 prior LOT and LEN-refractory settings. These findings support use of Isa SC administered by the novel OBI plus Pd in RRMM pts regardless of number of prior LOT.

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Myeloma and other monoclonal gammopathies

LAMBDA LIGHT CHAIN AS AN INDEPENDENT DETERMINANT OF ARTERIAL STIFFNESS IN MGUS

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Introduction. According to recent evidence, Monoclonal Gammopathy of Undetermined Significance (MGUS) is associated with an increased cardiovascular risk. However, the pathophysiological mechanisms remain partially unknown. Arterial stiffness, and in particular its main parameter, Pulse Wave Velocity (PWV), is a robust predictor of cardiovascular outcomes.

Methods. 100 patients diagnosed with MGUS were enrolled. For each subject, heavy and light chain isotype, eGFR (CKD-EPI), hemoglobin, calcium, Ig κ, Ig λ, and Beta-2 microglobulin (B2M) were assessed. Arterial stiffness, measured with the SphygmoCor instrument, was defined by mean PWV, augmentation pressure (AP), augmentation index (AI%), central blood pressures (c-SBP, c-DBP) and Ankle-Brachial Index (ABI index). Statistical analysis, included Pearson correlation tests, receiver operating characteristic curve analysis, and multiple linear regression models to adjust for potential confounders, was performed to elucidate potential association between MGUS-defining parameters and arterial stiffness.

Results. Initial analysis showed a positive correlation between B2M levels and PWV (r = 0.324; p = 0.001). ROC curve analysis confirmed the ability of B2M to discriminate patients with high stiffness (AUC = 0.616; p = 0.046); however, in multiple linear regression analysis, B2M lost statistical significance (p = 0.115), being confounded by age (p = 0.029). Subsequently, isotype-based analysis revealed that patients with λ light chain had significantly higher PWV values than subjects with κ chain (7.73 ± 1.59 vs 6.98 ± 1.91 m/s; p = 0.046). When this variable was entered into a multiple regression model adjusted for age, eGFR and c-SBP, λ isotype emerged as an independent predictor of arterial stiffness (p = 0.008), contributing to a substantial increase in the variance explained by the model (R^2 = 0.201).

Conclusions. Our results indicate that, although B2M correlates with vascular damage, it primarily reflects the aging process. Conversely, the λ isotype emerges as an independent biological determinant of arterial stiffness in MGUS. This suggests a potential angio-toxic role specific to λ light chains, whose increased tendency to precipitate and aggregate, mimicking AL amyloidosis, could promote structural remodeling of the arterial wall even in the subclinical phase. These data underscore the need for cardiovascular risk stratification based on the patient's immunochemical profile.

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Myeloma and other monoclonal gammopathies

FLOW CYTOMETRY REVEALS KIR EXPRESSION IMBALANCE ASSOCIATED WITH AN ALTERED NK CELL PHENOTYPE IN ACTIVE MULTIPLE MYELOMA

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Background. Natural killer (NK) cells are part of the immune system's surveillance against tumors, and their activity depends on the balance between activating and inhibitory receptors, including KIRs. In multiple myeloma (MM), the immune environment is clearly altered and contributes to disease progression, but how KIR expression behaves in active disease is still not fully understood.

Methods. We looked at the expression of NK inhibitory receptors in peripheral blood from about 60 patients with active MM and 20 healthy controls using multiparametric flow cytometry. We focused on the proportion of NK cells expressing NKG2A and selected KIR receptors (KIR2DL2/DL3, KIR2DL1, KIR3DL1), comparing the two groups. In our routine laboratory setting, flow cytometry proved to be a practical and reliable way to assess these markers.

Results. Overall, patients with active MM showed a more variable KIR expression profile compared to controls. KIR2DL2/DL3 expression tended to be higher in MM, with median values around 20–25% versus about 5–10% in controls, and exceeding 30% in several patients. NKG2A values were also more spread out, with some clearly increased levels. On the other hand, KIR3DL1 expression was often reduced or even absent in a subset of MM patients, while it was generally detectable in controls. Taken together, these patterns point to a shift toward inhibitory signaling within the NK cell compartment.

Conclusions. In patients with active MM, NK cells seem to show an imbalance toward inhibitory receptor expression. This may reflect altered immune regulation and could play a role in reduced immune surveillance. Further studies will be needed to understand how relevant this is from a clinical point of view.

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Myeloma and other monoclonal gammopathies

SECOND MYELOID NEOPLASMS AFTER MULTIPLE MYELOMA ARE CHARACTERIZED BY ADVERSE-RISK FEATURES: A SINGLE-CENTER CASE SERIES

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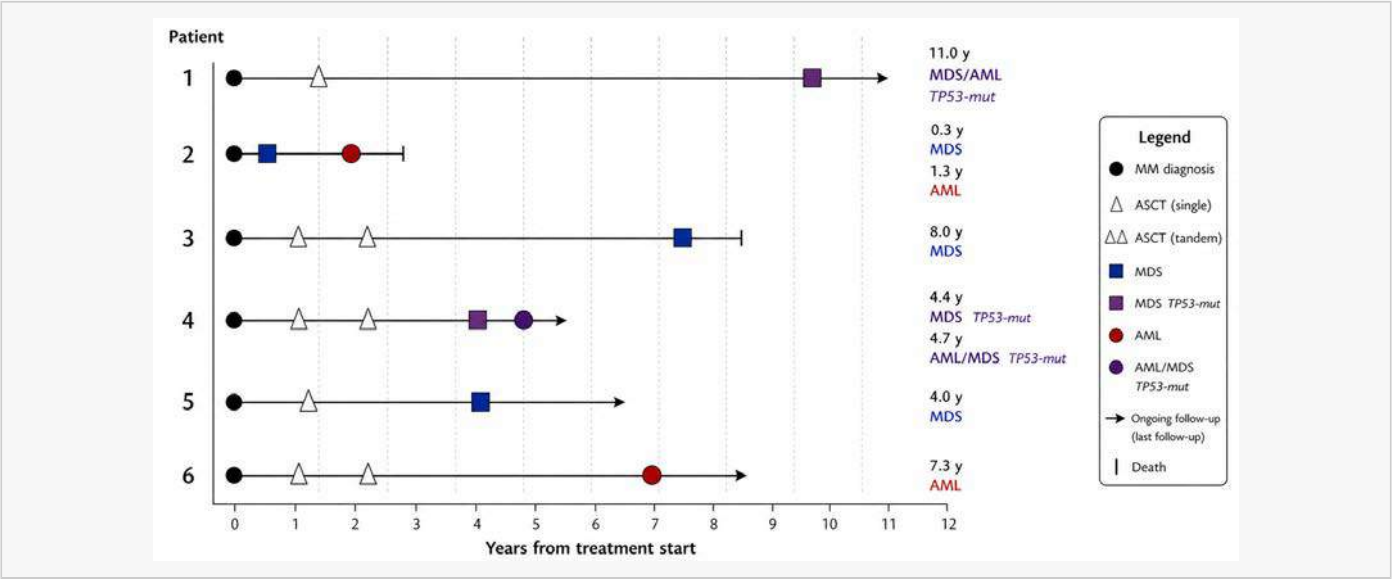
With increasing survival in multiple myeloma (MM), second myeloid neoplasms have emerged as an uncommon but clinically relevant long-term complication. Available evidence suggests that this excess risk mainly involves myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), driven by a multifactorial interplay of host susceptibility, disease biology and cumulative treatment exposure. However, real-world data integrating baseline MM features, myeloid risk classification and clinical course remain limited.We retrospectively analyzed 82 patients with MM who were considered for autologous stem cell transplantation (ASCT) or had undergone at least stem cell mobilization at our center from January 2016 to data cutoff and identified those who developed a second myeloid neoplasm. Clinical, cytogenetic and molecular features, prior MM treatments, latency, and outcomes were collected.Six patients were identified, 5 males (83.3%) and 1 female. Median age at MM diagnosis was 61 years, and median age at second myeloid neoplasm diagnosis was 68 years. Median time from MM diagnosis to second neoplasm was 5.7 years (range 0.3–11.0), with a median cumulative treatment duration of 0.7 years (IQR 0.3–1.4; range 0.3–3.2). Baseline MM FISH was abnormal in 5/6 patients (83.3%), with 1q abnormalities in 3/6 (50%), t(11;14) in 2/6 (33.3%), and del1p, t(4;14) and delTP53 in 1/6 ones (16.7%). Five patients (83.3%) developed MDS, including 1 case classified as MDS/AML with mutated TP53 and 2 progressing to AML; 1 additional patient (16.7%) developed AML without prior MDS. Among MDS cases, ICC 2022 categories were predominantly high-risk entities, including MDS-EB in 3/5 cases (60%) and TP53-mutated entities in 2/5 (40%). IPSS-R was high in 3/5 patients (60%), while IPSS-M was high in 3/5 evaluable cases (60%). Overall, AML occurred in 4/6 patients (66.7%) and was uniformly ELN 2024 adverse risk. Adverse features included complex karyotype and TP53 alterations in 2 cases, and mutations such as NRAS/ASXL1/RUNX1/WT1 in 2. Treatment exposure was substantial: all patients received proteasome inhibitor-based induction, 5/6 (83.3%) underwent ASCT, including 3 patients who underwent tandem tranpslant, and 4/6 (66.7%) received lenalidomide maintenance. Exposure to newer immune-based therapies was limited, with 1 patient treated with anti-CD38 therapy and bispecific antibodies. At last follow-up, 4 patients (66.7%) were alive.In this real-world series, second myeloid neoplasms after MM emerged as predominantly high-risk malignancies with adverse molecular features, arising after substantial treatment exposure. These findings support prolonged hematologic surveillance in MM survivors.



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Myeloma and other monoclonal gammopathies

REAL-WORLD TREATMENT PATTERNS AND CLINICAL OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH TWO TO FOUR LINES OF TREATMENT IN THE PREAMBLE REGISTRY

C. Cerchione[1], R. Vij[2], D. Cella[3], Y. -H. Shih[4], J. Fang[4], K. Gravagna[4], A. Crosbie[4], G. Hernandez-Rivera[5], J. B. Li[4], K. Ramasamy[6]

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Background. Despite numerous treatment options, patients with relapsed/refractory multiple myeloma (RRMM) continue to experience poor outcomes. Understanding unmet need is critical to improve care in earlier lines of therapy (LOTs) in RRMM patients.Aim: This study aimed to describe real-world characteristics, treatment patterns, and clinical outcomes in RRMM patients who received second-line (2L) therapy or progressed to third-line (3L) or fourth-line (4L).

Methods. This analysis included adult RRMM patients in the prospective PREAMBLE study (NCT01838512) who received 2L or progressed to 3L/4L. Patients whose 2L therapy began before country-level daratumumab (DARA), lenalidomide (LEN), and dexamethasone (DEX) (DRd) approval dates were excluded. Index date was the start date of each LOT. Descriptive statistics were used to interpret results by LOT. Kaplan–Meier methods were used for survival outcomes.

Results. Overall, 653 patients received 2L therapy, of whom 348 and 167 went on to receive 3L and 4L therapy, respectively. Median age was 71 years, and median follow-up was 25.9 months. Most 2L patients were male (57%), white (71%), and in Europe (69%). Characteristics were similar across LOTs. Prior to start of 2L, 3L, and 4L therapy, 70%, 83%, and 96% of patients were exposed to LEN, 94%, 94%, and 98% to bortezomib (BORT) and 6%, 36%, and 64% to an anti-CD38 monoclonal antibody (mAb), respectively. Prior to LOT start, 13% (2L), 31% (3L), and 43% (4L) of patients were LEN-refractory; 22% (2L), 35% (3L), and 49% (4L) of patients were BORT-refractory; and 5% (2L), 32% (3L), and 54% (4L) were DARA-refractory. For 2L patients, median progression-free survival (mPFS) was 11.3 months (95% confidence interval [CI], 10.1–13.1) and median overall survival was 67.9 months (95% CI, 53.2–not reached) (Table). Each additional LOT had increasingly worse survival outcomes. Patients who received anti-CD38 mAbs (n=39), BORT (n=521), or LEN (n=269) as part of their 1L treatments had numerically shorter 2L mPFS compared with patients who did not (anti-CD38 mAbs: 6.0 months [95% CI, 2.5–9.7] vs 12.0 months [95% CI, 10.5–14.1]; BORT: 10.8 months [95% CI, 9.2–12.6] vs 13.2 months [95% CI, 10.2–18.0]; LEN: 10.5 months [95% CI, 7.9–13.1] vs 12.0 months [95% CI, 10.2–14.3]).

Summary/Conclusions. Despite numerous options for RRMM treatment, outcomes remain poor, even in early lines. Our findings show the impact of prior therapies on treatment outcomes, with worsening survival in later LOTs underscoring the need for new treatment options.

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Table. Clinical outcomes[a]

	Patients who received LOT		
	2L (n=653)	3L[b] (n=348)	4L[c] (n=167)
PFS, months Median 95% CI	 11.3 10.1-13.1	 7.9 6.4-9.3	 3.0 2.5-4.6
OS[d], months Median 95% CI	 67.9 53.2-NR	 34.5 27.7-55.7	 19.3 12.3-28.7

[a]Deaths were not captured after patients completed the study; [b]Subset of patients who received 2L therapy progressing to 3L; [c]Subset of patients who received 3L therapy progressing to 4L; [d]OS may be inflated due to over-censoring.

2L, second line; 3L, third line; 4L, fourth line; CI, confidence interval; LOT, line of therapy; NR, not reached; OS, overall survival; PFS, progression-free survival

Myeloma and other monoclonal gammopathies

ANTI BCMA THERAPY WITH TECLISTAMAB IN AL AMYLOIDOSIS: REAL WORLD EXPERIENCE IN R/R CASES

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Background. First-line treatment of AL amyloidosis has improved with Daratumumab based regimens; Dara-VCD is the current standard first line. However, options for relapsed/refractory (R/R) disease remain limited. Preliminary results support the therapeutic activity of anti-BCMA bispecific antibodies in R/R AL Amyloidosis in the setting of monoclonal gammopathy of clinical significance (MGCS) or multiple myeloma (MM); no data are reported yet in Waldentrom Macroglobulinemia (WM). We here report our real-world experience with Teclistamab (TEC).

Methods. Retrospective analysis of R/R AL amyloidosis patients treated with TEC at our Center. Data cutoff: April 14, 2026. Hematologic and organ response was evaluated according to consensus criteria. Safety was assessed according to CTCAE.

Results. The characteristics of the 4 patients included into this analysis are summarize in Table 1. These included: MGCS (n=2), smoldering myeloma (n=1), WM (n=1). All patients received prior therapy (1–4 lines), including at least one Daratumumab based treatment. Median follow-up from the beginning of TEC was 9.5 months (range 4–16); at cutoff all patients are alive and still receiving TEC. All 4 patients achieved hematologic complete response (hCR). Median time to hCR was 48 days (26–74). Cardiac involvement was present in all patients (Cardiac Mayo Score 2004 stage I=1, II=2, IIIA=1), renal and hepatic involvement in 3 (75%) and in 1 patient, respectively and other sites (gastro-intestinal, skin, lung) in 1. Best cardiac response was observed in 2 patients at 99 (PR) and 259 days (VGPR); 1 patient had stable disease while in 1 the response was not evaluable (NT-proBNP not assessable because of concurrent hemodialisis). Best renal response occurred in 2 patients at 26 (PR) and 147 (CR) days; in 1 the response was not evaluable because of end-stage renal disease. The patient with hepatic involvement remained stable. Two patients developed grade 1–2 CRS; 1 received Tocilizumab. No ICANS occurred. Hematologic toxicity was minimal. One serious infection (Gram negative sepsis) occurred; no other significant infections were observed.

Conclusions. TEC induced rapid and deep hematologic responses and organ function improvement with a favourable safety profile in R/R AL amyloidosis. This is the first report of the use of TEC in WM related AL- amyloidosis. Early organ responses, particularly cardiac, support its potential role in this high-risk population and warrant further investigation.

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Patient	Patient # 1	Patient # 2	Patient # 3	Patient # 4
Age at treatment	59	68	71	52
Sex	Male	Female	Male	Male
Date of diagnosis	September 2022	January 2011	April 2024	March 2025
Amyloid clone and M component	SMM IgA lambda	MGCS IgA lambda + IgM lambda	MGCS IgA lambda	WM IgM lambda
Organ involvement and stage	Heart: MCS 2004 II Kidney: end stage	Heart: MCS 2004 I Kidney: stage I Gastrointestinal Lung Skin	Heart: MCS 2004 II	Heart: MCS 2004 IIIA Kidney: stage not avaible Liver
Line of previous therapy	1st line: Dara-VCD 4 cycles + 14 cycles of Dara maintenance	1st line: Vd 14 cycles 2nd line: Rd 2 cycles 3rd line: Dara 6 cycles 4th line: Pd 1 cycles	1st line: Dara-VCD 6 cycles 2nd line: Pd 2 cycles 3rd line: Rd 1 cycle	1st line: RVD 3 cycles 2nd line: RB 3 cycles 3rd line: Dara-VCD 2 cycles
Start date of TEC	01/10/2025	07/01/2025	07/22/2025	12/17/2025
Last dose of TEC	04/14/2026	04/14/2026	04/14/2026	04/14/2026
Response, TTR (days) Hematological Cardiac Renal Liver	 CR, 74 NA NA	 CR, 63 PR, 91 → VGPR, 259 PR, 63 → CR, 147	 CR, 28 SD	 CR, 26 PR, 99 PR, 26 SD

Legend to Table 1: SMM: smoldering myeloma; MGCS: monoclonal gammmopathy of clinical significance; WM: Waldenstrom Macroglobulinemia; MCS: Mayo Clinic Score; Vd: Bortezomib + dexamethasone; Rd: Lenalidomide + dexamethasone; Dara: Daratumumab; PD: Pomalidomide + dexamethasone; Dara-VCD: Daratumumab-Bortezomib + Cyclophosphamide + Dexamethasone; RVD: Rituximab + Bortezomib + Dexamethasone; RB: Rituximab + Bendamustine; TTR: time to response; CR: complete response, VGPR: very good partial response; PR: partial response; SD: stable disease; NA: not evaluable.

Myeloma and other monoclonal gammopathies

DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: REAL-WORLD EVIDENCE IN THE ERA OF NEW ANTI-CD38 QUADRUPLETS

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UOC di Ematologia, ASST Ovest Milanese

Daratumumab, lenalidomide and dexamethasone (D-Rd) is a standard frontline option for transplant-ineligible newly diagnosed multiple myeloma (NDMM) basing on the results of the MAIA trial. Real-world data are valuable not only to confirm treatment effectiveness outside the controlled setting of clinical trials, but also to better inform therapeutic decision-making in a setting of patients, in whom balancing efficacy and tolerability is crucial.We retrospectively analysed 35 transplant-ineligible NDMM patients treated with D-Rd at our center from January 2022 to March 2026. Median age at treatment start was 73 years (<70 years (n=5), 70–75 (n=14), 75–80 (n=12), >80 (n=4)); 51% were male.At a median follow-up of 29 months, the median treatment duration was 29 months, with a median of 31 administered cycles, suggesting sustained treatment exposure and good feasibility in routine clinical practice. A Very Good Partial Response (VGPR) or better was achieved in 89% of patients. Median progression-free survival (PFS) was not reached at the time of analysis. The estimated PFS rates were 94% at 12 months, 94% at 24 months, 86% at 36 months, and 72% at 48 months; although the latter estimate was based on a limited number of patients and should therefore be interpreted with caution. Treatment discontinuation for reasons other than disease progression or death occurred in 6% of cases, further supporting the tolerability of this regimen in a real-world setting. Overall, our real-world experience supports the effectiveness and feasibility of D-Rd in transplant-ineligible NDMM, with outcomes broadly consistent with those reported in the interim analysis of the MAIA trial, which was used as the main reference because of the comparable follow-up duration. Despite the limitations of the retrospective nature of the study and the small sample size, we confirm that this combination is tolerable and effective even in patients with an advanced age, namely 75 and over. In this setting, a well-established and widely adopted triplet such as D-Rd may represent an effective and clinically balanced option, potentially helping to avoid overtreatment as newer anti-CD38-based quadruplets become available. Thus, adequate patient selection remains a challenge.

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Myeloma and other monoclonal gammopathies

EFFICACY AND SAFETY OF MELPHALAN FLUFENAMIDE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS WITH SEVERE RENAL DYSFUNCTION

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Renal impairment (RI) is a frequent complication of multiple myeloma (MM), occurring in approximately 20–50% of patients and negatively affecting survival outcomes. Melphalan flufenamide (melflufen) is a peptide–drug conjugate approved in Europe for patients with relapsed/refractory MM (RRMM) who have received ≥3 prior lines of therapy. Its clinical activity has been demonstrated in the phase 2 HORIZON and phase 3 OCEAN trials. Renal impairment is defined by estimated glomerular filtration rate (eGFR) <60mL/min/1.73m^2. No dose modification is required for eGFR >45 mL/min/1.73m^2, while a reduced dose is recommended for eGFR 30–45 mL/min/1.73m^2. Limited evidence is available for patients with eGFR <30 mL/min/1.73m^2. Aim of the present study is to evaluate the efficacy and safety of melflufen in RRMM patients with severe renal impairment (eGFR <30mL/min/1.73m^2), including those requiring dialysis, in a real-world setting. We conducted a single-center observational analysis including five consecutive RRMM patients with severe RI secondary to MM treated with melflufen. Data were collected both retrospectively and prospectively. Baseline renal function was assessed by sCr and eGFR calculated using the CKD-EPI creatinine equation. Hematologic and renal responses were evaluated according to International Myeloma Working Group criteria. Three patients underwent high cut-off hemodialysis before or during treatment. Median follow-up of living patients was 8 months (CI95%: 8 – 11 months). Median time to best hematologic response was 3 months (range 1–5). The overall hematologic response rate was 40% (2 partial responses, 2 minimal responses, 1 stable disease). The renal response rate was 60%, including 2 complete and 1 partial renal responses. Two patients (40%) achieved dialysis independence after a median of 20 days. Median overall survival and progression free survival from treatment initiation was 5.2 months (CI 95%: 1.8 – 5.6 months) and 5.1 months (CI95%: 1.1 – 5.2 months), respectively. Treatment was generally well tolerated. No unexpected toxicities occurred; one patient developed grade 3 anemia, which subsequently resolved. In this small real-world cohort of RRMM patients with severe renal impairment, melflufen demonstrated clinically meaningful hematologic and renal responses with an acceptable safety profile. These findings suggest that melflufen may represent a feasible therapeutic option in this high-risk population, including patients requiring dialysis.

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Table 1. Patient's characteristics

	Entire cohort (N=5) Median (IQR) N (%)
Age, years	73 (71 -81)
Male sex	4 (80)
M protein isotype	
IgGk/ IgAλ/ IgAk / LC kappa	2 (40) / 1 (20) / 1 (20) / 1 (20)
ISS	
I / II / III	0 /4 (80) / 1(20)
Serum creatinine, mg/dL	2.38 (1.86 - 9.1)
eGFR (CDK – EPI), mL/min/1.73mq	25 (4-35)
Stage of RI	
III (moderate) / IV (severe) / V (failure)	3 (60) / 1 (20) / 2 (40)
Median time from diagnosis to melflufen, months	58 (32-180)
Median number of lines of therapy before melflufen	3 (3-10)
Previous ASCT	3 (60)

Legend: ASCT, autologous stem cell transplant; CDK-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ISS, international staging system; RI, renal insufficiency.

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Myeloma and other monoclonal gammopathies

TOCILIZUMAB PROPHYLAXIS FOR OUTPATIENT ADMINISTRATION OF BISPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

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Bispecific antibodies (BiAbs) have improved outcomes of patients (pts) with relapsed/refractory multiple myeloma (RRMM). Besides efficacy, BiAbs are burdened by toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), that require close monitoring during step up dosing. Several mitigation strategies have been implemented, such as additional prophylaxis with dexamethasone (dexa) or tocilizumab (toci).We developed an institutional program for outpatient administration of BiAbs in RRMM at Pescara Hospital. Inclusion criteria were age ≥18 years, adequate hematological (ANC ≥1000/uL; PLT ≥75000/uL; Hb ≥8.0 gr/dL) and organ function (AST/ALT ≥2.5 ULN; total bilirubin ≥1.5 ULN; creatinine clearance ≥30 mL/min); low tumor burden (bone marrow plasma cell ≥60%; absence of extramedullary disease; no rapidly progressive disease); good clinical condition (ECOG performance status ≥2 and IMWG frailty score ≥2); stay within 30 minutes away from hospital and presence of a competent caregiver at all times from step-up dose 1 (SU1) until 48 hours after administration of the first treatment dose. Pts received treatments in accordance with Summaries of Product Characteristics (SPC). Premedication with dexa 20 mg, cetirizine 10 mg and paracetamol 1 gr was given 1-3 h before each SU and first treatment dose. Additional toci 8 mg/kg was given 1-3 h before SU1. Pts and caregivers were made aware of the presenting signs and symptoms of BiAbs toxicities. A paper form was provided to monitor vital signs every 4 hours and neurological condition (ICE score) 2 times per day to ensure timely and accurate recording. Predefined alert criteria were provided to identify situations requiring sudden notification to the hematology team. Pts had direct access to day hospital for 8 hours daily, and a hematologist was available on site on a 24/7 basis.From May 2025 to February 2026, 7 pts received outpatient BiAbs (Table 1). All doses were regularly administered as per SPC. Adherence to self-monitoring was 95% for vital signs and 80% for neurological condition. During first month, 1 pts (15%) had neutropenia grade 3, whereas no hospitalizations, CRS and ICANS were reported. Overall response rate was 71% (≥VGPR 33%). All pts had IgG <400 mg/dL and received subcutaneous Ig prophylaxis. Infections occurred in 4 pts (57%; grade ≥3 0%). At last follow up, 1 pts (15%) discontinued treatment due to disease progression.

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Table 1. Characteristics of patients

Charactieristics	n=7
Age, median (range)	61 (28 – 77)
Sex, male (%)	6 (85%)
Time from diagnosis to BiAbs, months (range)	90 (26 – 264)
ECOG performance status, n (%)	
• 0	6 (85%)
• 1	1 (15%)
Charlson Comorbidity Index, median (range)	2 (0 – 5)
Prior LOT, median (range)	3 (3 – 6)
Prior ASCT, n (%)	4 (57%)
Triple-class exposed, n (%)	7 (100%)
Triple-class refractory, n (%)	2 (38%)
Penta-class exposed, n (%)	5 (71%)
Penta-class refractory, n (%)	1 (14%)
Prior anti-BCMA exposure, n (%)	2 (28%)
Relapse, symptomatic, n (%)	7 (100%)
HRCA, n (%)	5 (71%)
EMD, n (%)	0 (0%)
BiAbs administered, n (%)	
• Teclistamab	2 (28%)
• Elranatamab	1 (14%)
• Talquetamab	4 (58%)

BiAbs: bispecific antibodies; LOT: line of therapy, ASCT: autologous stem-cell transplantation; HRCA: high risk cytogenetic abnormalities, including del(17p13), t(4;14), t(14;16), abn(1q21); EMD: extramedullary disease.

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Myeloma and other monoclonal gammopathies

COEXISTENCE OF CHRONIC LYMPHOCYTIC LEUKEMIA AND MULTIPLE MYELOMA: COINCIDENTAL OR PATHOGENETICALLY LINKED?

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Background. Concurrent chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM) is extremely rare, with only isolated case reports and small series described. Both are B-cell malignancies arising at different stages of differentiation: CLL derives from mature CD5+ B lymphocytes, whereas MM originates from terminally differentiated plasma cells. In a large ERIC/HARMONY multicentre study of 19,705 CLL patients, MM occurred in 26 cases (0.13%) after CLL diagnosis, making it the third most frequent haematological second malignancy after myelodysplastic syndromes and acute myeloid leukaemia.

Patients and Methods. We report five patients with concurrent or sequential diagnosis of MM and CLL observed in two haematology centres in Rome. Clinical, haematological, and immunological features were reviewed.

Results. The cohort included four males and one female with a median age of 68 years (range 45–81). Identical light chain expression was observed in three patients (2 λ, 1 κ), discordant κ and λ expression in one, and in one case light chain expression pattern was too weak to define. CLL preceded MM in two patients, while both diagnoses were simultaneous in three. No specific clinical features of CLL were observed. One patient presented MM with extra-osseous involvement of the uvula and soft palate. One patient is under watch-and-wait management for both conditions (CLL and smouldering MM). Four patients received MM-directed therapy: one underwent autologous bone marrow transplantation, one received VMP, one started Isa-VRd, and one was treated with radiotherapy alone, achieving complete remission exceeding 35 months. Overall survival in treated patients was 33 and 57 months.

Conclusions. The clonal relationship between the two diseases remains debated. Most studies using immunoglobulin gene rearrangement analysis and anti-idiotypic antibodies suggest distinct clonal origins (biclonal disease). However, rare cases indicate a single clonal origin, supporting the hypothesis that CLL B cells may differentiate into malignant plasma cells via isotype switching. Clarification of these scenarios requires detailed molecular studies, including V(D)J sequencing and somatic hypermutation analysis. Larger case series with clonality assessment are needed to determine whether coexistence reflects a pathogenetic link or a coincidental association.

	SEX	AGE	I° DIAGNOSIS	II° DIAGNOSIS	TREATMENT	RESPONSE	OS (months)
1	M	79	CLL	MMIgG(K)	Isa-VRd	NE	NE
2	M	81	CLL(L)	SMMIgG(L)	W&W	NE	NE
3	M	45	CLL	Extraosseous plasmacytoma	RT	CR	35+
4	M	60	CLL(K)	MM(L)	VAD+ASCT	CR	33
5	F	68	CLL(L)	MMIgA(L)	VMP	PR	57

CR= Complete Response; ***Isa-VRd***= Isatuximab, Bortezomib, Lenalidomide, dexamethasone; ***NE***= Not Evaluable; ***OS***= Overall Survival; ***PR***= Partial Response; ***RT=*** Radiotherapy; ***SMM=*** Smoldering MM; ***VAD+ASCT***= Vincristine, Adriamycin, Dexamethasone plus Autologous Stem Cell Transplantation; ***VMP***= Bortezomib, Melphalan, Prednisone; ***W&W***=watch and wait.

Myeloma and other monoclonal gammopathies

ROLE OF THE COMBINATION OF 3 T WHOLE-BODY MRI AND 18F-FDG PET/CT IN THE MANAGEMENT OF MULTIPLE MYELOMA AND SMOLDERING MYELOMA

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Introduction. FDG-PET/TC and MRI are both imaging diagnostic tools adopted in diagnosis and/or response assessment in multiple myeloma (MM) which can be useful in smoldering, newly diagnosed as well in relapsed myeloma.
Methods. From January 2021 to April 2026, we enrolled into a prospective trial 159 consecutive patients (63 Male; mean age, 67 years ą 10 [SD]) divided into 3 groups; 51 newly diagnosed MM (group 1); 23 in follow-up after autologous stem cell transplantation with clinical or laboratory data suspicious for relapse or progression (group 2) and 38 relapsed/refractory MM (group 3). In addition we enrolled 47 newly diagnosed high risk SMM, according to IMWG (19 Male, mean age 59 years+-10 [SD]).
Results. On a per-patient basis, 144/159 (90%) had concordant PET/CT and WB-MRI scans, while 16/159 (10%) had discordant scans in terms of positivity/negativity. Among concordant studies, 54/159 (34%) were negative with both imaging methods while 103/159 (65%) were positive at both (including FLs and/or BMI). Among discordant studies, 14/16 had a positive WB-MRI scan and a negative PET-CT scan (6 cases with BMI or micronodular involvement alone), whereas 2/16 had a positive PET-CT and a negative WB-MRI. PET/CT detected FLs pattern in 103/159 patients, WB-MRI alone identified FLs pattern in 11 patients. The combination of the two methods led to a change of management in 99/159 (62%), highlighted in the case of suspected post-transplant relapse. Furthermore, WB-MRI led to a change of management for incidental findings in additional 9 patients (8 suspected malignancies and 1 spinal cord compression). Interim analysis in HR-SMM showed discordance between the two imaging modalities in 32/159 (21%). WB-MRI detected BMI pattern without any overt focal lesion in 14 patients (only 1 correlated with PET/CT) and FLs pattern in 9 patients (4 confirmed also in PET/CT), while PET/CT detected an additional FLs pattern in 1 patient, without bone lytic lesion evidence at the CT images.
Conclusions. Our preliminary data underline the fundamental role of functional imaging in the evaluation of FLs and BMI in MM with a superior detection rate of WB-MRI related to the ability to identify diffuse and micronodular pattern. A potential complementary role of the two methods in clinical management could be suggested in suspicion of relapsed or progressing MM. Furthermore our prospective trial supports the utmost role of WB-MRI (performed according to MY-RADS) in the assessment of high risk Smoldering Myeloma.

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Myeloma and other monoclonal gammopathies

SKY92 ACROSS MULTIPLE MYELOMA DISEASE STAGES TO IDENTIFY HIGH-RISK OF DISEASE PROGRESSION

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Background. An accurate and timely identification of high--risk (HR) disease is crucial to maximize therapeutic opportunities nowadays available for myeloma patients.
Methods. 105 consecutive patients with smoldering (SMM = 33), newly diagnosed (NDMM = 42) and relapse/refractory (RRMM = 30) myeloma were enrolled. Bone marrow samples were processed by SKY92 assay to detect HR gene expression (GE) signature and cytogenetics.
Results. Based on SKY92 quality requirements, this test was feasible in the 81.1% of SMM, 92.8% of NDMM and 80.0% of RRMM cases, showing an increased detection of HR SKY92 signature frequency from SMM (18%) toward NDMM (43.5%) and RRMM (67%, P= 0.0018). By comparing SKY92 virtual FISH with available standard FISH data we observed a high performance of t(4;14), t(14;16/20) and gain1q detection with an accuracy [95%(CI)] of 97.9 (93.9-100), 85.2 (71.8-98.6) and 87.2 (77.7-96.8) respectively, decreasing to 66.7 (49.8-83.5) for del17p suggesting that this chromosomal aberrancy can be less likely recapitulated by GE-based projections. NDMM HR SKY92 showed a worst overall survival compared to standard risk (SR, P= 0.0079), a trend maintained in RRMM with a nearly significant statistics due to the cohort sample size (P= 0.093). These results suggested that HR could share a transcriptional trademark across disease stages. This hypothesis was tested by comparing SKY92 HR NDMM and RRMM versus SR GE data showing: (i) relative risk-related clusterization by a principal component analysis (PCA) and (ii) modulation of canonical pathways frequently altered in cancer by a gene set enrichment analysis (GSEA). To test the predictivity of GE-based approaches in the asymptomatic phase we projected GE data of SMM on the PCA bi-dimensional space previously generated with NDMM and RRMM data and we observed a partial overlap based on SKY92 risk profiles across MM stages. Interestingly, a GSEA comparing SKY92 HR vs SR SMM outlined deregulated gene pathways associated with inflammation and aggressive disease. Consistently, available follow up data show a progression rate of 60% for HR SKY92 SMM compared with 0% of the SR group (P = 0.173).
Conclusions. Our findings support the use of GE-based tools for MM patient's risk profiling and HR-related cytogenetic detection. Furthermore, HR patients share transcriptional traits across asymptomatic and symptomatic phases consistent with recent findings underlying common genomic features shared by a portion of SMM with MM.

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PHASE 1/2 UMBRELLA TRIAL EVALUATING ISATUXIMAB IN COMBINATION WITH NOVEL AGENTS IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA: STUDY DESIGN TO EVALUATE ISATUXIMAB WITH DEXAMETHASONE AND BELUMOSUDIL OR EVORPACEPT

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Despite therapeutic advancements, heavily pretreated patients with relapsed/refractory MM (RRMM) continue to have a poor prognosis. Individuals with RRMM who have progressed through multiple lines of therapy require novel targeted therapies. Isatuximab (Isa) is an anti-CD38 monoclonal antibody approved in combination with other therapies for RRMM, transplant-ineligible newly diagnosed MM, and in the EU, transplant-eligible newly diagnosed MM. The ongoing multinational phase 1/2 UMBRELLA trial (NCT04643002) evaluates Isa combined with novel agents in RRMM. We present the design of 2 open and ongoing UMBRELLA sub studies evaluating belumosudil + Isa + dexamethasone (dex) and evorpacept + Isa + dex, respectively. The objectives are to determine the recommended dose of belumosudil and evorpacept in combination with Isa and dex and evaluate their clinical benefit in different settings of RRMM. The sub study with belumosudil is in dose escalation and the sub study with evorpacept is in dose optimization as of February 26, 2026.

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Myeloma and other monoclonal gammopathies

ROMIPLOSTIM SUPPORT IN MULTIPLE MYELOMA PATIENTS WITH SEVERE CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA: PRELIMINARY REAL-WORLD EXPERIENCE

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Introduction. Chemotherapy-induced thrombocytopenia (C-IT) is a major obstacle in the management of Multiple Myeloma (MM), where persistent thrombocytopenia often leads to prolonged treatment delays, compromising the Relative Dose Intensity (RDI) and overall clinical outcomes. Romiplostim, a thrombopoietin receptor agonist, may serve as an essential supportive care tool to overcome these limitations.
Methods. We analyzed preliminary data from 6 MM patients (median age 69 years, median previous lines 4, range 3-6) experiencing severe and persistent CIT. The median baseline platelet (PLT) count was critically low at 26,000/mm^3 (range: 16,000–53,000/mm^3). Romiplostim was administered weekly with a dose-escalation strategy (range: 2–10 µg/kg) based on individual response and the need to resume therapy.
Results. Upon initiation of Romiplostim, which was titrated between 2 and 10 µg/kg based on individual requirements, a rapid recovery to the critical safety threshold of ≥30,000/mm^3 was observed in a median of 2.5 weeks (range 1–3). All patients received at least 1 PLT transfusion (median 3, range 1- 14), and 5/6 patients required also red cells transfusions (median 3, range 1-16). This prompt stabilization of PLT counts facilitated the resumption of specialized hematological therapies, including Melphalan Flufenamide (N=3), and Talquetamab (N=3), in all eligible patients. Notably, peak PLT counts reached 79,000/mm^3 during support, with 3/5 patients achieved a hematological, response with stable platelets count above 30,000/mmc, despite significant baseline cytopenias. The safety profile remained favorable throughout the observation period; no thromboembolic events, treatment-related toxicities, or interference with primary disease monitoring were reported, demonstrating that Romiplostim titration is a feasible and effective strategy to safeguard dose intensity in heavily pre-treated MM patients.
Conclusions. Our preliminary experience suggests that Romiplostim is a vital resource for managing severe CIT in Multiple Myeloma. By providing a rapid recovery (median <2 weeks) to safe platelet levels, it permits the administration of life-saving therapies that would otherwise be delayed. These findings support the use of TPO-RAs as a proactive strategy to maintain dose intensity in the era of novel myelotoxic immunotherapies.

Myeloma and other monoclonal gammopathies

MULTIPLE MYELOMA WITH SPLENIC EXTRAMEDULLARY LOCALISATIONSCOMPLICATED BY PROGRESSIVE MULTIFOCAL ENCEPHALOPATHY: CLINICAL ANALYSIS AND THERAPEUTIC CHALLANGES IN A REFRACTORY PATIENT

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Multiple Myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells in the bone marrow (BM). While traditionally confined to the BM,up to 18% at diagnosis and 40% at relapse it develops extramedullary disease (EMD) with malignant plasma cells spread to soft tissues or visceral organs. Splenic involvement, nodular or diffuse, is extremely rare and is associated to profound genomic instability and poor prognosis.July 2020, a 43-year-old male was diagnosed with IgG/k MM (R-ISS II), FISH analysis showed del 17p13.1 (p53) in 95% of plasma cells.No EMD was detected with total-body CT/PET. Following VTD chemotherapy and double autoTMO, the patient achieved a stringent Complete Response and began Lenalidomide maintenance (10 mg, days 1-28) according guidelines. In July 2025, the patient relapsed with acute anemia (Hgb 6.2 g/dL), thrombocytopenia (38x10^3/µL), elevated IgG (41 g/L), elevated urine light k chains (3480 mg/L), and mild elevation of creatinine (1.53 mg/dL). Bone marrow aspiration showed 70% plasma cells infiltration (CD138++, CD38+, CD20++, CD56-, CD19-/+). FISH demonstrated monosomy 13 (89%), 1q and 1p abnormalities, del 17p and TP53 (86%), and t (13;14) (91%). CT/PET identified multiple hypermetabolic osteolytic lesions and visceral EMD, characterized by hypodense nodular formations in the spleen. Contrast-enhanced ultrasound confirmed visceral EMD, identifying 7 hypovascular areas compatible with secondaries. Salvage therapy with IsaKD regimen (Isatuximab, Carfilzomib, and Dexamethasone) was started. After three cycles, the patient achieved a Very Good Partial Response (VGPR). However, after the fifth cycle, he developed severe neurological symptoms,deep lethargy and loss of consciounsness; brain CT and cerebrospinal fluid analysis were negative for plasma cells or acute hemorrhage but a brain MRI indicated progressive multifocal leukoencephalopathy (PML). Despite splenic clearance, the disease progressed in the bones and liver. A third-line attempt withEloPd regimen (EloPd: Elotuzumab, Pomalidomide, Dexamethasone) failed as the patient developed hepato-renal syndrome and died on December 2025. EMD in MM is rare and aggressive. Splenic localizations remain rare and typically fatal. While regimens like IsaKD can provide visceral remission, they may be burdened by severe toxicities, including PML. Management remains a challenge, necessitating the validation of new strategies like CAR-T or bispecific antibodies.

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CARFILZOMIB-ASSOCIATED THROMBOTIC MICROANGIOPATHY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: THE ROLE OF A MULTIDISCIPLINARY APPROACH

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Background. The management of relapsed/refractory Multiple Myeloma (MM) in elderly patients is challenging because of cumulative toxicities related to prolonged exposure to multiple lines of therapy. Renal complications are often multifactorial and require prompt diagnostic assessment, particularly in patients receiving proteasome inhibitor-based regimens.

Case presentation. We report the case of a 76-year-old woman diagnosed with IgG-kappa MM in 2006. She received first-line treatment with VTD (Bortezomib, Thalidomide, and Dexamethasone), followed by autologous stem cell transplantation in 2012. At relapse in 2015, second-line Lenalidomide-Dexamethasone (Rd) was initiated and continued until 2022, achieving prolonged disease control. Following further progression, third-line treatment with Isatuximab, Carfilzomib, and Dexamethasone (IsaKd) was started.After 34 cycles of IsaKd, the patient achieved a Very Good Partial Response (VGPR), with hemoglobin of 11.6 g/dL and preserved renal function (creatinine 0.98 mg/dL), confirming sustained hematologic response. During treatment, grade 2 diarrhea occurred, requiring a dose reduction of Carfilzomib. Shortly thereafter, the patient developed severe gastrointestinal symptoms, oligo-anuria, and acute kidney injury (AKI). Laboratory tests revealed creatinine of 4.48 mg/dL and urea of 159 mg/dL, requiring urgent hemodialysis. Kidney biopsy demonstrated acute thrombotic microangiopathy (TMA) involving both glomeruli and arterioles, suggesting treatment-related toxicity.

Conclusions. This case highlights the complexity of managing long-term MM survivors receiving proteasome inhibitor-based regimens. Carfilzomib-associated TMA should be considered in the differential diagnosis of acute renal failure in MM patients treated with IsaKd. Early multidisciplinary collaboration between hematologists and nephrologists, together with prompt histological assessment, is essential to define the etiology of renal impairment and optimize therapeutic strategies while minimizing severe treatment-related toxicities.

Fitness, palliation, quality of life and pharmacoeconomics

RELATIONSHIP BETWEEN ORAL MUCOSITIS AND SYSTEMIC INFECTION IN AUTOLOGOUS STEM CELL TRANSPLANTS PATIENTS: EXPERIENCE OF A SINGLE CENTER

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Oral mucositis(OM),a common side effect during autologous stem cell transplants(auto SCT) procedure,is characterized by inflammation and ulceration of the oral mucosa,after conditioning high-dose chemotherapy and cause significant pain.The aim of this retrospective, single center study was to investigate the incidence of systemic infections in relation to the development of ulcerative oral mucositis in auto SCT recipients. 191 consecutive patients were transplanted between 2015 and 2026 in our single center,140 patients were diagnosed with multiple myeloma and treated with high-dose melphalan and 51 patients with non hodgkin and hodgkin lymphoma and treated with FEAM /BEAM chemotherapy followed by autoSCT.105 were male (55%) and 86 female(45%),the mean age was 58 years, with a range 18-72 years old. In our center prophylaxis policy for autoSCT is fluconazole and levofloxacine.The patients were evaluated daily with clinical visit and one times weekly oral cavity culture.We explored whether the presence of severe oral mucositis (OM) could be predictive for invasive infections (pneumonia or sepsis)during aplasia.After autoSCT, based on WHO grading score OM,patients were divided into two groups:patients that presented severe oral mucositis (ulcerative withWHO ≥2, 34 equal 18%)and 157 patients without OM((WHO = 0) or only mild,non-ulcerative OM(WHO=1) equal to 82% The oral culture test in patients with severe OM WHO ≥2 showed Streptococcus viridans (34% of total test), followed by Enterococcus faecalis (31%),Escherichia Coli(15%) Staphylococcus aureus plus haemoliticus(10%),Candida Albicans (7,5%)and Pseudomonas Aeruginosa(2.5%).In 25(78%) of 34 patients with severe OM(WHO ≥ 2)we observed a higher incidence ($p<0.01$)of pneumonia and sepsis due to those microrganisms.Therefore,we can conclude that there is a statistically significant difference in the risk of sepsis or pneumonia between patients with severe mucositis compared to those without or with mild mucositis.Ulceration of the oral mucosa leads to a breach in the natural defense barrier and provides oral microorganisms and inflammatory cytokines to entry into underlying tissues and the systemic blood.Oral mucositis could be associated with sepsis due to alteration of the oral mucosal barrier and the local microbiota Probiotics could help to reduce oral microbioma alteration and dysbiosis,further investigation could confirm this hypotesis and improve the quality of life of patients.

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Fitness, palliation, quality of life and pharmacoeconomics

IMPACT OF FRAILTY AND SARCOPENIA ON TREATMENT-RELATED TOXICITY IN ELDERLY PATIENTS WITH MULTIPLE MYELOMA AND LYMPHOPROLIFERATIVE DISEASES

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The proportion of older adults >70 years with newly diagnosed Multiple Myeloma and Lymphoproliferative diseases is projected to increase, highlighting the need to evaluate and optimize the treatment approach for older adults.A total of 22 patients were enrolled in the SALICE (Impatto della diagnosi di fragilità sulla toSsicità da terapia in pazienti Anziani affetti da tumore oncoLogIco e onCoEmatologico) study from March 2025. 15 patients were diagnosed with MM and 7 with lymphoproliferative diseases. The median age was 79 years and 59% of patients were male.At baseline, ECOG PS was 0 in 27% of patients, 1 in 50%; 2 in 18% and 4 in 1 patient (4%).The most common comorbidities were arterial hypertension (64%), diabetes mellitus (27%) and heart disease (27%).Among patients with MM, 10 received DRd, 3 Isa-VRd, 1 D-CyBorD and 1 Vel-Dex. Nine patients required a dose reduction at treatment initiation.5 patients with NHL were treated with PolaR-CHOP, 1 with R-BENDAMUSTINE and 1 case with R-COMP.Geriatric and nutritional assessments performed at the screening showed a population with marked clinical frailty. A G8 score achieved < 15 was observed in 55% of patients. Almost the entire sample showed clinically significant comorbidities, as indicated by CCI scores (91%). However, 86% of patients were still able to maintain functional independence according to the IADL score. The SPPB (Short Physical Performance Battery) revealed reduced physical performance in 82% of cases.Despite screening with MUST, a nutritional risk was found in 59% of the sample. According to the MNA, only 2 patients was malnourished.Regarding cognitive function, the Mini-Cog showed a pathological score in 23 % of patients.Finally, the assessment of treatment-related toxicity risk using the CARG score confirmed a high-risk profile.No statistically significant association was found between sarcopenia diagnosis assessed by BIA (bioimpedance analysis, 41%) and that assessed by TC/MRI at baseline (68%).The preliminaries results suggest that multidimensional assessment tools can help to identify early stage of vulnerability which is not immediately evident through the standard clinical evaluation. The analysis of subsequent timepoints (6 and 12 months) and the expansion of the sample will provide further insight into the evolution of frailty, nutritional status, and sarcopenia over time.

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Assessments Scores	N. of patients	Percentage (%)
G8		
< 15	12/22	55.00
≥ 15	10/22	45.00
IADL		
< 4	3/22	14.00
≥ 4	19/22	86.00
CCI		
< 3	2/22	9.00
≥ 3	20/22	91.00
SPPB		
< 9	18/22	82.00
≥ 9	54/22	18.00
MNA		
< 17	2/22	9.00
≥ 17	20/22	91.00
Mini-Cog		
< 3	5/22	23.00
≥ 3	17/22	77.00
CARG Toxicity		
< 6	2/22	9.00
≥ 6	20/22	91.00
CARG Risk		
< 50	5/22	23.00
≥ 50	17/22	77.00
MUST		
< 1	13/22	59.00
≥ 1	9/22	41.00

Sarcopenia	yes	no	NA
Sarcopenia BIA	9/22 (41%)	11 (50%)	2/22 (9%)
Sarcopenia TC/RM	15/22 (68%)	4/22 (18%)	3/22 (14%)

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Fitness, palliation, quality of life and pharmacoeconomics

PATIENT-REPORTED OUTCOMES AND UNMET NEEDS IN MYELOPROLIFERATIVE NEOPLASMS: A CROSS-SECTIONAL SURVEY

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This survey analyzes clinical characteristics, quality of life, and unmet needs in patients affected by myeloproliferative neoplasms (CML, MF, PV, and ET). The sample mainly includes older adults (mean age approximately 65–75 years), with a balanced gender distribution. Disease duration is highly variable, ranging from a few months to over 10 years, confirming the chronic and long-term nature of these conditions. Most patients (around 70–80%) are receiving active treatment. This reflects a model of care largely based on outpatient management, although hospital visits remain frequent.Self-perceived health is generally positive: about 60% of patients report their condition as good or acceptable, while only a minority (less than 10%) describe it as poor. Compared to the previous month, most patients report stable health, with limited cases of significant worsening. Functional limitations are present but moderate. Activities requiring physical effort - such as running or climbing stairs - are frequently impaired (reported by over 40% of patients), whereas basic daily activities (e.g., dressing, washing, eating) remain preserved in the majority (>80%). Fatigue is one of the most reported symptoms, affecting more than half of respondents, and is often associated with sleep disturbances. Psychosocial support appears underutilized. Less than 30% of patients are aware of or have used psychological services, relaxation techniques, or sexual health support. The main reasons include lack of awareness and perceived lack of necessity. The disease impacts quality of life mainly through physical limitations, emotional burden, and concerns about disease progression. Economic impact is generally mild to moderate, although approximately 20–30% of patients report increased healthcare and transportation costs.A key finding is the strong demand for home-based care: over 60% of patients express interest in services such as home blood sampling, drug delivery, or home-administered therapies. Telemedicine is well accepted, with high satisfaction rates (>70%) among users and minimal technical difficulties.In conclusion, MPN patients show relatively stable clinical conditions but experience significant unmet needs, particularly in supportive care and service accessibility. Expanding home care and improving patient education could substantially enhance overall quality of life.

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Myelodysplastic syndromes

SINGLE AND MULTIPLE TET2 MUTATIONS IN MYELOID NEOPLASMS AND PRE-LEUKEMIC CONDITIONS: PROGNOSTIC IMPACT AND CO-MUTATIONS ANALYSIS

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Background. Ten-eleven translocation 2 (TET2) is one of the most commonly mutated genes in myeloid neoplasms, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), acting as a key epigenetic regulator of DNA methylation. TET2 mutations also frequently occur in Clonal Cytopenia of Undetermined Significance (CCUS), a pre-leukemic condition. Despite its high frequency, the prognostic impact and the specific clinical phenotype of having multiple TET2 mutations (mTET2) versus a single (sTET2) are still subject to investigation.

Methods. Data from 45 diagnosed MDS, AML, CCUS (WHO 2022) seen at our center were collected. A retrospective chart review was carried out for patients harboring single or multiple mutations identified via NGS (Sophia Genetics). We collected data on hematologic parameters, bone marrow evaluation, and comorbidities (cardiovascular, renal, smoking, autoimmune). We analyzed patients with AML and MDS/AML versus MDS-CCUS. Comparisons were performed using Wilcoxon, Chi-Square or Fisher's exact tests. OS were estimated using Kaplan-Meier and log-rank tests.

Results. Forty-five TET2-mutated patients were stratified into multi-hit (mTET2, n=16, 35.6%) and single-hit (sTET2, n=29, 64.4%) groups, and according to variant clinical significance (42 significant, 3 non-significant) based on 2026 NCCN MDS guidelines. Patients aged >75 years showed a trend toward a higher likelihood of harboring TET2 variants compared with younger individuals (p=0.08). Baseline hematologic parameters (hemoglobin, neutrophils, platelets) were comparable between mTET2 and sTET2 groups. Abnormal karyotype was more frequently associated with sTET2 (p=0.05), with a similar trend observed in MDS-CCUS subgroup (p=0.07). Notably, in the AML/MDS-AML subgroup, ASXL1 co-mutation was significantly enriched in mTET2 patients (3/3 vs 1/10 in sTET2; p=0.03). No significant differences were observed between groups in terms of comorbidities. Regarding clinical outcomes, no significant difference in overall survival (OS) was observed between mTET2 and sTET2 groups (p=0.17).

Conclusions. In our cohort, mTET2 was not associated with inferior OS compared with sTET2. Notably, sTET2 mutations were more common in older patients. The enrichment of ASXL1 co-mutations in mTET2 cases within AML/MDS-AML subgroup suggests a distinct, potentially synergistic genetic trajectory underlying disease progression, warranting further investigation.

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MYELODYSPLASTIC SYNDROMES

ELRISE: A PHASE 3 STUDY OF ELRITERCEPT VS EPOETIN ALFA IN ERYTHROPOIESIS-STIMULATING AGENT-NAÏVE ADULTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES AND TRANSFUSION-DEPENDENT ANEMIA

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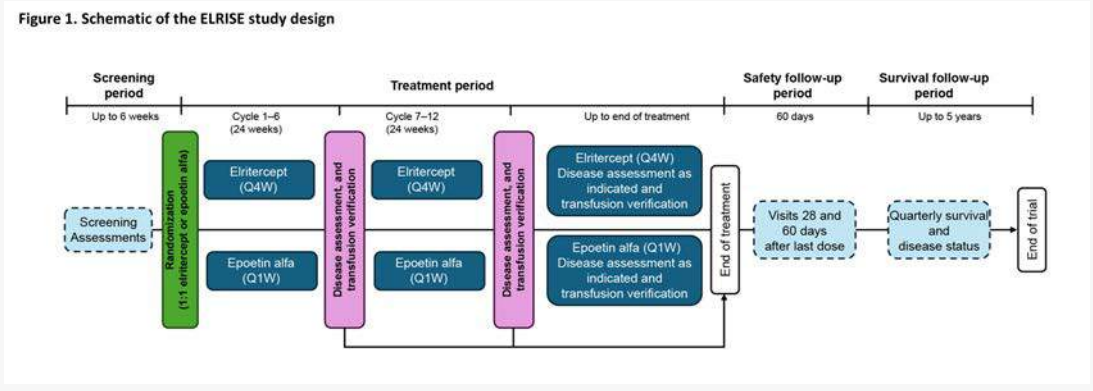
Anemia is a key clinical consequence of MDS. Long-term red blood cell (RBC) transfusions can cause iron overload and end-organ complications, reduced quality of life (QoL), and decreased survival. ESAs can lessen transfusion needs but most patients (pts) do not respond or become unresponsive. Elritercept (TAK-226), an investigational modified activin receptor type IIA ligand trap that rebalances transforming growth factor-β superfamily ligands (Activin A/B and GDF 8/11), is being evaluated in MDS; in phase 2 studies, elritercept resulted in durable transfusion independence (TI) and QoL improvements in lower-risk MDS (LR-MDS), including transfusion-dependent (TD) pts.This open-label, randomized phase 3 study will evaluate the efficacy and safety of elritercept vs epoetin alfa for the treatment of anemia in pts with LR-MDS (NCT07422480). Eligible pts are ESA-naïve (≥18 years) with anemia due to LR-MDS (per Revised International Prognostic Scoring System) and TD (≥2-6 RBC units/8 weeks [wks]), serum erythropoietin (EPO) <500 U/L (>2 wks post-transfusion), bone marrow blasts <5%, and hemoglobin (Hgb) <11.0 g/dL. Pts are randomized 1:1 to receive subcutaneous elritercept 3.75 mg/kg once every 4 wks (up-titrate to 5 mg/kg after ≥8 wks) or epoetin alfa 450 IU/kg weekly (up-titrate to 1050 IU/kg after ≥8 wks; maximum total dose 80,000 IU). Randomization is stratified by ringed-sideroblast (RS) status (RS+ vs RS-), baseline EPO (≤200 vs >200 U/L), and transfusion burden (2-3 vs 4-6 units/8 wks). RBC transfusions allowed per investigator for low Hgb. The study will enroll 210-300 pts across ~150 sites; follow-up up to 5 years.Primary endpoint is the proportion of pts achieving TI ≥12 wks from first dose through Week 24 with concurrent mean Hgb increase ≥1.5 g/dL from baseline. Key secondary/exploratory endpoints include TI and hematological improvement-erythroid at other time points, QoL (e.g., Functional Assessment of Chronic Illness Therapy-Fatigue), safety (treatment-emergent adverse events per NCI CTCAE v5.0), pharmacokinetic, and biomarker analyses.ELRISE is an actively recruiting phase 3 study evaluating elritercept for the treatment of anemia in pts with TD LR-MDS.*2026 European Hematology Association (EHA). Reused with permission. This abstract was previously accepted at the 2026 EHA Annual Meeting. All rights reserved.*



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Myelodysplastic syndromes

THERAPY-RELATED MYELOID NEOPLASMS FOLLOWING TREATMENT FOR PRIMARY HEMATOLOGICAL MALIGNANCIES: A MULTICENTER RETROSPECTIVE ANALYSIS

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Background. therapy-related myeloid neoplasms (t-MNs) are myeloid neoplasms arising after chemotherapy (CT) and/or radiotherapy (RT) for prior malignancies and usually carry poor prognosis. Treatment for hematologic malignancies also confers high risk for t-MN.This study aims to analyze clinical characteristics, risk factors, and outcomes of patients who develop t-MNs after treatment for primary hematological malignancies (pHM).

Methods. we conducted a retrospective analysis on 64 t-MN cases diagnosed at IRCCS Ospedale San Raffaele and ASST Grande Ospedale Metropolitano Niguarda (2009–2025) after pHM treatment. Data included type, cytogenetics, molecular features, treatment, and survival for both pHM and t-MN.

Results. our cohort included 43 males (67%) and 21 females (33%), with median age at t-MN diagnosis of 68 years (IQR 13 years). Median latency from pHM therapy completion to t-MN onset was 37 months (IQR 105). pHM were lymphomas (40, 62%; 31 non-Hodgkin, 9 Hodgkin), multiple myeloma and AML (8, 12% each, *figure 1A*). All but two patients received CT for pHM, often combined with RT (n=18), immunotherapy (n=37) and bone marrow transplant (BMT, n=25: 18 autologous, 7 allogeneic).CT regimens included alkylating agents (72%), anthracyclines (59%), antimetabolites (56%), vinca alkaloids (48%), topoisomerase inhibitors (30%), platinum compounds (20%), bendamustine (13%), and tyrosine kinase inhibitors (9%).At t-MN diagnosis 44 patients (72%) had MDS, 18 (25%) AML, 2 (3%) MDS/MPN; 9 MDS (14%) progressed to AML. In 7 cases, tMN were represented by donor-derived leukemia after allo-BMT.-Cytogenetics (n=61) showed complex karyotype in 18 cases (30%). NGS (n=40) revealed recurrent mutations in TP53 (30%), DNMT3A and TET2 (17.5% each), ASXL1 and RUNX1 (15% each), and SF3B1 and NRAS (10% each).High-risk t-MN occurred in 40 patients: 24 MDS (59%, IPSS-R ≥3.5), 15 AML (83%, ELN 2022 intermediate/adverse risk), and 1 MDS/MPN.Median overall survival (mOS) was 15.5 months; in high-risk patients allo-BMT improved mOS (42 vs 8 months, *figure 1B*); low risk patients had a mOS of 31 months.Multivariate analysis (TP53, complex karyotype, treatment with hypomethylating agents) showed no significant impact on survival.

Conclusions. Our findings align with prior published data. Analysis of larger cohorts might further elucidate the prognostic impact of disease characteristics on clinical outcomes. Allo-BMT remains the only potentially curative option for t-MNs.

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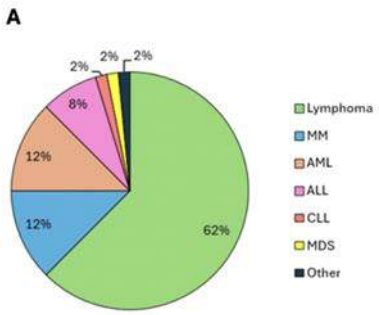

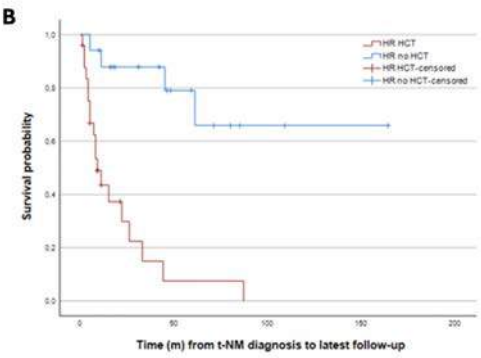

Figure 1. **A**: Distribution of patients according to type of pHM; **B**: Kaplan-Meier estimates of OS in patients with high-risk t-MN (blue line: allo-BMT recipients; red line: did not receive allo-BMT).

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Myelodysplastic syndromes

PERIPHERAL BLOOD FLOW CYTOMETRY IDENTIFIES EARLY CHANGES IN CIRCULATING ERYTHROID PRECURSORS ANTICIPATING LOSS OF RESPONSE AND LEUKEMIC EVOLUTION IN LUSPATERCEPT-TREATED MDS

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Background. Multiparametric flow cytometry (FC) is a sensitive tool for the characterization of hematopoietic compartments, although its use for erythroid maturation is mainly limited to bone marrow. In myelodysplastic syndromes (MDS), the impact of erythroid-targeted therapies such as Luspatercept on circulating erythroid precursors is still not well defined.

Methods. We performed a longitudinal FC analysis on peripheral blood samples from two patients with SF3B1-mutated MDS treated with Luspatercept. Evaluations were carried out at baseline and then approximately every three months, including hemoglobin (Hb) levels and erythroid populations such as CD45^dim/− precursors and orthochromatic erythroblasts.

Results. Both patients showed an initial Hb improvement with reduced transfusion requirements. FC analysis highlighted changes in the erythroid compartment over time, with an early expansion of circulating CD45^dim/− erythroid precursors, showing either transient or more progressive patterns. In both cases, a gradual reduction of these rare circulating cells preceded the loss of Hb response. This decrease was followed, after some time, by progression to acute myeloid leukemia. The detection of erythroid precursors in peripheral blood, which is not routinely described, suggests that FC can reveal early alterations in erythropoiesis not captured by standard laboratory parameters.

Conclusions. Peripheral blood FC may detect early changes in the erythroid compartment during Luspatercept therapy, before both loss of hematologic response and leukemic evolution. Although erythroid maturation is not routinely assessed in peripheral blood, repeated evaluation of circulating erythroid precursors may provide additional information on disease course and help anticipate clinical progression in patients with MDS.

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Myelodysplastic syndromes

MOLECULAR RESPONSE AND TREATMENT DISCONTINUATION FOLLOWING AZACYTIDINE IN VEXAS SYNDROME WITH LOW-RISK MDS

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Background. VEXAS syndrome is a recently described autoinflammatory disorder caused by somatic myeloid lineage UBA1 mutations, characterized by late-onset systemic inflammation, associated in 40-50% patients with myelodysplastic syndromes (MDS). The disease is heavily burdened by significant morbidity due to treatment refractoriness, transient response to anti-inflammation therapies and high risk of infections. Hypomethylating agents have emerged as a potential clone-directed strategy; however, data on molecular remission and treatment discontinuation remain limited.

Case description. A 67-year-old man, followed by Rheumatology for steroid-dependent relapsing polychondritis, refractory to multiple therapies (methotrexate, azathioprine), in December 2020 was admitted for fever, panniculitis-like skin lesions, periorbital oedema, subcutaneous infiltration and worsening of polychondritis. Blood tests showed macrocytic anaemia and a low IgG kappa monoclonal component. Bone marrow aspiration revealed low-risk MDS (IPSS 0, normal karyotype) with multilineage dysplasia and characteristic cytoplasmic vacuolization, suggestive of VEXAS. Sanger sequencing identified a UBA1 mutation (c.122T>C, p.Met41Thr), confirming the diagnosis.Upadacitinib (JAK1-inhibitor) plus corticosteroids was initiated in January 2021; erythropoietin was added for transfusion dependence. However, steroid tapering led to symptoms recurrence, and the patient required two hospitalisation for dyspnoea with pulmonary infiltrates.Azacytidine (AZA) was started in January 2022, with progressive clinical improvement, resolution of inflammatory manifestations, no further hospitalization, haemoglobin normalization (Fig. 1). From September 2024, AZA was given every 6 weeks. Corticosteroids were gradually reduced and discontinued in January 2025.After 33 cycles, UBA1 mutation became undetectable. After 37 cycles (May 2025), AZA was stopped. At last follow-up (December 2025), the patient remains in clinical remission with persistent molecular negativity.

Conclusions. This case supports AZA as a potential treatment for VEXAS syndrome, targeting the mutant haematopoietic clone. Prolonged treatment may eradicate the UBA1 mutation and promote a deep and durable molecular response. Further prospective studies are required for VEXAS treatment and to profile patients who would benefit most from this approach and enable safe drug discontinuation.

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Fig.1 – C-reactive protein reduction and haemoglobin improvement during AZA treatment

Legend: AZA: azacytidine; CRP: C-reactive protein; Hb: haemoglobin

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Myeloproliferative Neoplasms

THROMBOTIC BURDEN AND RISK FACTORS FOR PROGRESSION TO OVERT MYELOFIBROSIS IN PRE-FIBROTIC MYELOFIBROSIS: A MULTICENTER PROSPECTIVE COHORT STUDY

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Pre-fibrotic myelofibrosis (pre-MF) is a heterogeneous myeloproliferative neoplasm characterized by variable thrombotic risk and potential progression to overt myelofibrosis (MF). Risk stratification tools are largely derived from overt MF or essential thrombocythemia settings and may not fully capture disease-specific prognostic features in pre-MF.We conducted a multicenter prospective cohort study of 80 patients with primary or post-PV/post-ET pre-MF (WHO 2022 criteria) in 4 Italian centers. Clinical, hematologic, and molecular data were collected at diagnosis and during up to 60 months of follow-up. Outcomes included OS, TFS, MFS, thrombosis incidence, and MF progression, analyzed using Kaplan–Meier and Cox models.Median age was 62 years and 66% harbored JAK2V617F. Median follow-up was 3.36 years. Five-year OS was 96.8%. Fourteen patients (18%) had prior thrombosis and 3 events occurred during follow-up. Five-year TFS was 80.9%, reflecting both prior and incident events. IPSET significantly stratified TFS (p=0.02), with 5-year TFS rates of 100% in very low/low-risk, 90% in intermediate-risk, and 72% in high-risk patients. In multivariate analysis, spleen size independently predicted worse TFS (HR 1.2, 95% CI 1.03–1.39, p=0.017). A spleen size ≥14.5 cm (ultrasound longitudinal diameter) identified patients with significantly inferior 5-year TFS (62% vs 87%, p=0.008).Treatment strategies (hydroxyurea, peg-interferon, ruxolitinib) did not significantly impact outcomes.Eight patients (10%) progressed to overt MF. Five-year MFS was 85.8%, and IPSS was not predictive. Higher hemoglobin levels were associated with improved MFS (HR 0.62, p=0.033). A hemoglobin cut-off of 11.2 g/dL effectively stratified risk, with 5-year MFS of 54% in patients <11.2 g/dL versus 97% in those ≥11.2 g/dL (p=0.00034).Pre-MF shows favorable survival but relevant thrombotic and progression risks. IPSET remains a valid tool for thrombotic risk stratification, while spleen size emerges as an independent predictor of thrombosis. Hemoglobin ≥11.2 g/dL identifies patients at lower risk of fibrotic evolution, suggesting the need for recalibration of prognostic thresholds in pre-PMF. These findings suggest the need for disease-specific risk scores.

Myeloproliferative Neoplasms

IMPACT OF ROPEGINTERFERON AND RUXOLITINIB ON JAK2 VARIANT ALLELE FREQUENCY IN POLYCYTHEMIA VERA: A SINGLE-CENTER REAL-LIFE STUDY

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Background. Over recent decades, polycythemia vera (PV) patients have benefited from advances such as JAK2 inhibitors and interferons. The variant allele frequency (VAF) of JAK2 correlates with disease severity. Evidence shows that drugs like ruxolitinib and interferon can decrease JAK2 VAF; however, real-world data on how treatments affect JAK2 VAF and clinical response are limited, and the real prognostic value of its reduction remains uncertain.

Aims. The aim of this study was to evaluate JAK2 VAF in PV patients, using real-world data and assess its correlation with hematologic responses and treatment type.

Methods. A single-center retrospective study was performed at "Città della Salute e della Scienza" Hospital, Turin. Responses were evaluated according to Barosi G et al., Blood 2013. JAK2 V617F was quantified with the Ipsogen JAK2 MutaQuant kit. GraphPad Prism was used for statistical analysis.

Results. Ninety-two patients (56 male, 36 females; median age 58 years) were included: 19 treated with Hydroxyurea (HU) (21%), 27 with Ropeginterferon (Ropeg) (29%), 40 with Ruxolitinib (Ruxo) (43%), 3 with Ruxo+Ropeg (3%) (Table 1). Median follow-up was 10 years; median treatment duration was 2 years for HU and Ropeg, 3 for Ruxo. Complete remission (CR) rates at 12/24/36 months were 54/58/73% for Ruxo, 35/54/57% for Ropeg, and 44/33/50% for HU (Fig. 1).Mean JAK2 VAF at diagnosis was 45.4±22.9%. A significant reduction between pre and post treatment values was detected (45.1 vs 33.1, p=0.023) (Fig. 2). Median interval between tests was 44 months, with 15 months between therapy initiation and post-test. No significant changes were seen among JAK2 VAF pre and post therapy in Ropeg patients (38.8 vs 31.9, p=0.3) and HU patients, while a significant decrease of JAK2 VAF was shown among Ruxo patients (64 vs 41.7, p=0.034) (Fig. 3).When correlating post-treatment JAK2 VAF with response, 3 out of 4 Ropeg patients with no response showed VAF increase; Ruxo patients withouth VAF reduction achieved only partial response, whereas those with marked VAF decrease reached CR (Fig. 4). Median overall survival was not reached; 16 -year survival probability was 78% (Fig. 5). Myelofibrosis transformation occurred in 13 patients (14%) after a median time of 12.7 years from diagnosis.

Conclusions. Therapy influences JAK2 VAF and hematologic response in PV. Monitoring and modulating JAK2 VAF may help achieve durable remissions, improving prognosis and quality of life.

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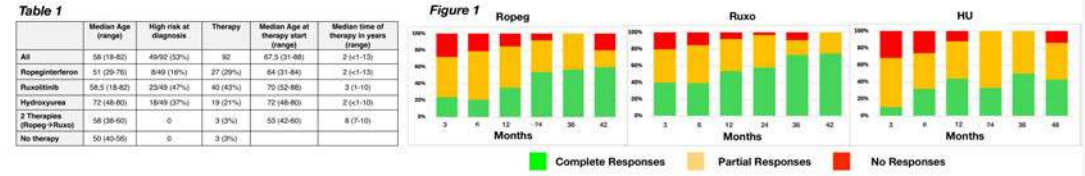
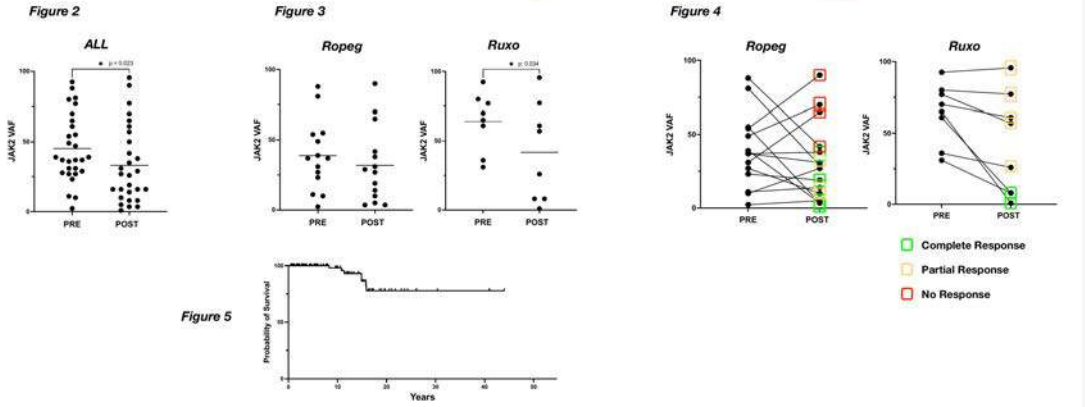
Table 1

	Median Age (range)	High risk at diagnosis	Therapy	Median Age at therapy start (range)	Median time of therapy in years (range)
All	58 (18-82)	49/92 (53%)	92	67,5 (31-88)	2 (<1-13)
Ropeginterferon	51 (29-76)	8/49 (16%)	27 (29%)	64 (31-84)	2 (<1-13)
Ruxolitinib	58,5 (18-82)	23/49 (47%)	40 (43%)	70 (52-88)	3 (1-10)
Hydroxyurea	72 (48-80)	18/49 (37%)	19 (21%)	72 (48-80)	2 (<1-10)
2 Therapies (Ropeg->Ruxo)	58 (38-60)	0	3 (3%)	53 (42-60)	8 (7-10)
No therapy	50 (40-56)	0	3 (3%)		





Myeloproliferative Neoplasms

FROM HEMATOCRIT NORMALIZATION TO BIOLOGICAL REMISSION: OUTCOMES OF ROPEGINTERFERON ALFA-2B IN POLYCYTHEMIA VERA AT AN ITALIAN TERTIARY CARE CENTER

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Background. Polycythemia vera (PV) is a chronic myeloproliferative neoplasm associated with reduced survival. Risk stratification based solely on cardiovascular risk does not incorporate biological features; reduction of JAK2V617F variant allele frequency (VAF) correlates with improved outcomes. Ropeginterferon alfa-2b (RopegIFN) is capable of inducing deep and durable hematologic and molecular responses.

Aims. To evaluate hematologic and molecular responses in a PV cohort at a tertiary care center.

Methods. Retrospective single-center study on 156 patients with PV (2017–2025); 24 (15%) were treated with RopegIFN. Diagnoses were reassessed according to WHO/ICC 2022 criteria. Response, changes in JAK2 VAF, tolerability, and reasons for discontinuation were analyzed.

Results. Median age was 49 years (23–65); median follow-up 9.2 years (0.2–17.7); median treatment duration 2.2 years (0.1–6.6). Splenomegaly was present in 54% (median 14 cm); Hb 17.6 g/dL, platelets 516×10^9/L, WBC 10.1×10^9/L; EPO was suppressed in 88%. All patients were JAK2V617F-positive (median VAF 38%, range 6.7–94.8). RopegIFN was used as first-line therapy in 57% and after hydroxyurea in 43%. Complete hematologic response (CHR) was achieved in 20/23 patients (87%), with a median time to response of 7 months (1–18), without the need for phlebotomy or additional cytoreduction. VAF progressively decreased over time: 43.5% at 12 months, 24.0% at 24 months, 17.0% at 36 months, and 10.0% at 60 months, with a mean relative reduction of 58%. A molecular response was achieved in 65% of patients (15/23), including deep responses. Toxicity was manageable; three patients (12%) permanently discontinued treatment (2 due to cutaneous toxicity, 1 due to development of Graves' disease). Four patients discontinued therapy due to reimbursement issues: among them, the duration of post-discontinuation hematologic remission was longer in molecular responders (median 10 months, range 9–11), whereas a single non-responder showed early loss of CHR.

Conclusions. RopegIFN is confirmed to be well tolerated and effective, with high CHR rates and significant VAF reduction, supporting a potential disease-modifying effect. Identification of early predictors of response/resistance may guide more personalized treatment choices, particularly in the second-line setting (RopegIFN vs ruxolitinib).

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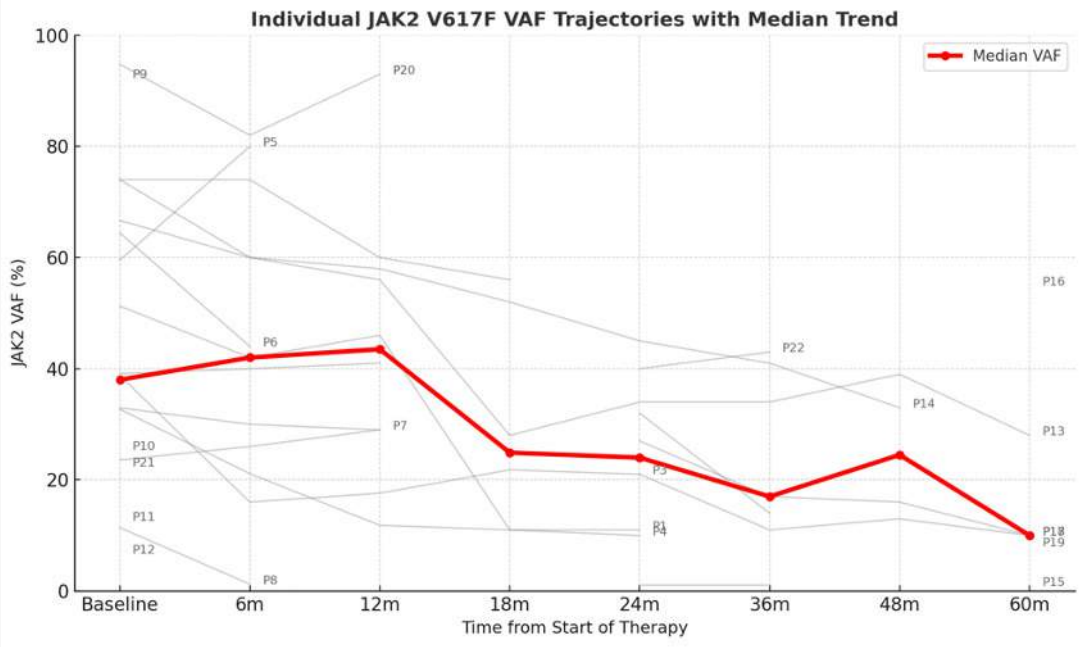
Individual JAK2 V617F VAF Trajectories with Median Trend
Median VAF
JAK2 VAF (%)
Time from Start of Therapy
Baseline
6m
12m
18m
24m
36m
48m
60m
0
20
40
60
80
100
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Myeloproliferative Neoplasms

EFFICACY AND SAFETY OF ROPEGINTERFERON ALFA-2B IN EARLY AND LOWER RISK PRIMARY AND SECONDARY MYELOFIBROSIS: A PROSPECTIVE MONOCENTRIC EXPERIENCE

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Background. Currently, no consensus exists on optimal treatment for early/lower-risk primary (PMF) or secondary (SMF) myelofibrosis (MF). Pegylated interferon-alpha is recommended for symptomatic lower-risk PMF based on phase 2 studies and expert opinion. Ropeginterferon alfa-2b (Ropeg), a next-generation pegylated interferon with favorable pharmacokinetics and superior safety profile, is EMA/FDA-approved for Polycythemia Vera.

Aims. We evaluated efficacy and safety of Ropeg in a prospective monocenter series of pts with "early/lower-risk MF" (pre-fibrotic PMF or SMF at low/intermediate-1 risk per IPSS/MySEC-PM) requiring cytoreduction. Primary endpoint: complete hematological response (CHR: Hb >10 g/dL, WBC <10x10^9/L, PLT ≤400x10^9/L) at 24 and 48 weeks. Secondary outcomes: symptom response, Neutrophil-to-Lymphocyte Ratio (NLR) trends, and adverse events (AEs).

Results. Seven pts (2 men, 5 women; median age 38.6 years) received off-label Ropeg for pre-fibrotic PMF (n=3) or SMF (n=4). Most pts (71.4%) were JAK2 V617F mutated (median VAF: 26.7%). All had normal karyotype and no High molecular risk mutations (HMR) in NGS analysis. IPSET score was low-Intermediate in 85.7% of pts. Most pts had microvascular symptoms at baseline, none had palpable splenomegaly > 5 cm. Prior cytoreductive therapies included hydroxyurea (n=5), anagrelide (n=2) or interferon alfa-2a (n=5). Of those on interferon alfa-2a, 4 pts switched to Ropeg due to a national drug shortage and one due to intolerance.Ropeg was started after a median of 24.7 months (range: 0.9-149) from diagnosis (median baseline dose: 250 mcg/month). The median value of Hb, WBC and PLT were 13.8 g/dl, 6.9 x 10^9/L and 540 x 10^9/L, respectively. Median NLR at baseline was 3.CHR was achieved in 50% of pts at 24 weeks and 100% at 48 weeks. The median NLR decreased to 1.8 at 24 weeks. Microvascular symptoms resolved in 85.7% of cases, and no progressive splenomegaly occurred. The median dosage of Ropeg overtime was reported in Figure 1.Most common AEs were transaminitis (G 1–2: n= 1) and transient neutropenia (G2: n = 1); no pts discontinued for toxicity. After a median follow-up of 35.7 months from diagnosis no leukemia evolution, thrombotic complications or second neoplasia were reported.

Conclusions. Our findings suggest that Ropeg is well-tolerated and induces favorable clinical and hematological responses in pts with early/lower-risk MF. Larger studies are warranted to validate these preliminary results.

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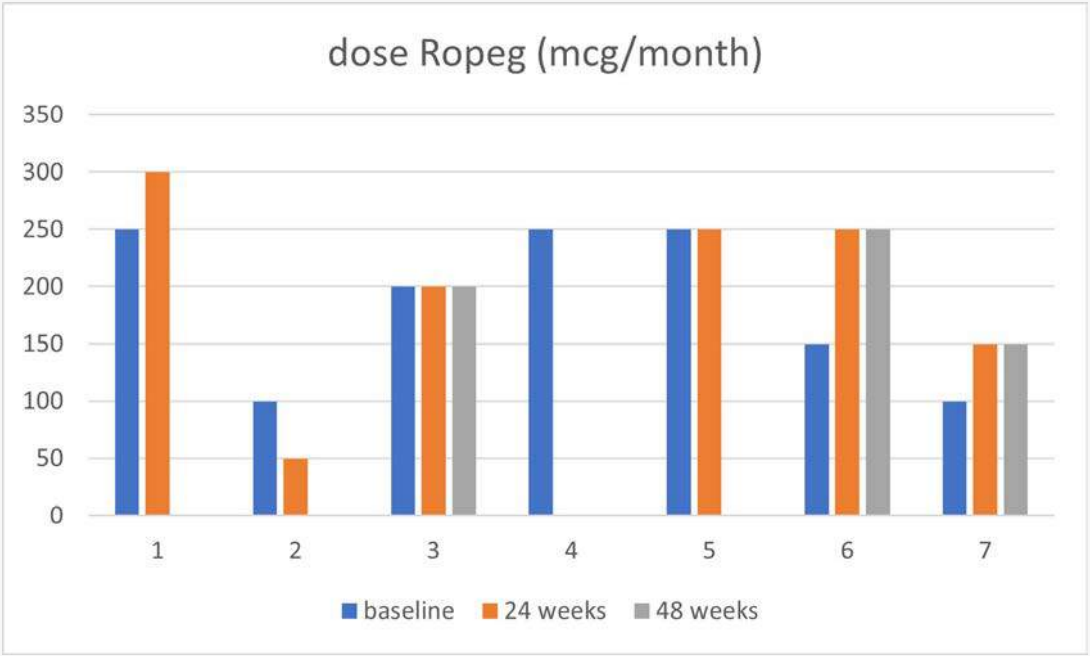

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Myeloproliferative Neoplasms

AAA^{PLUS} MODEL PREDICTS THROMBOSIS IN POLYCYTHEMIA VERA

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Background. Polycythemia Vera (PV) is a classical myeloproliferative neoplasm characterized by an increased red blood cell mass and thrombotic risk. Disease risk assessment traditionally include thrombosis history and age, and guide cytoreduction start in high-risk patients (pts) alongside phlebotomies and aspirin prophylaxis. Recently, AAA^{plus} has emerged as a promising new tool for the thrombotic risk assessment in Essential Thrombocythemia. Age (8 pts > 70, 2 pts 50-70), ANC (1 pt >8x10^9/L), ALC (1 pts <1.7x10^9/L), AMC (1 pts >0.5x10^9/L), male sex (1 pt), arterial thrombosis (1 pt) and arterial hypertension (1 pt) define the AAA^{plus} risk as ultra-low (UL, 0-1 pt), low (L, 2-4 pts), intermediate (I, 5 pts), and high (H, 6-14 pts). Aim of the study was to apply AAA^{plus} model in our PV cohort to test its range of applicability in myeloproliferative neoplasms.Methods We analyzed 104 WHO-defined PV pts diagnosed from 2009 to 2024 at the Division of Hematology of Udine. Thrombosis-free survival (TFS) was estimated from diagnosis to thrombosis using Kaplan-Meier method.

Results. Of 104 evaluable pts (62% males), median age at presentation was 59 yrs and median follow up was 9 yrs. Median hematocrit was 53% (range: 50-58), hemoglobin was 17.5 g/dl (range: 16.6-19.0), leukocyte count was 9.4 x109/L (range 7.5-11.2), and platelet count was 448 x109/L (range: 318-650). Median *JAK2* variant allele frequency was 36% (range: 18-64). Ten (11%) had previous thrombosis, 41 (46%) had symptoms, and 10 (11%) had splenomegaly, 59 (66%) had at least a cardiovascular risk factor. According to the AAA^{plus} model, 32 (36%) were at H risk, 15 (17%) at I risk, 39 (43%) at L risk, and 4 (4%) at UL risk. Overall, 11 (11%) pts had subsequent thrombosis, at a median time of 8 yrs: 7 arterials (4 TIA, 1 stroke, 1 AMI, 1 CLI), and 4 venous (3 DVT, 1 PE). AAA^{plus} risk was H in 35 (34%), I in 21 (20%), L in 42 (40%), and UL in 6 (6%) pts. TFS was statistically different among AAA^{plus} risk classes (p=0.023, Figure), with 10 yrs TFS of 100% (IC95: 100-100), 95% (IC95: 85-100), 91% (IC95: 75-100), 78% (IC95: 57-100) in UL, L, I, and H risk pts, respectively.

Conclusions. The AAA^{plus} model is a new easy and comprehensive tool that may flank the traditional thrombotic risk assessment in PV. Further studies are needed to better elucidate the clinical utility of this tool, especially for treatment decisions.

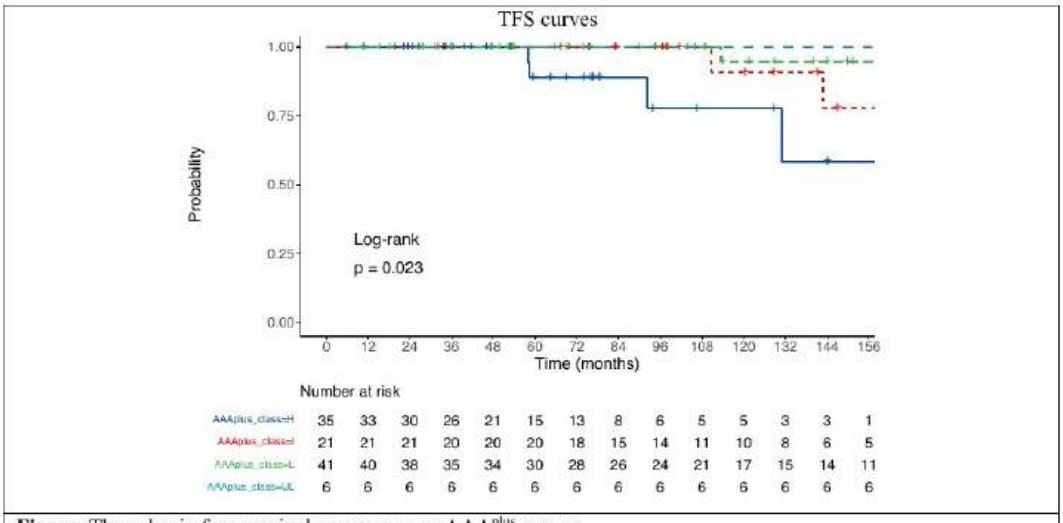

Figure. Thrombosis-free survival curves among AAA^{plus} groups.

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Myeloproliferative Neoplasms

LONG-TERM EFFICACY AND SAFETY OF MOMELOTINIB IN PATIENTS WITH MYELOFIBROSIS AND ANEMIA: A TWO-YEAR MULTICENTER REAL LIFE STUDY

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Introduction. Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by cytopenias, splenomegaly, and constitutional symptoms, with anemia often worsened by JAK inhibitors. Momelotinib, a novel JAK1/2 and ACVR1 inhibitor, has been approved for MF with anemia. In Italy, this drug has been recently introduced in clinical practice, therefore long-term follow-up of real-life studies is limited.

Methods. In this retrospective observational multicenter study, a total of 39 consecutive patients with primary or secondary MF treated with momelotinib between March 2022 and April 2026 was included. The primary endpoint was anemia response according to revised IWG-ELN criteria. Secondary endpoints included spleen reduction, improvement of constitutional symptoms, safety and OS.

Results. At baseline, median age was 71 (range 5-85) years, 16 (41%) patients were transfusion-dependent, and 84% of cases were previously exposed to ruxolitinib and 36% to fedratinib. The overall response rate (ORR) in transfusion-dependent patients was 9/16 (56%), including 6/16 (37%) major and 3/16 (19%) minor responses. Among transfusion-independent patients (n=23), ORR was 12 (46%), with 7 (30%) major and 5 (22%) minor responses. Median time to transfusion independence was 55 (range 31-360) days. At 24 weeks, a hemoglobin increase >1.5 g/dL was observed in 13 subjects (33%) and constitutional symptoms improved in 20 cases (51%). A ≥35% spleen reduction was achieved in 11 patients (28%), with a significant decrease in median spleen longitudinal diameter (p=0.0003). The median duration of treatment was 14 months (range, 2-24), and the overall response rate at 12 weeks was 67% in transfusion-dependent patients and 25% in the transfusion-independent group. At 12-week treatment, 67% of patients with transfusion dependency achieved transfusion independency. Therapy discontinuation occurred in 29% of patients, due to secondary malignancies or disease progression. Dose reduction was applied in 43% of patients. The safety profile was similar to clinical trials, with most toxicities of grade I-II. On a median follow-up of 18.1 months (range 6-26), no deaths occurred and no long-term toxicities were observed.

Discussion. These real-world data confirm long-term efficacy of momelotinib in improving anemia in MF patients, including those heavily pretreated. Moreover, momelotinib showed a good safety profile, manageable with dose reduction.

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ANEMIA RESPONSE TO MOMELOTINIB IN MYELOFIBROSIS: APPLICATION OF THE NEW 2024 IWG-ELN CRITERIA IN CLINICAL PRACTICE

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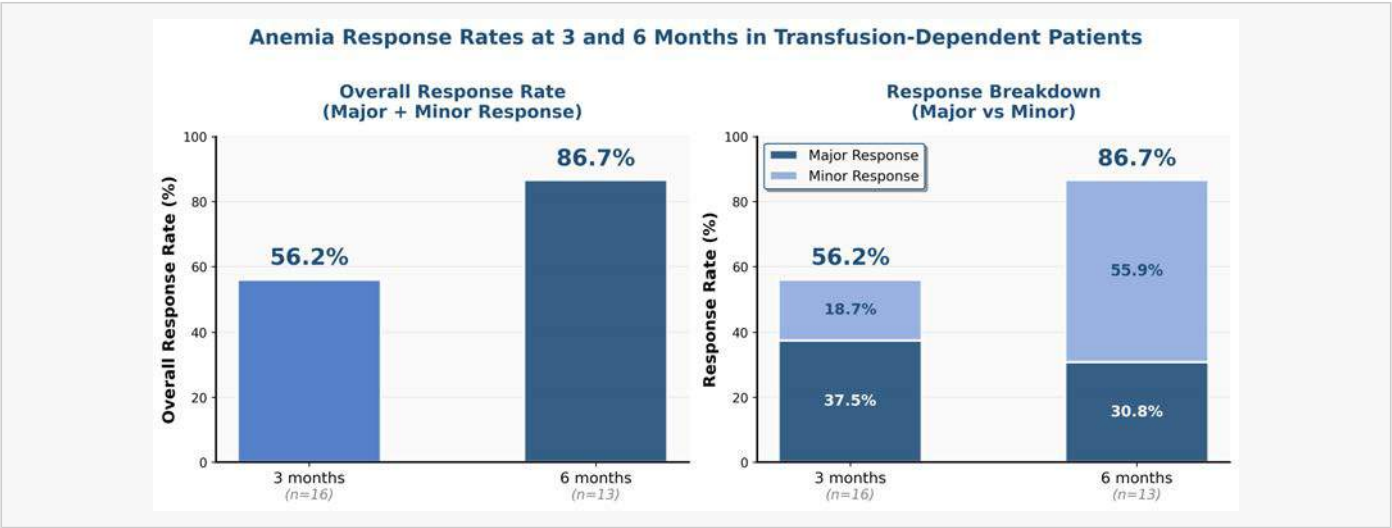
Background. Myelofibrosis (MF) treatment with JAK inhibitors (JAKi) is limited by cytopenias. Momelotinib (MMB) improves erythropoiesis via ACVR1; however, real-world data using 2024 IWG-ELN criteria for anemia response (AR) remain scarce.

Aims. Primary endpoint was to evaluate AR in a real-world cohort of MF pts (JAK-naive or JAK-pretreated) using the recently proposed 2024 IWG-ELN criteria. The secondary endpoint was to describe the safety profile of MMB treatment.

Methods. We conducted a real-world, single-center analysis of MF pts treated with MMB (08/2023-02/2026). All pts were anemic at baseline and 2 subgroups were identified based on transfusion dependence (TD) status. AR was assessed using 2024 IWG-ELN criteria at 3, 6, and 12 months. Adverse events (AEs) were graded according to CTCAE v5.0.

Results. We enrolled 29 pts (median age 76 years) with primary (15) or secondary MF (14). At MMB initiation, 83% were intermediate-2 and 14% high-risk according DIPSS score. 20 pts (69%) were JAKi-pretreated (95% ruxolitinib, Rux). Among those, 68% received Rux ≤10 mg BID before discontinuation (median duration 12.3 months). At baseline, 69% were TD and 24% had thrombocytopenia (PLT <100 $\times 10^9$/L). All pts received MMB 200 mg/day.In TD pts (Fig.1), overall response rate (ORR; major + minor) increased from 56% (3 months) to 87% (6 months), mainly via minor responses (19% to 56%) ensuring significant transfusion burden reduction. All non-TD pts maintained transfusion independence (TI): median Hb increased from 9.8 to 12.6 g/dL at 3 months and remained stable at 6 months.AR rates were similar in JAKi-naive vs pretreated pts (ORR 100% vs 88% at 6 months). Overall TI rates were 55%, 44%, and 40% at 3, 6, and 12 months. After a median follow-up of 10.7 months, 72% of pts were on treatment.Safety profile was favorable: only 7% of pts required dose reduction and 4 (14%) pts permanently discontinued for toxicity. Most common hematological AES were thrombocytopenia (n=1, G3) and paradoxical erythrocytosis (n=2, G4) requiring phlebotomy. Extra-hematological AEs (G 2-4) included infections (n=2), hepatotoxicity (n=1), rash (n=1), dizziness (n=1), and hyperamylasemia (n=1).

Conclusions. Our real word application of 2024 IWG-ELN anemia criteria show progressive ORR in TD patients and stable TI in non-TD, mirroring clinical trials. Favorable safety and low discontinuation support MMB efficacy in real-world practice; predictive factors for AR durability require further study.



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Myeloproliferative Neoplasms

A REAL-LIFE SINGLE CENTER EXPERIENCE WITH ROPEGINTERFERON-ALFA-2B IN LOW AND HIGH-RISK POLYCYTHEMIA VERA

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Ropeginterferon-alfa2b (ropegIFNα2b) is a pegylated recombinant human IFN approved for the treatment of polycythemia vera (PV). Beyond hematologic control, ropegIFNα2b has shown potential disease-modifying activity through reduction of the JAK2V617F allele burden. The aim of this study was to evaluate the efficacy, safety, and molecular response of RopegIFNα2b in a real-world cohort of PV patients. Twenty-eight patients were treated at our institution (table 1). The cohort included 15 low-risk (LR) and 13 high-risk (HR) patients. Indications for treatment were symptoms (n=3), extreme thrombocytosis (n=4), high phlebotomy requirements (n=3), participation in clinical trials (n=4), and hydroxyurea intolerance (n=14). RopegIFNα2b was used as first-line therapy in 14 out of 15 LR patients, while all HR patients were treated in second line due to hydroxyurea intolerance. Five patients (18%) discontinued treatment. Adverse events occurred in 6 patients and were all grade 1 or 2 according to CTCAE (G1 xerophthalmia, G2 hypothyroidism, G1 anemia, G1 thrombocytopenia, G2 pruritus, G2 depression). G2 pruritus and depression led to treatment discontinuation. With a median follow up of 1.6 years, a vascular event and a case of myelofibrotic evolution were observed. Among patients treated for at least 12 months, 11 out of 18 patients (61.1%) achieved a complete hematological response (CHR). All patients with baseline pruritus (n=5) experienced complete symptom resolution. In the LR group, with a median follow up of 2 years (0.7-6.9), 77.8% of patients achieved a CHR after a median time of 12.5 months. The mean maximum RopegIFNα2b dose was 125 µg every two weeks (range 100–250 µg). Among LR patients treated for more than 24 months, the median JAK2V617F allele burden decreased from 27% to 5.9%. In the HR group, with a median follow up of 1.2 years (0.5-2.1), CHR was achieved in 44.4% of patients after a mean time to response of 8 months. The mean maximum RopegIFNα2b dose was higher than in LR group, at 250 µg every two weeks (range 100–300 µg). For patients in treatment for more than 24 months, the median JAK2V617F allele burden decreased from 36% to 16%. In conclusion, RopegIFNα2b showed clinically efficacy and an acceptable safety profile in both low- and high-risk PV patients. Higher rates of complete hematological and molecular responses were observed in the low-risk patients, likely reflecting earlier use of RopegIFNα2b and longer treatment exposure.

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	N=28	LR N=15	HR N=13	p
Age, *median (IQR)*	54.2 (44.7-70.7)	47.3 (41.6-52.7)	71.6 (66.9-74.4)	<0.001
Male sex, n (%)	17 (60.7%)	7 (46.7%)	10 (76.9%)	
First line	14 (50.0%)	14 (93.3%)	0 (0.0%)	<0.001
Second line	14 (50.0%)	1 (6.7%)	13 (100.0%)	
Hb (g/dl)	13.9 (12.8-15.0)	13.7 (12.8-15.1)	13.9 (13.0-14.9)	0.75
Hct (%)	45.0 (44.0-46.0)	44.0 (41.4-46.0)	45.0 (44.0-46.0)	0.099
PLT ($x10^9$/L)	650.0 (420.0-924.0)	715.0 (558.0-995.0)	577.0 (397.0-725.0)	0.26
WBC ($x10^9$/L)	10.2 (7.8-16.3)	10.1 (8.7-15.3)	10.2 (7.1-20.0)	0.92
Splenomegaly, *n (%)*	4 (14.3%)	1 (6.7%)	3 (23.1%)	0.31
Pruritus, *n (%)*	7 (25.0%)	3 (20.0%)	4 (30.8%)	0.67
Phlebotomies/year, *median (IQR)*	3.0 (2.0-4.5)	4.0 (2.0-6.0)	2.0 (2.0-4.0)	0.20
Vascular events, *n (%)*	7 (25.0%)	0 (0.0%)	7 (53.8%)	0.001
MF evolution, n (%)	2 (7.1%)	0 (0.0%)	2 (15.4%)	0.11
Time from diagnosis, *median (IQR)*	5.3 (1.6-11.0)	4.7 (0.2-5.5)	8.6 (5.4-11.9)	0.025

Table 1. Characteristics of patients

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Myeloproliferative Neoplasms

DEEP MOLECULAR RESPONSE AND BONE MARROW REMODELING DURING ROPEGINTERFERON ALFA-2B TREATMENT IN POLYCYTHEMIA VERA: A REAL-WORLD CASE REPORT

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Background. In JAK2V617F-positive myeloproliferative neoplasms (MPNs), a phenotype-driven approach without bone marrow biopsy may lead to misclassification and suboptimal treatment. Interferon may reduce JAK2V617F allele burden, although integrated histologic and molecular data remain limited.OBJECTIVESTo illustrate the role of bone marrow biopsy in distinguishing essential thrombocythemia (ET) from polycythemia vera (PV), and to describe hematologic, molecular, and histologic dynamics during interferon treatment.

Methods. A 40-year-old man was evaluated at an outside institution in October 2022 for JAK2V617F-positive MPN with thrombocytosis (>1,000×10^9/L), leukocytosis, Hct 49%, and suppressed erythropoietin. Without bone marrow evaluation, he was managed as ET and peginterferon alfa-2a was started. At referral in January 2023, biopsy was consistent with PV according to WHO/ICC criteria. Histology showed increased cellularity (90%), trilineage proliferation, prominent erythropoiesis and granulopoiesis, and pleomorphic megakaryocytes with loose clustering. CD34+ precursors were 2%, reticulin fibrosis grade I–II, and no hemosiderin deposits were observed. JAK2V617F allele burden was 7.92% while already on peginterferon alfa-2a; karyotype was normal. CHR was defined according to ELN/IWG-MRT criteria.

Results. CHR was achieved with peginterferon alfa-2a. Treatment was switched to ropeginterferon alfa-2b, 100 mcg every 2 weeks. JAK2V617F allele burden decreased from 7.92% at referral to 1.76%, 0.25%, and 0.0236% at 12, 24, and 36 months (Fig.1). According to laboratory thresholds (>0.1% positive; 0.05–0.1% gray zone; <0.05% negative), the last value was below the positivity threshold. Repeat biopsy at 36 months showed histologic improvement, with reduced cellularity (90% to 30%), restored adipose spaces, decreased megakaryocytic atypia with loss of clustering, minimal reticulin fibrosis, and no CD34+ blast increase (Fig.2). Dose de-escalation to 100 mcg every 4 weeks was feasible, with sustained CHR, no thrombosis, and good tolerability.

Conclusions. Bone marrow biopsy was pivotal in establishing PV, enabling a disease-oriented strategy. During ropeginterferon alfa-2b treatment, deep molecular response was associated with sustained hematologic remission and marrow remodeling. These findings suggest a coordinated biological effect on clonal burden and bone marrow architecture, supporting a potential disease-modifying effect in selected patients with PV.

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Figure 1

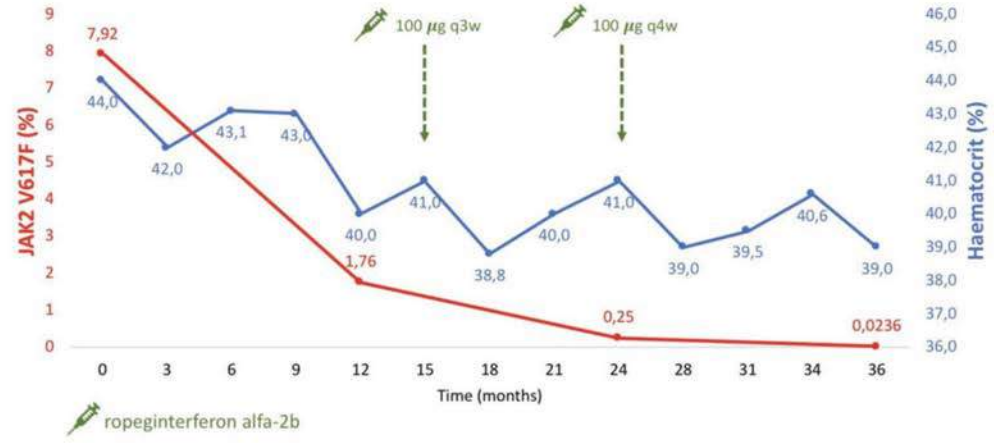
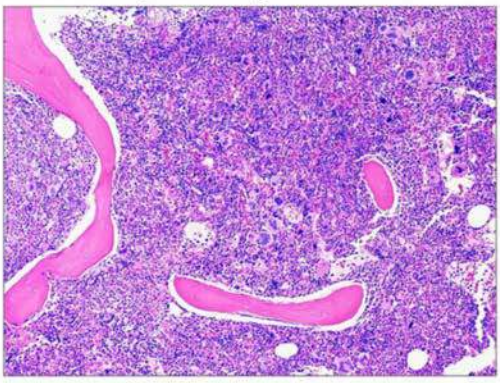
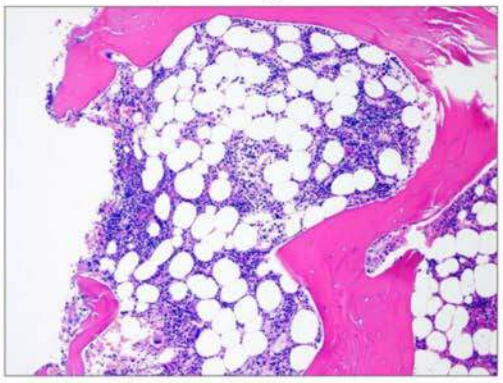


Figure 2

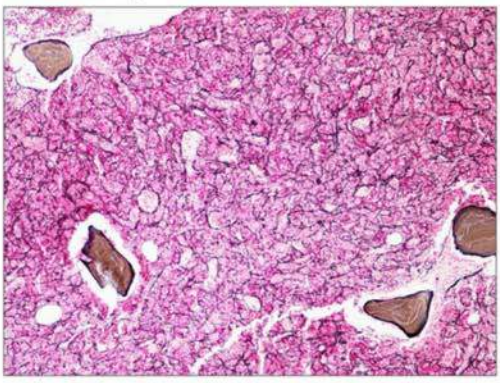
A. Baseline, hematoxylin and eosin



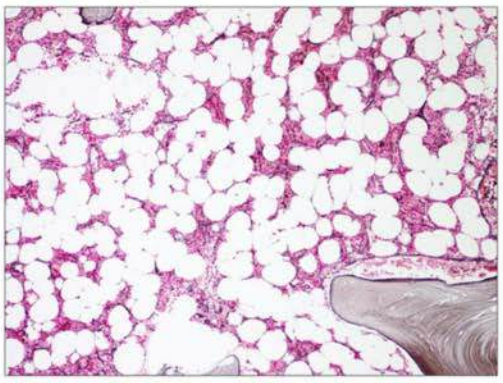
C. 36-month, hematoxylin and eosin



E. Baseline, reticulin stain



F. 36-month, reticulin stain



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Myeloproliferative Neoplasms

COEXISTENCE OF BCR::ABL1 AND CALR-MUTATED CLONES: EVIDENCE OF DUAL CLONAL ARCHITECTURE IN MYELOPROLIFERATIVE NEOPLASMS

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Background. Myeloproliferative neoplasms (MPNs) are classified into Philadelphia-positive (Ph+) and Ph-negative entities based on the presence of the BCR::ABL1 rearrangement. Although considered mutually exclusive, rare cases of co-occurrence with driver mutations of Ph-negative MPNs have been increasingly reported, defining atypical disease presentations.

Case presentation. We report an 80-year-old male with a previous diagnosis of essential thrombocythemia (ET), treated with cytoreductive therapy, referred to our Center for cytopenia. Bone marrow biopsy led to a diagnosis of secondary myelofibrosis. Molecular analysis by NGS identified a CALR type 1 variant (VAF 51%). Concurrently, RT-PCR detected the BCR::ABL1 p210 transcript, confirmed by karyotype showing t(9;22) and trisomy 6. These findings supported the concomitant diagnosis of post-ET myelofibrosis and chronic myeloid leukemia (CML).Treatment with imatinib was initiated in July 2025. At the 3-month assessment, BCR::ABL1 transcript levels decreased to 5.6% (IS), while CALR mutation persisted (VAF 47%), consistent with ongoing anemia. At 6 months, further reduction of BCR::ABL1 (4% IS) confirmed response of the Ph+ clone, with persistence of the CALR-mutated clone.

Discussion and Conclusions. This case provides evidence for the coexistence of genetically distinct Ph+ and Ph− clones within a single patient, highlighting complex clonal dynamics that may involve clonal independence, competition, or interaction. In the absence of baseline molecular data at initial ET diagnosis, a sequential clonal evolution model can be hypothesized, with an early CALR-mutated MPN followed by the subsequent acquisition of BCR::ABL1. Systematic reporting and in-depth molecular characterization of such rare cases are essential to elucidate their pathogenesis and inform therapeutic strategies.

Myeloproliferative Neoplasms

THROMBOTIC RISK IN PATIENTS WITH PRIMARY MYELOFIBROSIS: ROLE OF THE JAK2/TET2 MUTATIONS

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Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm characterized by hypercoagulability and thrombotic risk. JAK2V617F mutated endothelium releases von Willebrand factor (VWF) responsible for platelet aggregation and plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen (tPA) responsible for hypofibrinolysis. The ten-eleven translocation 2 (TET2) seems to be a key factor in driving thrombotic risk. However, its investigation is in progress. On this basis, we studied the TET2 mutation and the levels of VWF, PAI-1 and tPA in 20 patients diagnosed with PMF according to WHO/ICC criteria with mean age of 60 years (range, 45-60 years). All patients were classified according to low-risk IPSS and were JAK2V617F mutated. 8/20 were TET2 mutated. Nobody had surgery, prolonged hospitalization, central venous catheter placement, hormonal therapy or chemotherapy. Nobody had inherited thrombophilia. VWF, PAI-1 and tPA were measured by ELISA. JAK2V617F and TET2 mutations analysis was conducted by ARMS-PCR gel electrophoresis. VWF and PAI-1 levels were higher in JAK2/TET2 double positive patients than JAK2 positive patients (55±5 ng/mL and 88±5 ng/ml vs 30±2 ng/mL and 62±2 ng/ml) whereas tPA was lower in the former than in the latter (0.05 ng/ml vs 0.5 ng/ml). These findings suggest a possible association between non-driver genes and the thrombotic risk in patients with PMF. In short, more studies are needed to delineate the effect of TET2 on the pathogenesis of thrombosis.

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Allogeneic, Autologous transplant

EARLY CD34+ STEM CELL BOOST AFTER HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS AT HIGH RISK OF GRAFT FAILURE: A CASE SERIES

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Post-transplant cyclophosphamide (PTCy) is widely used as GVHD prophylaxis after haploidentical transplantation. However, it may affect donor stem cells proliferation, prolonging aplasia and increasing the risk of graft failure. CD34-selected stem cell boost is used as a salvage strategy in patients with poor graft function or delayed engraftment after transplantation.We report three patients undergoing haploidentical HSCT considered at high risk of graft failure. Donors were collected using G-CSF with a target yield as high as possible in 1 or 2 aphereses. A fraction of the product (≥ 2×10^6/kg) was infused unmanipulated at day 0, while the remaining fraction underwent CD34-positive selection using the CliniMACS system (Miltenyi Biotec) and was cryopreserved for subsequent infusion. All patients received PTCy on days +3 and +4 (total dose 100 or 80 mg/kg), followed by infusion of CD34-selected cells at least 12h after the last dose of Cy. In Table 1, we summarized patient characteristics.This strategy aimed to reduce the risk of graft failure and shorten the time to achieve a safe absolute neutrophil count.The median dose of unmanipulated CD34+ cells infused was 5.5 $\times10^6$/kg (range 5.2–5.9), compared with 7 $\times10^6$/kg (range 3.5–12) in other haploidentical HSCT performed at our center.The median dose of infused CD34-selected cells was 3.9 $\times10^6$/kg (range 3.6–4.2). Neutrophil engraftment occurred at day +14 in one patient and day +19 in two, while platelet engraftment was observed at day +28 and +34 in two patients and not reached in one.Following CD34+ boost infusion, neutrophil engraftment occurred at 8, 13, and 14 days, and platelet engraftment at 22 and 28 days in two patients, whereas one patient did not recover platelets. These results compared well with data of engraftment after regular haploidentical transplantation (median ANC 17 (range 13–30) and median platelet 28 days (range 12–58).In the 3 patients, infectious complications included ESBL-producing E. coli and K. pneumoniae bloodstream infections, E. faecalis bacteremia, pulmonary aspergillosis, and refractory EBV reactivation, leading to death in one patient at day +82.This case series suggests that early CD34 stem cell boost administered after PTCy is feasible and safe. This proactive strategy may support hematopoietic recovery in a particularly high-risk patient population.

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Allogeneic, Autologous transplant

PRELIMINARY RESULTS WITH THE USE OF TOTAL MARROW/TOTAL LYMPHOID IRRADIATION IN HEMATOLOGIC PATIENTS RECEIVING ALLOGENEIC STEM CELL TRANSPLANTATION

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Introduction. The intensity of the preparative regimen in HSCT recipients correlates with the risk of relapse, however the potential benefit may be outweighed by the associated risk of severe toxicity. The use of TMLI provides the opportunity to increase intensity with minimal additional toxicity.Aim of the study. We retrospectively evaluated the efficacy of TMLI-based conditioning regimens in hematologic patients in whom advanced age or the presence of comorbidities constituted criteria for selecting a reduced-toxicity conditioning.

Patients and methods. Between July 2023 and February 2026, 25 patients with a median age of 50 years (range 24-66) underwent HSCT with TMLI (as second transplant in 7/25). Seven patients had AML, 8 ALL, 9 lymphomas and 1 chronic myeloproliferative neoplasm. Three patients received grafts from HLA-identical related donors, 5 from matched unrelated donors, 6 from mismatched unrelated donors, and 11 from haploidentical related donors. At time of HSCT, 15 patients (60%) were in hematologic remission, whereas 10 had advanced or progressive disease. TMLI was delivered using the Tomotherapy Radixact system (Accuray, Sunnyvale, CA) at a dose of 12 Gy in 18 patients, 20 Gy in 4 patients, and 16 Gy in 1 patient, administered in two daily fractions separated by 6 hours. The median dose delivered to individual organs was significantly lower than with conventional TBI: 5.8 Gy to the lungs, 4.4 Gy to the oral cavity, 6 Gy to the heart, 4.5 Gy to the kidneys, and 5 Gy to the bowels. TMLI was administered in combination with fludarabine and melphalan at doses of 70 or 140 mg/mq.

Results. Neutrophil engraftment was achieved in 24 patients at a median of 18 days (range 13-26). Grade II-IV acute GVHD occurred in 10 patients (40%), while 6 of 18 evaluable patients (33%) developed moderate-severe chronic GVHD. Bloodstream infection was documented in 11 patients (44%) (n=7 Gram-negative; n=4 Gram-positive), 1 patient (4%) developed a candidemia, and 2 patients (8%) experienced enterocolitis. Four patients (16%) relapsed, of whom 3 died, 3 patients (12%) died due to toxicity (1 GVHD, 1 MOF, 1 pulmonary hemorrhage). With a median follow-up of 328 days (range 61-1001), 19 patients (76%) are alive.

Conclusions. Our preliminary results in high-risk patients characterized by advanced disease and second HSCT, suggest that TMLI is a conditioning strategy with limited transplant-related toxicity and effective control of the underlying disease.

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Allogeneic, Autologous transplant

ALLO-SCT WITH TREOSULFAN COMPARED WITH BU-BASED REGIMENS: RESULTS OF A MULTICENTER RETROSPECTIVE REAL-WORLD EXPERIENCE OF RETE EMATOLOGICA PUGLIESE

A. Mele[1], E. Prete[1], R. Defrancesco[1], D. Salvatore[2], E. Merla[2], I. Attolico[3], P. Carluccio[3], C. Ingrosso[4], A. Spina[5], V. Federico[6], F. Aji[1], G. Volpe[1],S. Citiso[1], Mr. Morciano[1], A. Maggi[5], P. Musto[3|7], V. Pavone[1], Am. Carella[2]

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Introduction. Treosulfan(TReo) has myeloablative and immunosuppressive properties shown lower transplant related mortality (TRM) compared to busulfan (Bu) in patients with Acute Leukemia (AL) or Myelodisplastic Syndromes (MDSs) and Myelofibrosys (MF). AIMS This retrospective analysis aimed to evaluate RW outcomes after Treo-conditioning. We compared TReo-conditioning efficacy and safety with Bu based regimens. METHODS The patients were grouped in TReo-group (n=59; TReo30-Flu150=54 and TT10-TReo30-Flu=5) and Bu-group (n=38;Bu12,8-Cy120=7,Bu8 or 12,8-Flu160:8+5,TT10-Flu150-Bu9=18). TReo was used in patients considered at increased risk for standard myeloablative conditioning (for age>=50y and/or HCT-CI>=2). Baseline allo-HSCT characteristics, engraftment and safety profiles between TReo and BU-group were compared. RESULTS Between 2020 and 2025,97 patients with >=3 months follow-up were analyzed. Patients' and transplants' characteristics were reported in table1. We observed in TReo-group a greater proportion of elderly patients (median age 67 years vs 51, p<0,001),MDSs (32% vs 13%, p<0,05) or >=3 HCT score (34% vs 5%, p<0,05). GvHD prophylaxis more frequently included ATG in TReo-group (63% vs 39%, p<0,02) vs post CY(23% vs 46%, p<0,006). No differences in terms of CR at allo-SCT, donor type, median CD34+ infused were observed. Time to neutrophyl or platelet engraftment was similar in the two groups, p 0,40. The hospital stay was 30 days (10-64) in TReo-group vs 33 in Bu(18-83),p0,58. Focusing on safety profiles, the incidence of febrile neutropenia (63% vs 86%, p<0,005) and mucosites (66% vs 89%,p<0,01) were lower in TReo-group. No differences in terms of onset acute GvHD(21% vs 34%), renal (7% vs 8%) or liver toxicity (19% vs 35%) and chronic GvHD (17% vs 15%) were observed. Moreover,the 2y cumulative incidence of relapse (30% vs 35%, p NS), 2y Overall Survival (61% vs 60%, p NS) was similar in the TReo or Bu-group. The Kaplan-Meier estimates for 1y TRM was 21% (8 patients experienced septic shock,1 aGvHD and 2 heart problems) and 19% (1 septic shock, 2 graft failure, 1 aGvHD, 1 MOF) in the TReo and Bu-group, respectively;p=0,33.

Conclusions. Despite a higher number of elderly and comorbid patients in TReo-group, the efficacy and safety of TReo was comparable with BU. We observed a lower incidence of febrile neutropenia and mucosites. Relapse incidence,OS and TRM were similar. This could suggest a potential role of TReo as "gold standard" regimen in this setting of patients.

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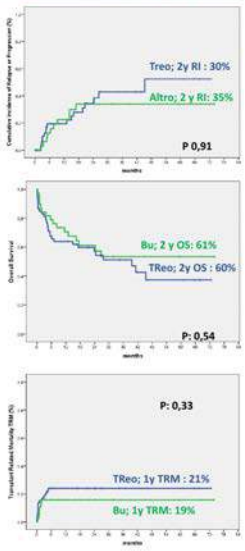
Allogeneic, Autologous transplant

Table 1: Baseline and transplant characteristics of enrolled patients

	Treo-group 59 (61)	BU-group 38 (39)	p
Male, n (%)	39 (66)	21 (55)	0,12
Median age, range > 55 years	67 (38-76) 49 (83)	51 (20-66) 15 (39)	 0,001
CR pre Allo-SCT, n (%)	55 (93)	34 (90)	0,53
Diagnosis, n (%) AL MDS MFI	 37 (63) 19 (32) 3 (5)	 31 (84) 5 (13) 1(3)	 0,05
Median prior Therapies pre TMO, (range) >1, n (%)	1 (1-3) 14 (24)	1 (0-4) 17 (45)	0,01
HCT Score, n (%) 0 >=3	 15 (25) 26 (34)	 25 (66) 2 (5)	 0,001
>=4 EBMT Score, n (%)	37 (71)	25 (68)	0,21
Donor type, n (%) Full Matched Sibling Haplo MUD MMUD	 12 (20) 8 (14) 39 (66) 76 (12)	 5 (29) 7 (18) 26 (68) 13 (34)	 0,09
PBSC Source, n (%)	56 (95)	35 (92)	0,14
Median CD34+ infused, range >6x10^6/Kg	6,2 (1,1-12,5) 31 (53)	5,78 (1,37-18,7) 18 (47)	 0,94
PT-CY prophylaxis , n (%)	13 (23)	16 (46)	0,006
ATG prophylaxis, n (%)	37 (63)	15 (39)	0,02

Figure 1: Cumulative Incidence of Relapse (RI), Overall Survival (OS) and Transplant Related Mortality (TRM) after Treo or Bu allo-SCT.



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Allogeneic, Autologous transplant

ALLOGENEIC HEMATOPOIETIC STEM-CELL TRANSPLANT IN RELAPSED/REFRACTORY MYCOSIS FUNGOIDES AND SÉZARY SYNDROME IN THE MOGAMULIZUMAB ERA: A REAL-WORLD, SINGLE-CENTER EXPERIENCE

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Mycosis fungoides(MF) and Sézary syndrome(SS) are the most common primary cutaneous T-cell lymphomas, a rare group of non-Hodgkin lymphomas. For eligible patients(pts) with SS and advanced stage MF, allogeneic hematopoietic stem cell transplant(alloHSCT) is the only potentially curative approach. We conducted a retrospective analysis of n=4 pts with MF and SS(respectively n=3 and n=1), who underwent alloHSCT at our centre between January 2020 and September 2025. Median age at diagnosis was 51.5 years(range 50-54), stages were IIA(pt.1), IVA(pt.2) and IIB(pt.3 and pt.4). Median number of therapies prior to alloHSCT was n=4(range 4-8). Three pts received the humanized anti-CCR4 antibody Mogamulizumab(Moga) and responded; in n=2 of these the response lasted at least 4 months(mo). Last therapies before alloHSCT were respectively chemotherapy(pt.1), Moga(pt.2), total skin irradiation(pt.3 and pt.4). Median time from diagnosis to alloHSCT was 59 mo(range 23-100) and only n=1 pt had progressive disease at the time of alloHSCT. Conditioning regimens included Thiotepa(total dose <10 mg/kg), Fludarabine and Cyclophosphamide and had low transplant conditioning intensity score. All pts received graft-versus-host disease(GVHD) prophylaxis with post-transplant cyclophosphamide(PTCy), a calcineurin inhibitor, and mycophenolate mofetil. No pt developed acute GVHD grade II–IV. The two pts who had haploidentical donors, both previously treated with Moga, developed severe and moderate chronic(c) GVHD, as well as major infectious complications during alloHSCT hospitalization and thereafter; infections were more severe in the pt who received Moga as bridging therapy(BT). Clinical and therapeutic features are reported in Table 1. With median follow-up of 13.5 mo(data cut-off 23/04/26), all pts were alive and in complete remission with no relapses after alloHSCT; only one(pt.1) had active cGVHD, which is currently improving from a pulmonary perspective and is presently classified as moderate. Despite the limitation of a small sample size, considering the rarity of MF/SS, our analysis supports the role of alloHSCT as the only potentially curative option, though with careful consideration of its associated toxicities. In our experience, Moga is a valid therapy for inducing remissions and can be used as a BT, however, discontinuation timing prior to alloHSCT should be closely evaluated to minimize complications.

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	Patient n.1	Patient n.2	Patient n.3	Patient n.4
Gender	Male	Male	Female	Male
Age at diagnosis (years)	50	54	51	52
Diagnosis	Micosis fungoides	Sézary syndrome	Micosis fungoides	Micosis fungoides
Stage TNMB at diagnosis	T1N2M0B0	T4NxM0B2	T3NxM0B0	T3NxM0B0
No. lines of therapy pre-alloHSCT	8	4	4	4
Chemotherapy	Yes	No	No	No
Brentuximab	Yes	No	No	No
Mogamulizumab	Yes	Yes	Yes	No
Mogamulizumab ORR4	No	Yes	Yes	/
Time from last Mogamulizumab to alloHSCT (months)	16	<1 (20 days)	4	/
Age at alloHSCT (years)	58	58	57	54
Stage at alloHSCT	T2NxM0BX*	T2NxM0B1	T1NxM0B0	T1NxM0B0
Disease status at alloHSCT	PD	PR	PR	PR
Donor type	Mismatched-related	Mismatched-related	Matched-unrelated	Matched-related
Conditioning regimen intensity**	RIC	RIC	RIC	RIC
Time of hospitalisation for alloHSCT (days)	46	154	36	30
Neutrophiles engraftment (No. of post-transplant days)	16	17	19	15
Platelets engraftment (No. of post-transplant days)	11	35	20	12
aGVHD prophylaxis	CsA-MMF-PTCy	CsA/Sirolimus-MMF-PTCy	CsA-MMF-PTCy	CsA-MMF-PTCy
aGVHD (Gluksberg grade)	I (cutaneous)	No	I (intestinal)	No
cGVHD (NIH grade)	Severe (ocular score 1, cutaneous score 2, pulmonal score 2)	Moderate (cutaneous score 2)	No	No
Infectious complications during the hospitalisation* (number)**	3	4	0	0
Infectious complications after the hospitalisation** (number)**	2	4	1	1
Disease status at last follow-up	CR	CR	CR	CR
Time from diagnosis to alloHSCT infusion (months)	100	46	72	23
Time from alloHSCT infusion to last f-up (months)	35	17	10	6

Table legend:
No.: number; alloHSCT: allogeneic Haematopoietic Stem Cell Transplant; ORR4: Mogamulizumab response lasting at least 4 months; CR: Complete Remission; PR:Partial Remission; CsA: Cyclosporine A; PTCy: Post-Transplant Cyclophosphamide; MMF: Mycophenolate Mofetil; aGVHD: acute Graft-versus-Host Disease; cGVHD: chronic Graft-versus-Host Disease.

*BX: blood cytofluorimetry not assessed.
** the conditioning regimen administrated was Thiotepa-Fludarabine-Cyclophosphamide, with Thiotepa total dose <10mg/kg.
*** Infectious complications during the hospitalisation: nosocomial pneumonia, Polyomavirus BK(BKV) haemorrhagic cystitis, Cytomegalovirus(CMV) reactivation for patient(pt) n.1; neurotoxoplasmosis, BKV haemorrhagic cystitis, Human Herpesvirus 6(HHV6) reactivation, Epstein-Barr virus(EBV) reactivation requiring Rituximab administration for pt. n.2.
**** Infectious complications after the hospitalisation: CMV reactivation and Clostridium Difficile colitis for pt.1; CMV colitis, Salmonella group C gastroenteritis, nosocomial pneumonia, Staphylococcus haemolyticus and Gordonia bacteraemia for pt.2; EBV reactivation requiring Rituximab administration for pt.3; BKV reactivation for pt.4.

Disease staging and responses were assessed according to internationally acknowledged recommendations.

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Allogeneic, Autologous transplant

HYPOMETHYLATING AGENTS–VENETOCLAX BEFORE HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA: A SINGLE CENTER REAL-WORLD EXPERIENCE

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Hypomethylating agents (HMA) combined with venetoclax are increasingly used in acute myeloid leukemia (AML) to induce remission before allogeneic hematopoietic stem-cell transplantation (HSCT).We conducted a retrospective analysis of 21 patients with AML who were treated between 2019 and 2026 with HMA plus venetoclax prior to HSCT at the Transplant Unit of “La Maddalena” in Palermo. The treatment was administered either as first-line therapy in patients ineligible for high-dose chemotherapy (n=9) or in patients who had relapsed after prior treatment (n=13).Baseline characteristics included age, sex, ELN 2022 risk, venetoclax dose, and number of cycles: median age was 62 years, 13 patients are males and 8 females. AML was de novo in 17 patients, secondary in 4 (myelodysplastic syndrome and therapy-related). ELN 2022 risk was favorable in 7, intermediate in 4, adverse in 6 and not classifiable in 4. Azacitidine was used in 18 patients and decitabine in 3; median cycles were 3.Outcomes included hematologic response and MRD status at HSCT, day +90 response, gastrointestinal toxicity according to CTCAE and GVHD. Correlation analysis was compared using Fisher’s exact, Mann–Whitney and Spearman tests.At HSTC 16/21 patients (76.2%) were in CR, MRD was available in 13 patients and was negative in 6/13 (46.2%). At day +90 15 patients were in CR (93.3%). Gastrointestinal toxicity occurred in 17 patients, grade 1 in 2, grade 2 in 6, and grade 3 in 9. GVHD occurred in 3/17 (17.6%). Relapse after HSCT occurred in 4 patients and death in 7.Comparing the two groups (patients who received first-line treatment and those who received subsequent-line treatment), the second ones were younger (55 vs 65 years; p=0.010), received fewer cycles (2 vs 4.5; p=0.011) and were all de novo AML. No significant differences were observed in CR at HSCT (77.8% vs 75.0%), MRD negativity among MRD-evaluable patients (50.0% vs 42.9%), grade ≥3 gastrointestinal toxicity (37.5% vs 66.7%; p=0.347), GVHD (12.5% vs 22.2%) or day +90 CR (100% vs 83.3%). Cycles number were not significantly associated with gastrointestinal toxicity, MRD negativity, GVHD or day +90 response, but correlated with CR at HSCT (p=0.029).In this real-world cohort, HMA–venetoclax before allogeneic HSCT was associated with a high rate of RC and encouraging post-transplant outcome. Larger prospective studies are needed to define the optimal number of cycles and the role of this combination strategy.

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Allogeneic, Autologous transplant

IN VIVO MONITORING OF CAR-T CELL THERAPY: THE ROLE OF MULTIPARAMETRIC FLOW CYTOMETRY IN LYMPHOCYTE EXPANSION ANALYSIS

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Chimeric Antigen Receptor (CAR) T-cell therapy represents a revolutionary immunotherapy for hematological malignancies. In vivo kinetic profile of CAR-T cells, specifically their expansion and persistence within the patient's system is a critical factor for clinical success.This study evaluates the role of multiparametric flow cytometry as a tool for the real-time monitoring of CAR-T cell populations. The study focuses on quantifying expansion phases and identifying specific CAR-T cellular phenotypes that correlate with therapeutic efficacy and potential toxicities (such as CRS and ICANS).This research analyzed 18 patients with different hematological malignancies undergoing CAR-T therapy with five different commercial products (Tisa-cel, Ide-cel, Brexu-cel, Axi-cel, and Liso-cel), focusing on real-time expansion monitoring through flow cytometry.The results confirm a three-phase CAR-T expansion kinetic profile with peak on the eighth day, mainly determined by CD8+ effector and central memory subsets, suggesting a crucial role in long-term CAR-T persistence and therapeutic durability. While early expansion may contribute to ICANS development, long-term CAR-T persistence does not appear to influence its onset. Regarding clinical efficacy, outcomes are more closely linked to sustained expansion and cellular persistence rather than the initial proliferative peak.In vivo monitoring is essential for understanding CAR-T cell kinetics and predicting their efficacy, opening the way to personalized therapies and optimized clinical management through advanced predictive algorithms.

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CONGRESSO NAZIONALE SIE

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MAIN PROGRAM

VACCINATION STRATEGIES IN HEMATOLOGIC MALIGNANCY PATIENTS UNDEGOING IMMUNOTHERAPY: TIMING, EFFICACY AND COMPLIANCE

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Background. Patients with hematological malignancies (HMs) receiving modern immunotherapies - including monoclonal antibodies (MoAbs), CAR-T cell therapy, immune checkpoint inhibitors (ICIs), and bispecific antibodies (BsAbs) - are at high risk for severe infectious complications from influenza, Streptococcus pneumoniae, SARS-CoV-2, Herpes Zoster Virus (HZV), and Respiratory Syncytial Virus (RSV). Establishing effective vaccination timing and strategies is critical to reducing morbidity and mortality.

Methods. Current international consensus guidelines (NCCN, ECIL, ASCO, AGIHO) emphasize pre-treatment immunization whenever feasible. In patients treated with anti-B-cell MoAbs or BsAbs, humoral antibody responses are markedly blunted for at least 6 months. Nevertheless, early administration (≥2 weeks prior to therapy onset or 3-6 months post-treatment in responders) helps maximize baseline immunity. Recombinant or high-dose seasonal influenza vaccines, PCV20 or PCV15-PPSV23 pneumococcal schedules, mRNA SARS-CoV-2 boosters, and Recombinant Zoster Vaccine (RZV) are strongly recommended. Less data are currently available for RSV vaccine, which is however recommended. In CAR-T cell recipients, despite low humoral seroconversion rates (~13%), T-cell-mediated immune responses remain remarkably robust (87–88%). Pre-CAR-T optimization and structured revaccination starting 3-6 months post-infusion effectively leverage this preserved cellular protection. In patients receiving ICIs, seasonal influenza and SARS-CoV-2 vaccines demonstrate favorable safety profiles and may exert a synergistic anti-tumor sensitizing effect through type I interferon induction and CD8+ T-cell activation, yielding tangible survival benefits.

Conclusion and practice implications. Vaccinations against influenza, Streptococcus pneumoniae, SARS-CoV-2, HZV, and RSV are recommended in HM patients. However, real-world vaccine compliance remains suboptimal. Establishing dedicated "in-hospital" vaccination delivery models is a proven strategy to eliminate logistical barriers, increase coverage, preserve cellular immunity, and improve overall survival.

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MINIMAL RESIDUAL DISEASE IN ACUTE MYELOID LEUKEMIA: INSTRUCTIONS FOR USE

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Measurable residual disease (MRD) quantifies leukemic cells detected at levels below conventional morphologic evaluation.[1] It has become a cornerstone of acute myeloid leukemia (AML) therapeutic algorithms, transitioning from research to routine clinical practice. Regardless of the methodology, systematic reviews confirm that MRD positivity at any treatment stage is an independent prognostic factor for relapse and survival; conversely, durable negativity signals excellent outcomes, enabling treatment de-escalation in selected cases.[2,3] MRD assessment relies on multiparameter flow cytometry (MFC) and molecular techniques. MFC applies to most patients by tracking abnormal phenotypes, but is operator-dependent with a 10^{-3}–10^{-4} sensitivity. Conversely, molecular assays (qPCR, ddPCR) offer higher sensitivity (10^{-5}–10^{-6}) for specific subsets (e.g., NPM1-mutated, CBF AML). NGS-based assays capture a broader mutational landscape, but require the exclusion of age-related clonal hematopoiesis variants (DNMT3A, TET2, ASXL1), which cannot serve as stand-alone markers.[4] The ELN MRD Working Party defined assessment timepoints, thresholds, and cross-technique interpretations. [1,4,5] The recent 2025 ELN--DAVID update provides 56 recommendations across clinical, MFC and molecular domains, reinforcing MRD as a dynamic tool aligned with ELN 2022 AML risk classification,[6] rather than a fixed diagnostic label.[4] The seven key update recommendations are reported in Table 1. Clinically, MRD assessment guides pre-transplant risk stratification, conditioning intensity selection, and post-transplant maintenance. Pre-transplant positivity does not contraindicate allogeneic transplantation; myeloablative conditioning should be considered if MRD is detectable. FLT3 inhibitor maintenance showed efficacy based on MRD status.[7,8] Robust evidence is lacking to guide treatment discontinuation based on MRD status in non-intensive regimens.[4,9] Beyond direct clinical applications, MRD is emerging as a trial surrogate endpoint to accelerate novel therapy approvals.[10] Table 2 summarizes intensive chemotherapy applications. Open challenges include assay standardization and biological differentiation from clonal hematopoiesis. Key clinical issues involve interpreting low-level positivity, resolving inter-technology discordance, incorporating leukemic stem cell markers, defining optimal testing schedules, and translating MRD data into tailored therapeutic decisions.

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Table 1. The seven key updates of the 2025 ELN-DAVID MRD recommendations

	Update
1	MRD guidance tailored to each genetic subgroup (ELN 2022 risk classification)
2	MRD burden is categorized as negative, low-level positive (MRD-LL), or positive
3	A qualitative MRD response category has been newly introduced: optimal, warning and high risk of treatment failure
4	The updated tables provide distinct MRD percentage cutoffs for each assay and target
5	Post-alloHSCT monitoring: MFC for 12 months, qPCR/UHS-NGS for 24 months
6	Lower MRD cutoffs have been introduced for NPM1-mutated AML with specific distinctions between PB and BM
7	UHS-NGS for *FLT3-ITD* MRD recommended after 2 chemotherapy cycles and prior to alloHSCT. Testing at EOT and during follow-up is suggested

MRD: measurable residual disease
allo HSCT: allogeneic hematopoietic stem cell transplantation
MFC: multiparameter flow cytometry
qPCR: quantitative Polymerase Chain Reaction
UHS-NGS: Ultra-High Sensitivity Next-Generation Sequencing
EOT: end of treatment

Table 2. Current clinical application of MRD in the context of intensive chemotherapy for AML

Indication/Clinical Phase	Frontline Treatment	Monitoring in remission	Pre and post-transplant setting
Primary Objectives	Prognostic assessment Evaluation of treatment response	Detection of molecular-level recurrence	Prognostication
Therapeutic modifications	• Treatment intensification or de-escalation • Pre-transplant MRD to guide allogeneic transplantation	Early intervention prior to clinical relapse (to optimize efficacy and minimize toxicities)	Inform transplant management: • to guide conditioning intensity • to guide pre-transplant intervention • to guide modulation of immunosuppression • to guide implementation of pre-emptive therapy (e.g.donor lymphocyte infusion, hypomethylating agents)
Trials	Surrogate endpoint for survival in clinical trials		
Maintenance			Patient selection for maintenance therapy

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NON-REPLACEMENT TREATMENT FOR HEMOPHILIA: RATIONALE, INDICATIONS, AND TREATMENT MANAGEMENT

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Over the last decade, the development of new biologic agents able to restore thrombin generation or mimicking the action of FVIII has become the focus of innovation in hemophilia management. Emicizumab, a humanized anti-FIXa/FX bispecific antibody mimicking FVIIIa function administered subcutaneously once every 1, 2 or 4 weeks, has revolutionized the treatment of patients with hemophilia (PWH) A, with or without inhibitors, providing for the first time an effective, noninvasive prophylaxis also for patients with inhibitors [1]. Furthermore, treatments which modulate anticoagulant pathways thus rebalancing thrombin potential (AT-lowering fitusiran, anti-tissue factor pathway inhibitor antibodies concizumab or marstacimab) have been also developed and recently approved for clinical practice [2]. Emicizumab is now widely available and the real-world results have substantially confirmed its efficacy and safety. However, PWH with inhibitors treated with activated prothrombin complex concentrates (aPCC) for ≥ 24 hours at dose exceeding 100 U/kg/24 hours for breakthrough bleeding may develop venous thrombosis or thrombotic microangiopathy due to its synergic effect in enhancing thrombin generation [3]. Thus, rFVIIa or lower dose of aPCC for breakthrough bleeds or during surgery is now recommended [4]. In patients without inhibitors dosing of FVIII concentrates for bleeds or surgery does not differ significantly compared to those not on emicizumab prophylaxis because emicizumab has a 5-10--fold lower affinity for FIXa/FX compared to FVIII [1,5,6]. The small interfering RNA (siRNA) Fitusiran suppresses the hepatic synthesis of AT [2]. It binds and degrades AT mRNA in hepatocytes, leading to the silencing of the AT gene expression and the prevention of AT synthesis. The reduction of AT levels leads to increased availability of thrombin, FXa and FIXa. Thrombotic events have been reported when AT levels drop below 15 % and thus dose modifications and prologed intervals between (even after 1 or more months) are now recommended. Guidelines for bleeding management suggest reduced doses of FVIII, FIX, aPCC and rFVIIa specified (10 IU/kg, 20 IU/kg, 30 IU/kg, and ≤45 µg/kg, respectively) [7]. Tissue Factor Pathway Inhibitor (TFPI) inhibition has been targeted as an alternative mode to induce thrombin generation (TG) by using the anti-TFPI humanized recombinant antibodies concizumab or marstacimab [2]. TFPI is a multivalent Kunitz-type serine protease inhibitor and consists of three domains with different roles. Domain 1 binds to TF-FVIIa complex, domain 2 binds to FXa while domain 3 interacts with PS. Concizumab is administered sc every day at 0.20 mg/kg after a loading dose of 1mg/kg. After 4 weeks conczumab concentration is checked to adjust the dose within a specific range to avoid the risk of thrombosis. In case of planned major surgery, concizumab pausing is recommended starting 4 days before, followed by standard perioperative management (8). Minor surgery on concizumab does not require treatment stop, while for major surgery in emergency stopping the treatment and starting replacement treatment at lower dose would probably be safe. The same approach is used for marstacimab which is administered sc once a week (150 mg, after a loading dose of 300 mg), although data regarding the management of bleeding and surgery are to date scarce.

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ANTICOAGULANT THERAPY FOR VENOUS THROMBOEMBOLISM IN 2026: DRUGS AND STRATEGIES

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Venous thromboembolism (VTE) treatment in 2026 combines established standard with individualized long-term strategies. Guidelines recommend direct oral anticoagulants (DOACs) for most DVT or pulmonary embolism for at least 3 months [1]. COBRRA showed less clinically relevant bleeding with apixaban than rivaroxaban, with similar efficacy [2]. LMWH is preferred during pregnancy; severe renal impairment or major drug interactions may favor LMWH or vitamin K antagonists (VKAs); VKAs remain required for mechanical heart valves. Antiphospholipid syndrome (APS) requires a nuanced approach. DOACs should be avoided in triple-positive and arterial APS, but may be considered in selected venous, single/double-positive APS [3]. After arterial events, the superiority of VKAs over antiplatelet strategies is uncertain; network meta-analysis suggests benefit from VKA plus antiplatelet therapy and a possible role for dual antiplatelet therapy [4]. Extended anticoagulation is recommended after unprovoked/recurrent VTE or persistent risk factors. Reduced-dose apixaban or rivaroxaban are established options. A 2026 meta-analysis of 5 RCTs (8,781 patients) found similar recurrence but less major/clinically relevant non-major bleeding with reduced versus full-dose DOACs [5]. The provoked/unprovoked dichotomy is now considered insufficient. Recurrence is low after surgery but may be relevant after intermediate/minor transient factors, including pregnancy/puerperium, estrogens, trauma, immobilization, or long-distance travel. Here, thrombophilia testing may refine extended-treatment decisions, with major thrombophilia and a strong family history carrying greatest weight [6]. Which high-risk patients can safely receive low-dose DOACs remains uncertain. RENOVE did not formally establish non-inferiority versus full-dose treatment, although bleeding was reduced [7]. Conversely, API-CAT established reduced-dose apixaban as non-inferior and safer in cancer-associated VTE [8]. Emerging evidence supports low-dose DOACs in splanchnic vein thrombosis, whereas evidence remains insufficient in major thrombophilia and cerebral venous thrombosis [9]. Finally, HI-PRO showed that patients with transiently provoked VTE plus enduring risk factors had fewer recurrences with apixaban 2.5 mg bid than placebo [10]. These findings support a recurrence-risk continuum and individualized drug, dose, and duration. FXI/FXIa inhibitors are promising, but their role in established VTE remains investigational.

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Table 1. Reduced-dose DOACs: evidence for extended treatment
Bid: bis in die; CRNMB: clinically relevant non-major bleeding; DOACs: direct oral anticoagulants; RCT: randomized clinical trial; SVT: splancnic venous thrombosis; VTE: venous thromboembolism.

Population / study	Comparison	Main finding
Extended VTE – meta-analysis 2026 [5]	Reduced vs full-dose DOACs	5 RCTs, 8,781 patients: similar recurrent VTE; full dose associated with more major bleeding and CRNMB
High-risk VTE - RENOVE [7]	Reduced vs full dose DOACs	Less bleeding with reduced doses, but formal non-inferiority for recurrence not demonstrated
Cancer - API-CAT [8]	Apixaban 2.5 vs 5 mg bid	Reduced dose non-inferior for recurrence and superior for clinically relevant bleeding
SVT - Sorella et al. [9]	Low vs full-dose DOACs	Encouraging observational evidence; prospective confirmation required
Provoked VTE - HI-PRO [10]	Apixaban 2.5 mg bid vs placebo	Extended low-dose therapy markedly reduced recurrence in patients with enduring risk factors

Table 2. Special populations and unresolved issues
APS: antiphospholipid syndrome; CVT: cerebral venous thrombosis; LMWH: low molecular weigth heparin; VKA: vitamin K antagonists; other abbreviations as in Table 1.

Clinical setting	Current approach	Evidence gap / perspective
Pregnancy	LMWH	DOACs not routinely recommended
Severe renal impairment / major drug interactions	LMWH or VKA	Individualized according to renal function and interacting drugs
Mechanical heart valves	VKA	DOACs should not be used
Venous APS, single/double positive	VKA standard; selected DOACs use may be considered [3]	Prospective evidence remains limited
Arterial / triple-positive APS	Avoid DOACs [3,4]	VKA vs antiplatelet or combined strategies remains an unresolved question
Major inherited thrombophilia	Extended anticoagulation often considered [6]	Optimal full vs reduced DOAC dose unknown
CVT / SVT	DOACs use increasing [9]	Dedicated reduced-dose trials lacking
FXI/FXIa inhibitors	Investigational	Potentially lower bleeding anticoagulation; role in VTE treatment remains undefined. (Capodanno et al., Nat Rev Cardiol. 22:896-912, 2025)

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EBV AND HHV-8 IN HEMATOLOGY: UPDATE ON RELATED-LYMPHOPROLIFERATIVE DISORDERS AND VIRAL SEPSIS

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While EBV is ubiquitous, HHV-8 seroprevalence rates are low (3-7%) in US and northern Europe but higher than 50% in some ethnic groups, in sub-Saharan Africa, Latin America, Caribbean, Mediterranean, and Middle Eastern countries, where the incidences of either “endemic” or “classic” clinical forms of the etiologically related Kaposi sarcoma (K-S) mirror this particular geo-distribution of HHV-8[1]. Mononucleosis-like syndrome following HHV-8 primary infection shows lymphadenopathy with giant germinal center hyperplasia and increased vascularity, differently from the classical histologic pattern of EBV-Infectious Mononucleosis (IM) [2]. Aplastic Anemia (AA) rarely follows EBV-IM and may be successfully treated with allogeneic hemopoietic stem cell transplantation (HSCT): an EBV-related molecular mimicry may represent a pathogenetic mechanism of immune-mediated AA[3]. HHV-8 is also rarely associated with bone marrow failure in solid organ transplant (SOT) and HSCT patients[4]. The diagnostic criteria of EBV- and HHV-8-related lymphoproliferative disorders have been revised by the International Consensus Classification and the WHO 5 in 2022[5]. EBV genomic alterations may be differentially observed in a variety of EBV+ lymphomas and IM. Variants of human HLA genes have been associated with differing susceptibilities to EBV-IM, EBV positive Hodgkin disease and EBV-related nasopharyngeal carcinoma. Contrary to HIV+HHV-8+ lymphoproliferative disorders (like primary effusion lymphomas and Multicentric Castleman Disease-MCD-), not only viral load but T cell functions predict the risk of HIV+EBV+ central nervous system lymphomas and post-transplant lymphoproliferative diseases (PTLDs) in HSCT/SOT patients[6,7]. Adoptive immunotherapies, including tabelecleucel, are recommended in relapsed/refractory PTLDs, following rituximab and rituximab with chemotherpay[7,8]. KS herpesvirus-associated inflammatory cytokine syndrome (KICS) is a viral sepsis, resembling MCD, and described in HIV+ individuals with a poor outcome[9], and as a result of primary infection, both donor- and non donor-derived, in SOT recipients (mainly liver) [10]. In the SOT setting, serological screening/molecular surveillance and early use of rituximab and switch to mTor inhibitors are life-saving[10]. The demarcation between KICS and HHV-8 related Hemophagocytic Lympho-Hystiocytosis (HLH) or EBV-HLH, may be blurred and serum cytokine profiling may help in the differential diagnosis among these cytokine storms[9,10].

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INQUADRAMENTO BIOLOGICO E DIAGNOSTICO

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T-cell lymphomas are a diverse group of mature T- and NK--cell neoplasms characterized by aggressive clinical behavior, biological heterogeneity, and considerable diagnostic complexity. They encompass several clinicopathological entities, including anaplastic large cell lymphoma (ALCL), both ALK-positive and ALK-negative, lymphomas of T-follicular helper (TFH) cell origin, primary nodal Epstein–Barr virus (EBV)-positive T/NK-cell lymphomas, and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).Over the past decade, major advances in genomics have significantly improved our understanding of the pathogenesis and the putative cell-of-origin of these entities. Recurrent genetic alterations involving the epigenetic regulators, including TET2, DNMT3A, and IDH2, together with the disease-defining $RHOA^{G17V}$ mutation have emerged as hallmark features of TFH-derived lymphomas. In contrast, PTCL-NOS comprises biologically distinct subsets characterized by recurrent abnormalities affecting the JAK/STAT pathway, T-cell receptor signaling, and epigenetic regulatory networks. In anaplastic large cell lymphoma (ALCL), genetic lesions involving ALK, DUSP22, and TP63 have important diagnostic, prognostic, and biological implications, contributing to refined disease stratification. Collectively, these discoveries have reshaped the taxonomy of mature T-cell neoplasms and improved diagnostic precision through the integration of molecular testing into routine clinical practice. The classification of T-cell lymphomas has undergone substantial revision with the introduction of the 5th edition of the World Health Organization classification of haematological malignancy (WHO-HAEM5) and the 2022 International Consensus Classification (ICC). These classifications combine clinical, morphological, immunophenotypic, and genetic data, providing a more precise categorization of T-cell neoplasms and facilitating both diagnostic accuracy and risk-adapted patient management. This presentation aims to provide an updated overview of the biological and diagnostic framework of T-cell lymphomas. Emphasis will be placed on the practical application of genomic profiling and ancillary molecular techniques in diagnostic work-up, disease classification, prognostic assessment, and therapeutic decision-making. Emerging research will also be discussed, focusing on the development of biologically driven treatment strategies.

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EOSINOPHILS: GUILTY OR BYSTANDER? HOW MORPHOLOGY CAN CONTRIBUTE TO THE DIAGNOSTIC PROCESS IN HYPEREOSINOPHILIA

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Eosinophilia is frequently encountered in routine hematology, yet its differential diagnosis ranges from transient reactive disorders to neoplastic diseases. Hypereosinophilia, defined as an absolute eosinophil count >1,500/µL, may reflect a non-clonal condition with or without organ involvement (idiopathic hypereosinophilia versus hypereosinophilic syndrome), represent a primary neoplastic disorder (myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions), or occur as a secondary feature of clonal myeloid or lymphoid diseases[1,2]. Beyond eosinophil count, accurate interpretation requires morphological evaluation within the hematological context. Morphological abnormalities of eosinophils are less well characterized than dysplastic changes affecting neutrophils, megakaryocytes, or erythroid cells. Reported abnormalities include nuclear alterations (band, oval, hyperlobated, ring-shaped or binucleated nuclei), variable hypogranularity, cytoplasmic vacuolation, and basophilic granules. Although eosinophil morphology alone cannot reliably distinguish reactive from clonal eosinophilia, certain findings are informative: basophilic granules are the strongest morphological clue to neoplasia, whereas marked vacuolation is typical of some clonal eosinophilias but lacks specificity[3]. Peripheral blood smear examination remains essential, as it may reveal blasts, lymphoma cells, mast cells, or parasites, while eosinophil morphology contributes to the overall diagnostic assessment. Bone marrow examination is indicated when peripheral blood findings are suspicious or eosinophilia persists without an identifiable cause. Features supporting clonality include hypercellularity, expansion of an abnormally maturing eosinophilic compartment, dysplasia involving eosinophils and/or other lineages, increased blasts, reticulin fibrosis, atypical megakaryocytes, and dense aggregates of atypical mast cells. In contrast, preserved maturation, absence of dysplasia or blast excess, and a mixed inflammatory infiltrate favor a reactive process[4]. Morphological assessment therefore represents an important first step in the diagnostic work-up, guiding priority for molecular and cytogenetic investigations within the complex diagnostic pathway of eosinophilia[5,6]. Correct identification of the underlying disorder is essential because management differs substantially and hypereosinophilia itself may require prompt treatment to prevent potentially severe organ damage.

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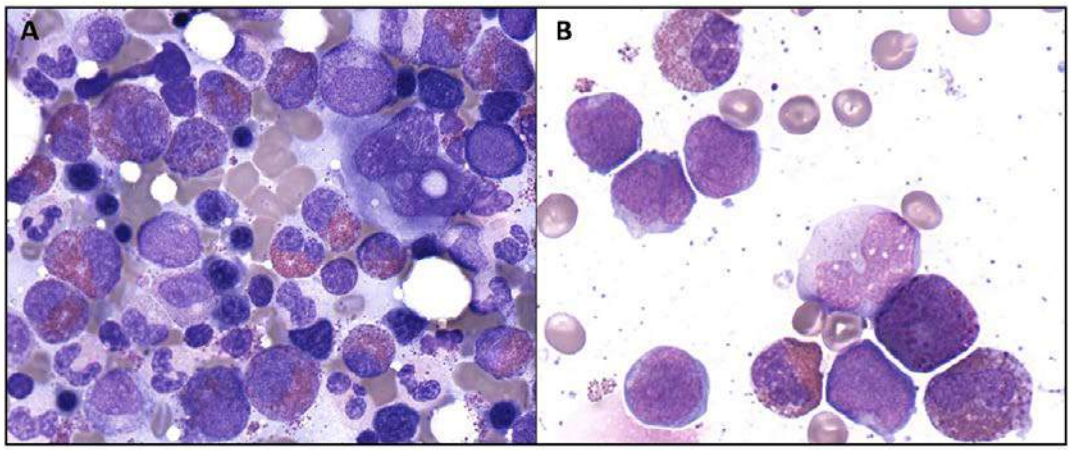

Figure 1. A) Idiopathic hypereosinophilia. Bone marrow aspirate showing increased eosinophilic granulopoiesis without significant morphological abnormalities (May-Grünwald-Giemsa, 60X objective). B) Acute Myeloid Leukemia with inv(16)(p13.1q22). Bone marrow aspirate showing an increased blast count, including blasts of monocytic lineage, together with increased eosinophilic granulopoiesis displaying abnormal granulation, particularly the presence of basophilic granules (May-Grünwald-Giemsa, 100X objective).

CLINICAL AND MOLECULAR PREDICTORS OF RESPONSE AND SURVIVAL IN PATIENTS WITH MYELOFIBROSIS TREATED WITH RUXOLITINIB

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Myelofibrosis (MF) is characterized by heterogeneous outcomes that are strongly influenced by disease genotype and phenotype. Ruxolitinib (RUX), the first approved JAK1/2 inhibitor (JAKi), remains the cornerstone of MF treatment, providing significant spleen response (SR) rates, symptom improvement, and a survival benefit demonstrated in the COMFORT-I/II trials and confirmed by real-world studies. However, treatment responses are heterogeneous, prompting interest in reliable predictors of outcome. Albeit several prognostic models have been developed, most were derived from cohorts of MF pts who had no access to JAKi and were designed to provide prognostic stratification at diagnosis. Nevertheless, several clinical and molecular variables have been associated with response to RUX. Among clinical variables, advanced age retains prognostic value, although it should not preclude treatment. Baseline anemia and thrombocytopenia are consistently associated with inferior spleen responses and shorter survival. The JUMP study confirmed the efficacy of RUX even in pts with PLTs <100 × 10^9/L, although with higher discontinuation rates. Cytopenias trajectories further refine prognosis: pts who remain "never cytopenic" have the best outcomes, compared with those who develop "treatment-emergent" cytopenias or have "persistent" cytopenias. Furthermore, adherence to PLTs-based starting-dose independently seem to influence both SR and OS. Among molecular variables, HMR mutations (ASXL1, EZH2, SRSF2, and IDH1/2) and a higher mutational burden (≥3 mutations) are associated with a shorter time to RUX discontinuation, although RUX appears to partially mitigate their adverse impact on survival. In contrast, RAS/CBL mutations seem to be independently associated with resistance to RUX and inferior OS. Prognostic tools that incorporate early on-treatment response, such as RR6 and its intermediate-1-specific counterpart iRR6, as well as molecularly integrated models, improve the identification of pts at risk of treatment failure. The recently developed R-PSS score may further assist clinicians in upfront treatment selection by providing prognostic stratification at the time of RUX initiation. In conclusion, RUX remains the most used JAKi in management of MF, but cytopenic phenotypes and specific molecular lesions identify subsets of pts who may derive limited benefit, for whom alternative JAKi or early treatment reassessment may be warranted.

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THERAPEUTIC SEQUENCING IN CHRONIC LYMPHOCYTIC LEUKEMIA

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The introduction of targeted therapies has profoundly changed the treatment landscape of chronic lymphocytic leukemia (CLL), providing multiple highly effective treatment options and making therapeutic sequencing an increasingly complex clinical challenge. The optimal sequence cannot be defined solely on the basis of the efficacy of individual agents, but should take into account how each treatment may influence subsequent therapeutic opportunities. This presentation will explore the main factors that should guide treatment sequencing across the different phases of the CLL disease course. Particular attention will be given to the consequences of treatment duration, distinguishing fixed-duration from continuous treatment strategies, and to the reasons for treatment discontinuation, including planned completion, intolerance and disease progression. The implications of these different scenarios for subsequent treatment choices will be discussed. The presentation will also address the rationale for sequencing therapies with different mechanisms of action, with a particular focus on the use of BTK- and BCL2-directed strategies in different treatment settings. Available evidence supporting treatment switching, retreatment and sequential use of targeted therapies will be considered, including emerging data in patients previously exposed to targeted agents. Finally, therapeutic sequencing will be discussed from a personalized perspective, integrating disease biology, previous treatment exposure, resistance mechanisms, comorbidities, concomitant medications, patient preferences and treatment accessibility. The aim is to provide a practical framework for approaching sequencing decisions in contemporary CLL, while highlighting the areas in which prospective evidence remains limited.