

CONVEGNO INTERREGIONALE SIE

Delegazioni Umbria e Marche

Società Italiana di Ematologia

NOVITÀ TERAPEUTICHE NEI LINFOMI NON-HODGKIN E MIELOMA MULTIPLO: FOCUS SU ANTICORPI BISPECIFICI E CAR-T

Assisi, Sala Conciliazione, Comune di Assisi
4 Novembre 2026

Novità terapeutiche nel Linfoma mantellare

Roberto Limongello (Perugia)

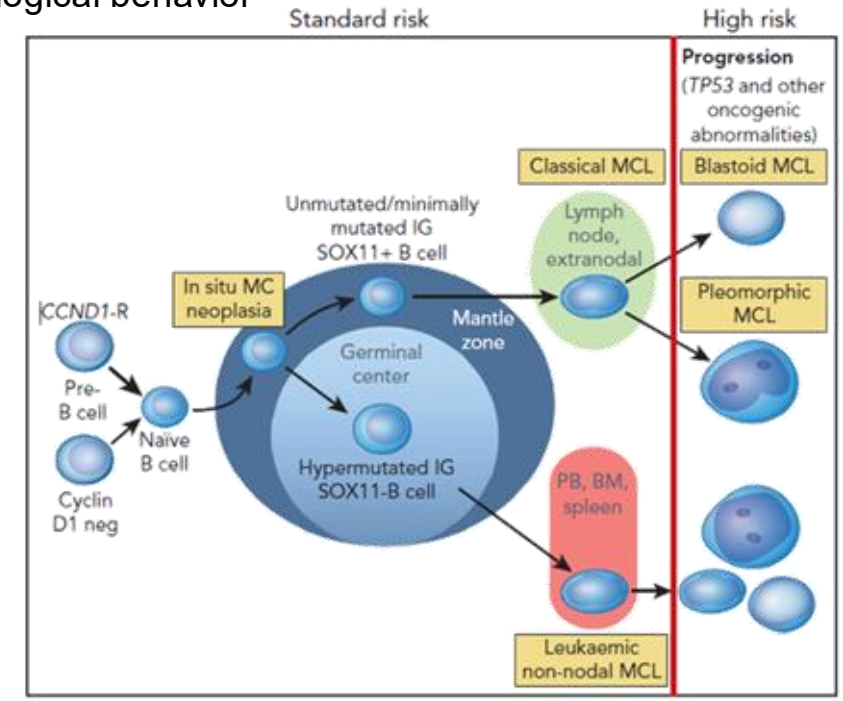
Disclosures of Roberto Limongello

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

No Disclosures

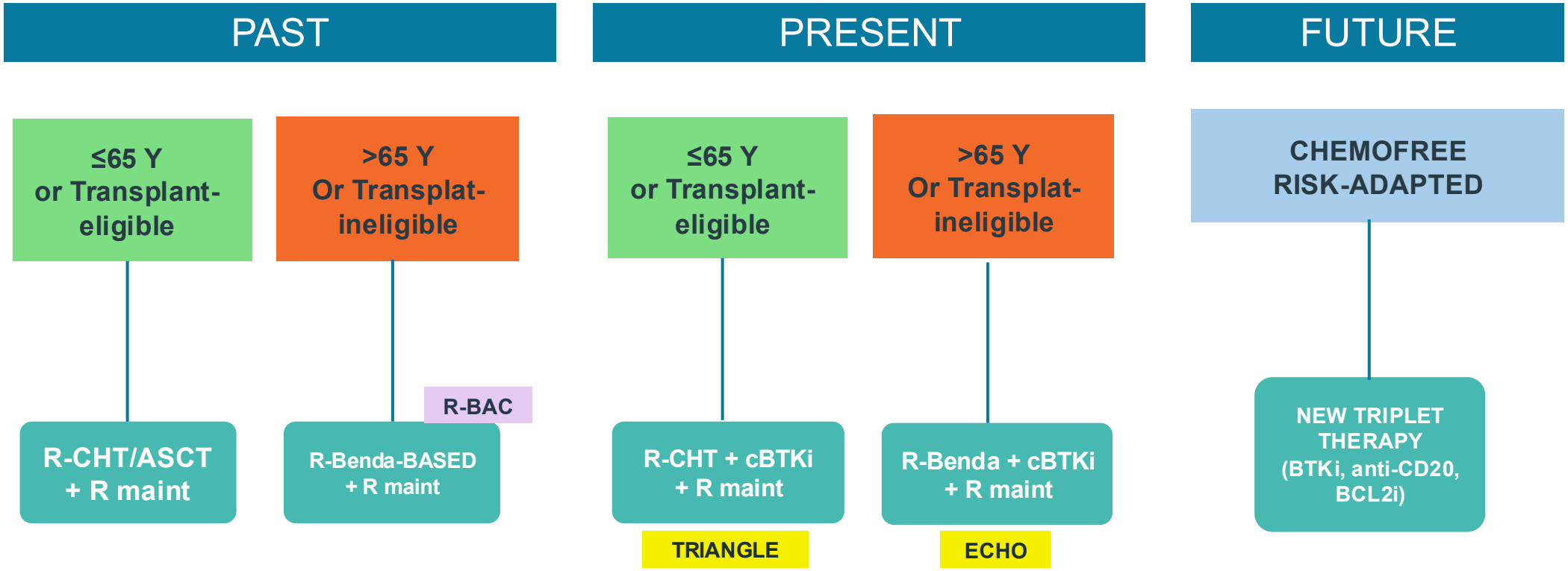
Mantle cell lymphoma (MCL)

- Heterogeneous behavior ranging from indolent cases to highly aggressive MCL with very limited prognosis
- Most of the patients diagnosed with advanced stage disease
- 90% Extranodal manifestations, including bone marrow (53%– 82%), blood (50%), liver (25%), gastrointestinal (20%–60%)
- 40% Spleen enlarged
- WHO 2016/2022 update of lymphoid malignancies, MCL now consists of **two distinct categories**.
  1) **Nodal MCL (80%–90%)** unmutated IGHV, SOX11 overexpression and more **aggressive** clinical behavior
  2) **Non nodal leukemic MCL (10%–20%)** mutated IGHV, **SOX11 negativity** and **indolent** biological behavior
- Histologically:
  > classical MCL
  > pleomorphic variant
  > blastoid variant



Dreyling M, et al. Ann Oncol. 2017
Silkenstedt E, Dreyling M. Hematological Oncology. 2021
Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Vol. 2, 4th ed. 2017
Alaggio R, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 5thEdition. Leukemia. 2022
Silkenstedt E, Dreyling M. Blood 2025

Newly diagnosed MCL: past, current & future treatment scenario



Drivers of therapeutic decision-making in MCL

PATIENT'S AGE/FITNESS

Age vs Transplant eligibility vs Cytarabine-based induction eligibility

1° vs 2° generation cBTKi

BIOLOGIC-RISK MCL

Tailored therapeutic strategies according to biologic risk in MCL?

OPTIMAL SEQUENCING

Is there an optimal sequencing strategy?

ESMO GUIDELINES: Patient's Age/Fitness And Eligibility To Treatment

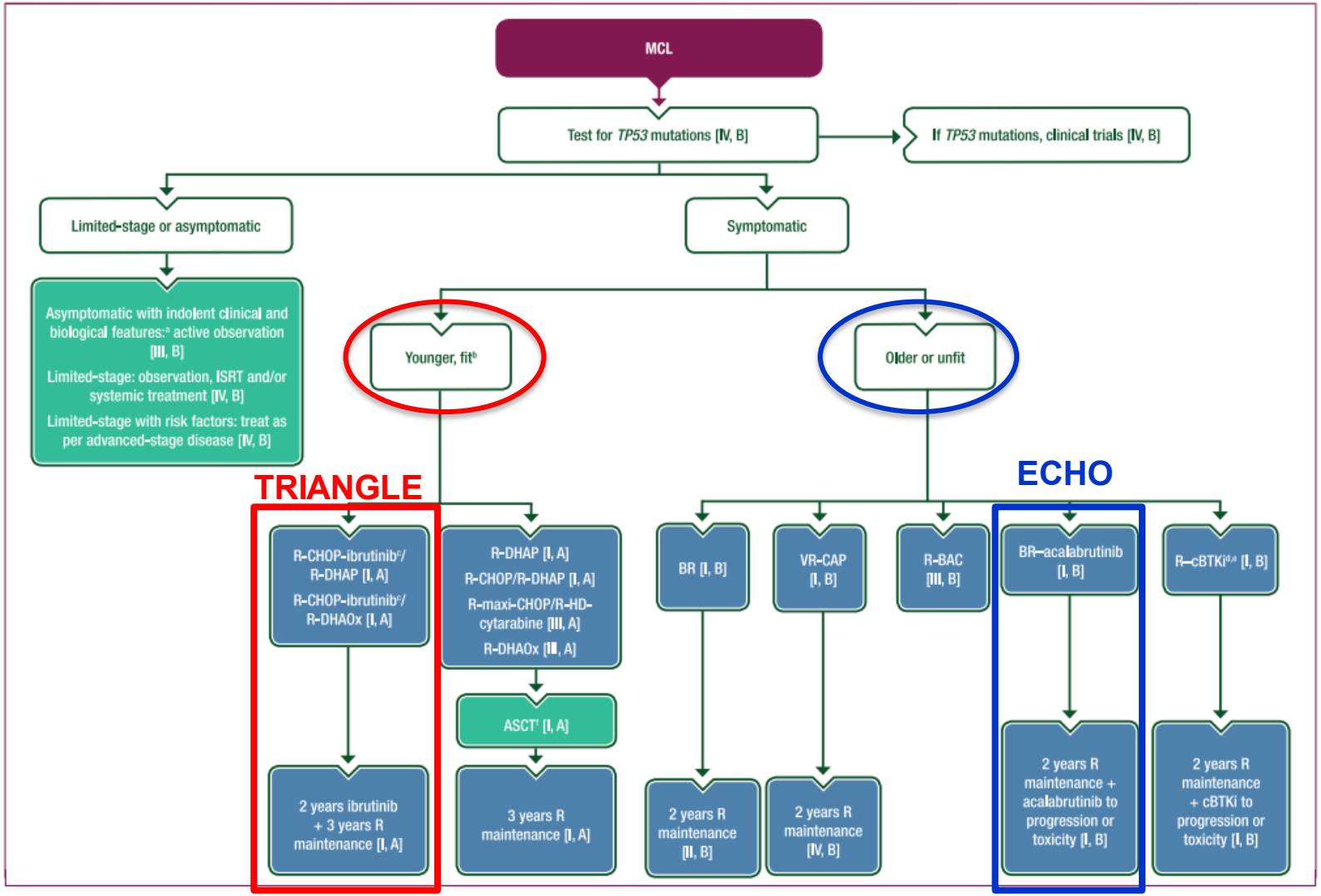
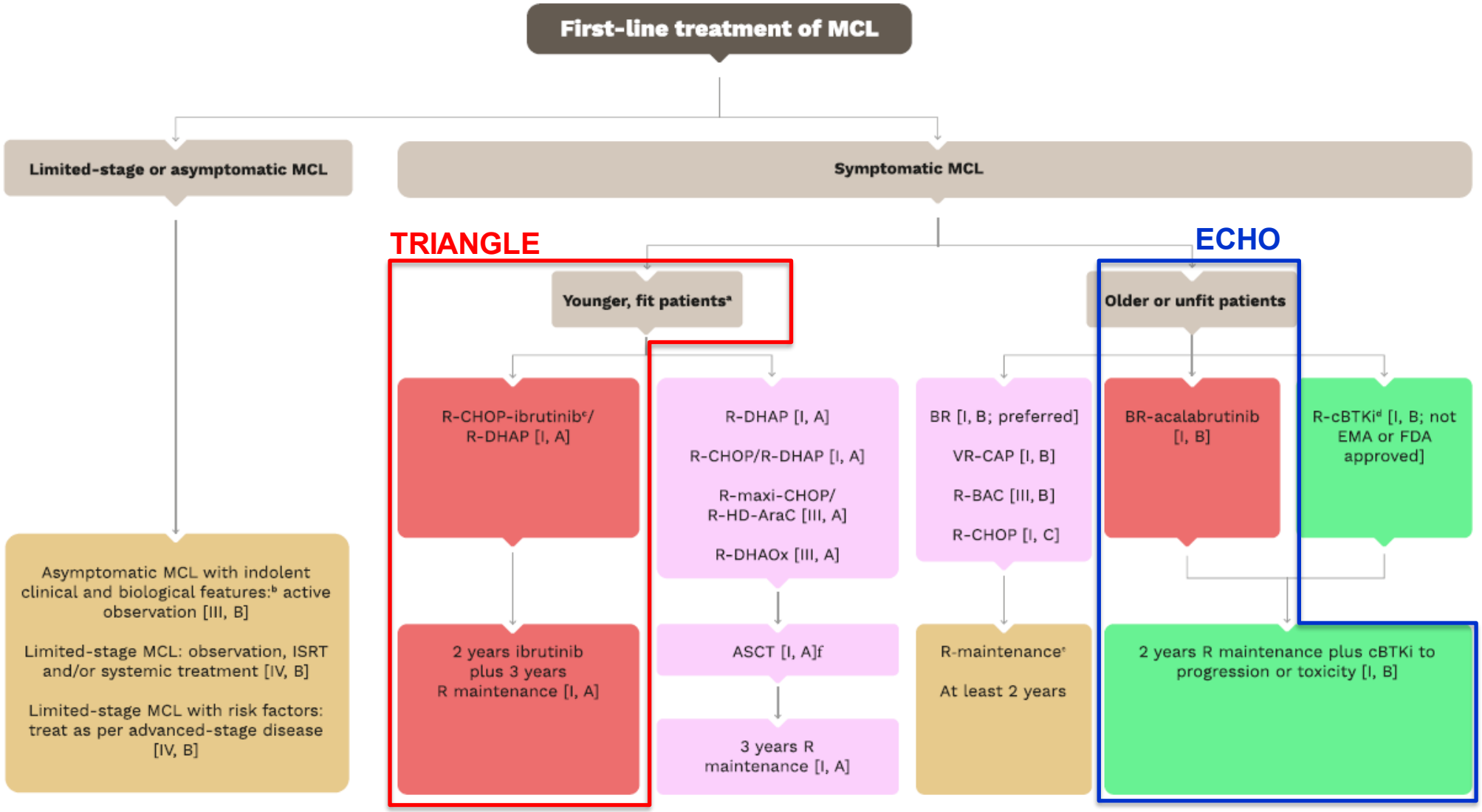


Figure 7. First-line management of MCL.

T. A. Eyre et al. Annals of Oncology 2025

EHA-EU MCL GUIDELINES : Patient's Age/Fitness And Eligibility To Treatment



Jerkeman M et al, Hemasphere 2025

How to identify High-Risk MCL

MIPI

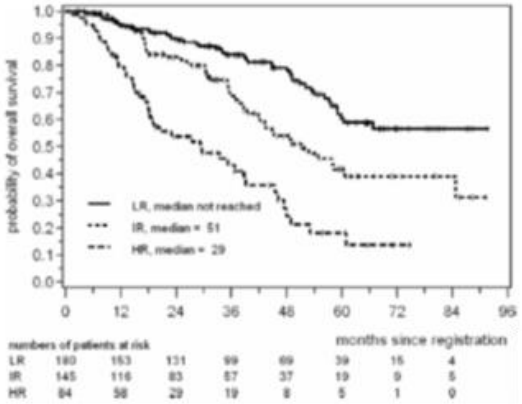
Ki-67

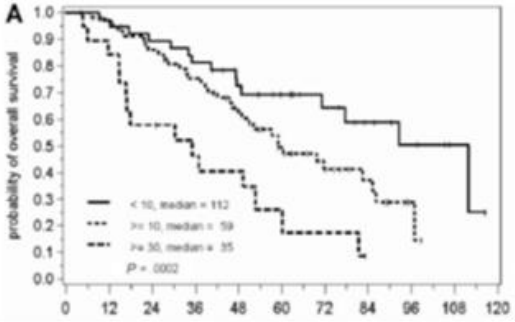
P53 expr.

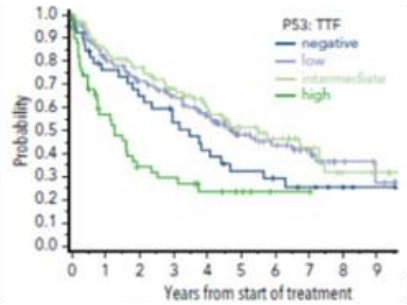
TP53 status

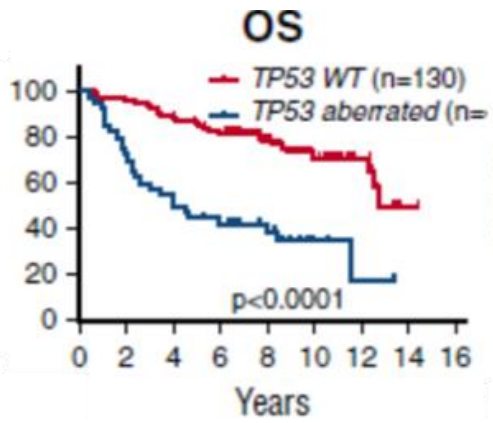
Histology

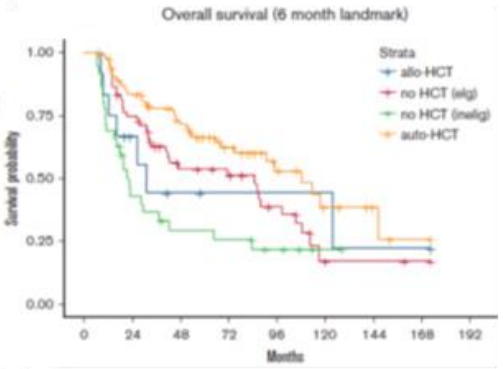
455 pts included in
3 clinical trials











Tiemann et al BJH 2005

Determann E et al, Blood 2008

Aukema et al, Blood 2018

Eskelund et al, Blood 2017

Gerson et al, Blood Adv 2023

MIPI ≥6.2 / MIPIb* ≥6.5 [high]

Ki67 >30/50%

p53 expr >50%

TP53 mut/del

Blastoid morphology

Poor outcome

* MIPIb (biological, MIPI + Ki67)

High-risk prognostic features in patients with newly diagnosed or relapsed MCL

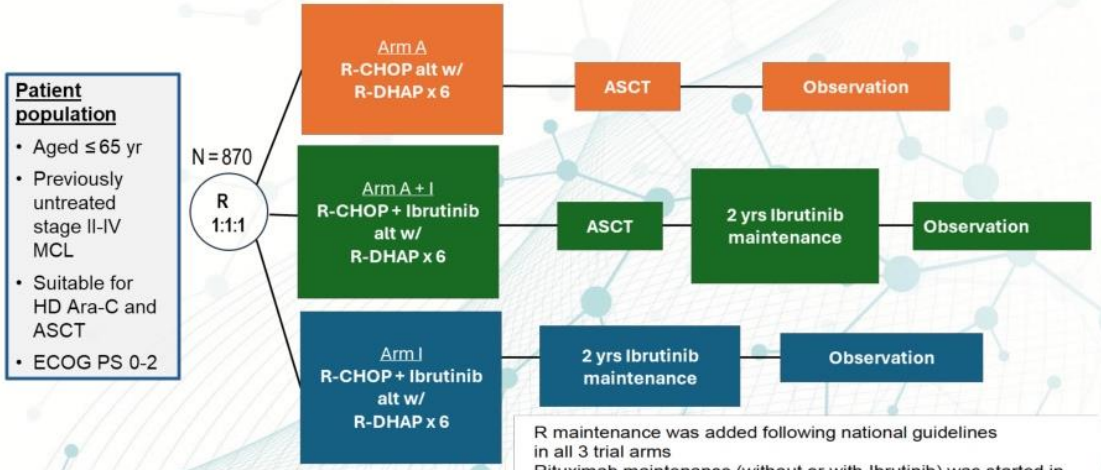
Features	Newly diagnosed MCL	R/R MCL*
Accepted ultra-high-risk features	De novo blastoid or pleomorphic histology with high-risk mutations[40] Ki-67% ≥50%† in involved tissue biopsy with blastoid or pleomorphic histology[12,41] ±*TP53* mutation (R273) with other high-risk gene mutations (*KMT2D*, *NSD2*, *CCND1*, *NOTCH1*, *CDKN2A*, *NOTCH2*, or *SMARCA4* mutations) and extensive disease burden[42] CNS involvement with systemic disease[43]	Transformed blastoid or pleomorphic histology (transformed from classic histology; ie, disease resistant to BTKi, venetoclax, and anti-CD19 CART)[40] Primary BTKi-refractory disease[12] Refractory to ≥3 previous lines of standard therapy (including BTKi)[12] Triple-resistant MCL (disease resistant to BTKi, venetoclax, and anti-CD19 CART)[12,33]
Accepted high-risk features	Blastoid or pleomorphic histology[40] Ki-67 ≥50%† in involved tissues with classic histology[12,41] *TP53* mutation[14] and/or del(17p) by FISH, *TP53* overexpression by IHC, and/or non-*TP53* mutations (*NOTCH1/NOTCH2*, *KMT2D*, *NSD2*, and *SMARCA4* mutations)[44] CK[45] (Complex karyotype) *MYC* rearrangement and/or amplification[46-50] *TP53* expression in >50% of cells or a high combined MIPI score Simplified MIPI score ≥6.2[51] Bulky disease‖	High-risk features for patients with newly diagnosed disease[12] ≤2 previous lines of standard therapy Progression within 24 months of first-line therapy[52] MRD$^+$ status after therapy§

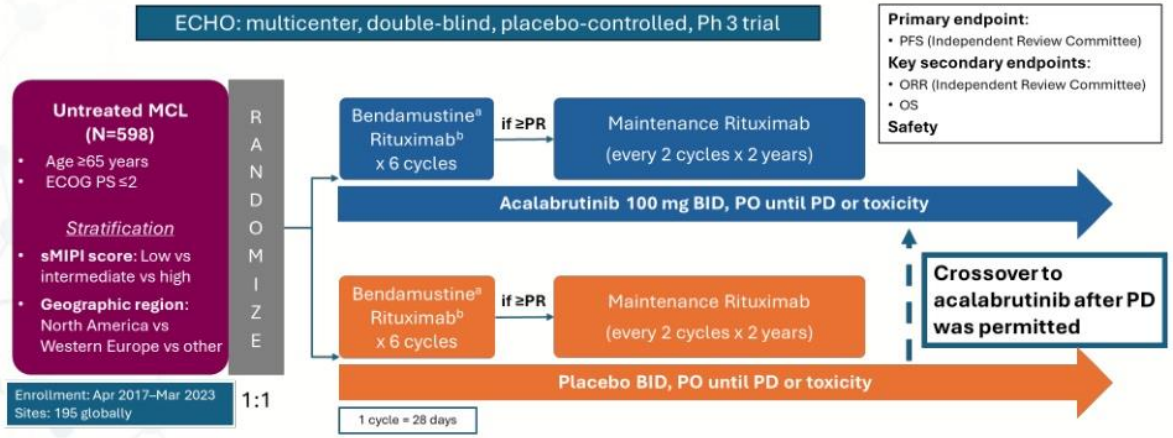
NGS

Jain P. and Wang M. – Blood 2025

cBTKi based 1L regimens

TRIANGLE ⟵ < 65 years > ⟶ ECHO





Primary Endpoint
• FFS
Key Secondary Endpoints
• Response rates • PFS • RD • OS • Safety

MIPI int-high 41-43%

Ki67 ≥30% 31-33%

Blastoid 11-13%

Primary Endpoint
• PFS by independent review committee (IRC)
Key Secondary Endpoints
• PFS by investigator (INV) • ORR by INV and IRC • DoR by IRC • OS

sMIPI int-high 66-67%

Ki67 ≥30% 46-49%

Blastoid/pleomorphic 13-14%

Dreyling M, et Al. Lancet. 2024

. Michael Wang et al.. J Clin Oncol 2025

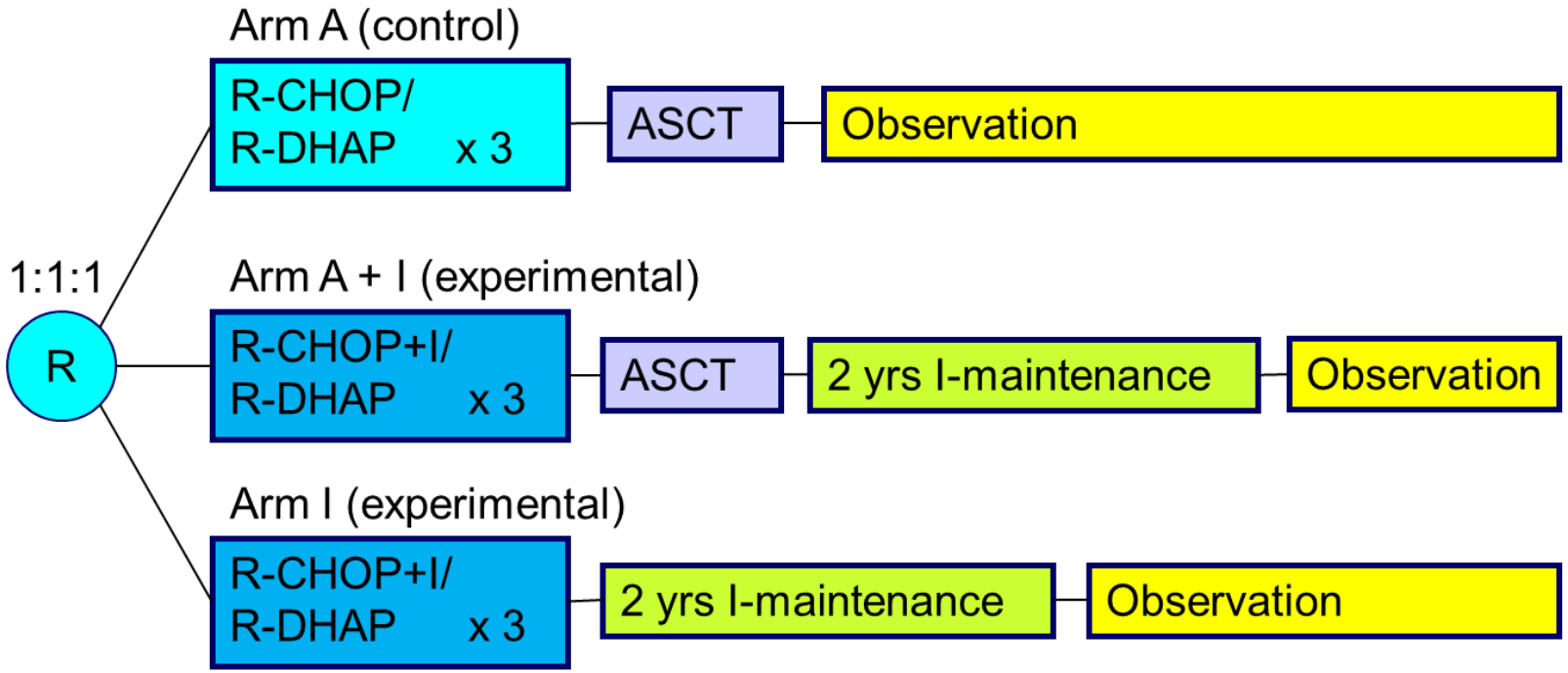
TRIANGLE: study design

- MCL patients
- Previously untreated
- Stage II–IV
- <66 years old
- Suitable for HA and ASCT
- ECOG PS 0–2

Primary outcome: FFS

Secondary outcomes:

- RR
- PFS
- OS
- Safety



R maintenance (with or without ibrutinib) started, per national guidelines, in:

- Arm A: 168 (58%) patients
- Arm A+I: 165 (57%) patients
- Arm I: 158 (54%) patients

ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; DHAP, dexamethasone, cytarabine, cisplatin; ECOG, Eastern Cooperative Oncology Group Performance Status; FFS, failure-free survival; HA, high-dose Ara-C; I, ibrutininb; OS, overall survival; PFS, progression-free survival; R, rituximab; RR, response rate.

Dreyling M, et al. ASH 2024 (Abstract No. 240 – oral presentation);
Dreyling M, et al. Lancet 2024;403:2293–2306.

4.5 years update

TRIANGLE: Response at End of Induction

	Overall	A	A+I/I	A+I	I
ED	2 (0.2%)	1 (0.4%)	1 (0.2%)	1 (0.4%)	0 (0%)
PD	17 (2%)	11 (4%)	6 (1%)	3 (1%)	3 (1%)
SD	7 (1%)	4 (1%)	3 (0.5%)	1 (0.4%)	2 (0.7%)
PR	458 (55%)	158 (58%)	300 (54%)	152 (54%)	148 (53%)
CR	347 (42%)	98 (36%)	249 (45%)	124 (44%)	125 (45%)
CR+PR	805 (97%)	256 (94%)	549 (98%)	276 (98%)	273 (98%)
Total	831	272	559	281	278
NE	29	11	18	8	10
ND	10	5	5	3	2

Dreyling M, et al. Lancet. 2026
Dreyling M, et al. Lancet. 2024

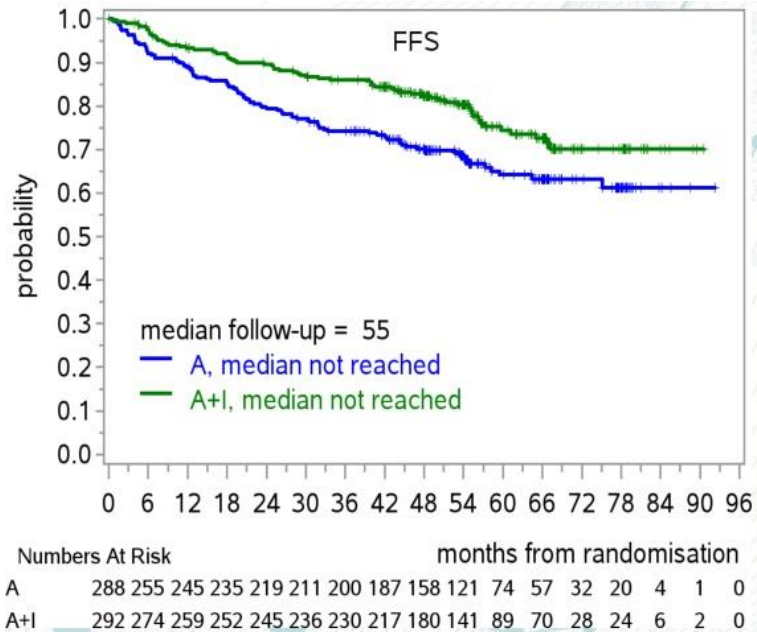
4.5 years update

EUROPEAN mcl NETWORK

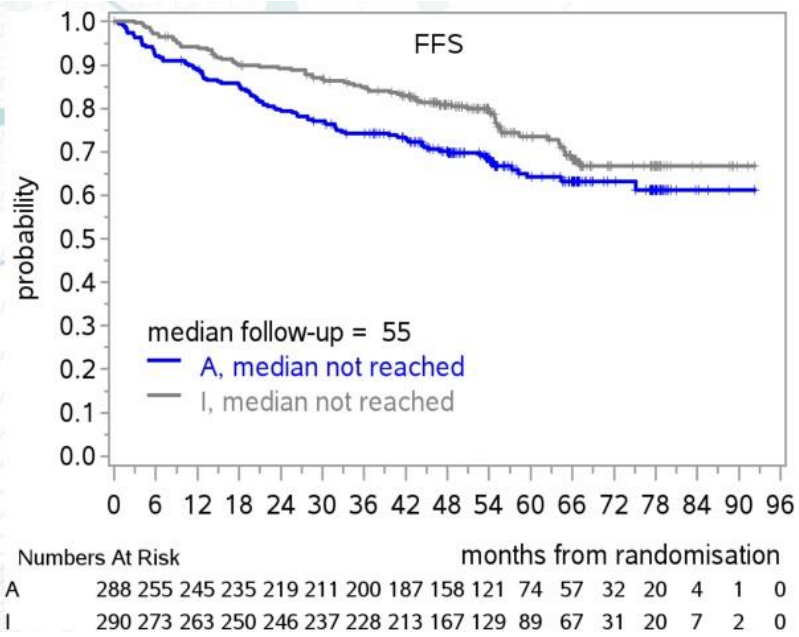
RANDOMIZED POPULATION

FFS (Failure-Free Survival)* FROM RANDOMIZATION (ITT ANALYSIS)

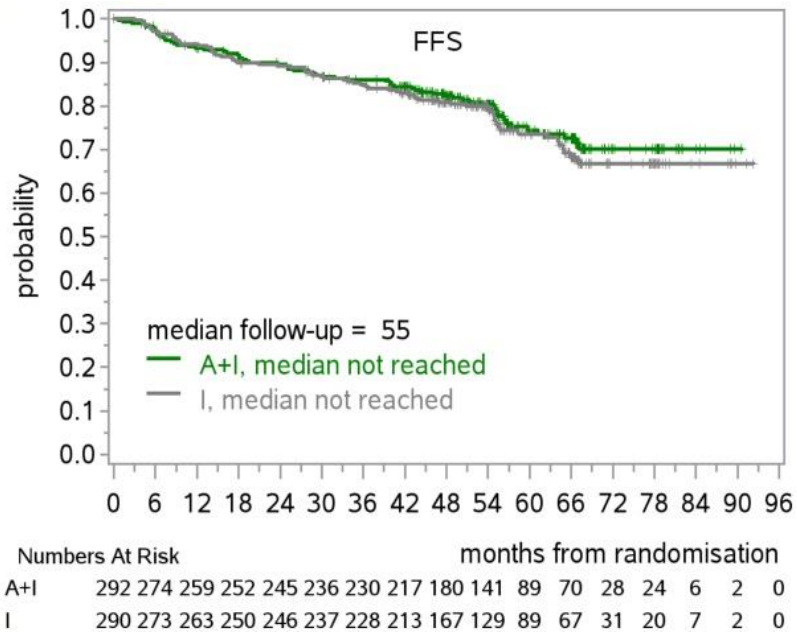
FFS Superiority of A+I vs. A



FFS Superiority of A vs. I



FFS Superiority of A+I vs. I



***FFS:** measures the length of time a patient lives after treatment without a defined "failure" event, such as disease progression, relapse, the addition of new systemic therapy, or death.

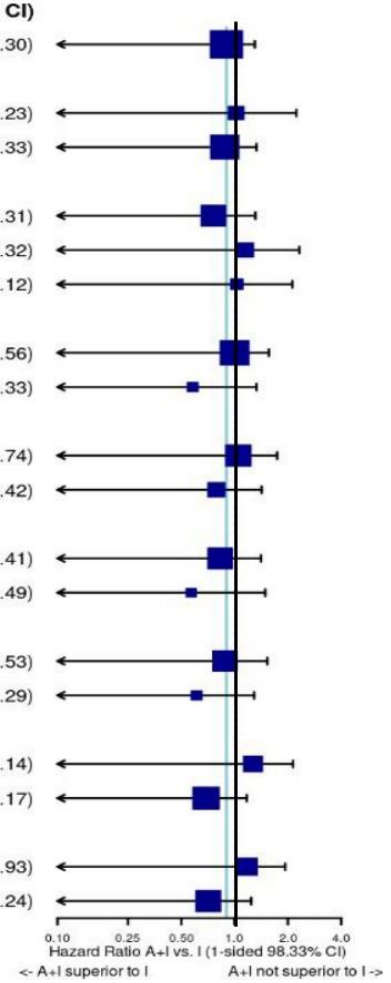
Dreyling M, et al. Lancet. 2026
Dreyling M, et al. Lancet. 2024
Dreyling M, et al. ASH 2024

4.5 years update

TRIANGLE: No FFS Superiority of A+I vs. I (subgroup analysis)

EUROPEAN MCL NETWORK

Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03 (0 - 2.12)
Cytology (p=0.15)			
Non-blastoid	461	92	1.00 (0 - 1.56)
Blastoid	65	27	0.58 (0 - 1.33)
Ki-67 (p=0.41)			
Low	357	71	1.05 (0 - 1.74)
High	164	54	0.79 (0 - 1.42)
P53 expression (p=0.43)			
Low	342	67	0.83 (0 - 1.41)
High	59	21	0.57 (0 - 1.49)
High risk biology (p=0.33)			
Low	323	60	0.88 (0 - 1.53)
High	64	34	0.61 (0 - 1.29)
R maintenance ITT (p=0.081)			
No	196	66	1.27 (0 - 2.14)
Yes	386	68	0.69 (0 - 1.17)
R maintenance mAT (p=0.14)			
No	228	76	1.18 (0 - 1.93)
Yes	354	58	0.71 (0 - 1.24)



*Trend towards **superiority of A+I over I** in patients in **high risk** patients:*

- **Ki-67 >30%**
- **blastoid cytology**
- **high p53 expression**
- **High risk biology***

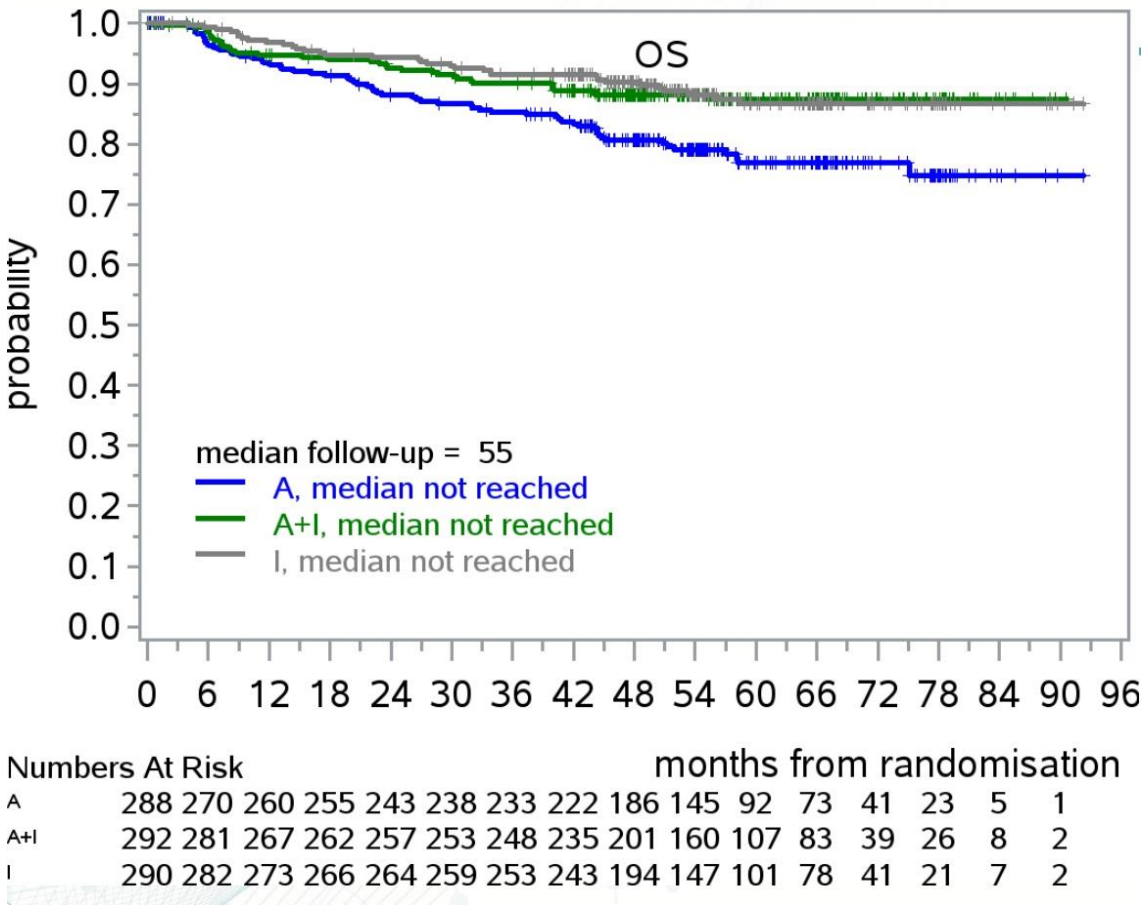
** Was classified as low (low, low intermediate or high intermediate combined MIPI an low p53 expression ≤50%) or high (high combined MIPI and high p53 expression > 50%)*

ASCT→ 3% mortality

Dreyling M, et al. Lancet. 2026
Dreyling M, et al. Lancet. 2024
Dreyling M, et al. ASH 2024

4.5 years update

TRIANGLE: Overall survival



4-year OS:

- A: 81%
  (MCL Younger exp.: 80%)
- A+I: 88%
- I: 90%

two-sided test, (α= 5%):

A vs. I: p=0.0019, HR: 0.565

A vs. A+I: p=0.0036, HR I: 0.587

A+I vs. I: ongoing

Dreyling M, et al. Lancet. 2026
Dreyling M, et al. Lancet. 2024
Dreyling M, et al. ASH 2024

Lack of Benefit of Autologous Hematopoietic Cell Transplantation (auto-HCT) in Mantle Cell Lymphoma (MCL) Patients (pts) in First Complete Remission (CR) With Undetectable Minimal Residual Disease (uMRD): Initial Report From the ECOG-ACRIN EA4151 Phase 3 Randomized Trial

ECOG-ACRIN cancer research group

ECOG-ACRIN EA4151: Study Design

International, Open-Label, Randomized Phase III Trial[1]

- Patients aged ≥18 and ≤70 years with MCL in first remission
- Candidates for autoHCT
- Any rituximab-containing induction regimen allowed (including BTKi)

N = 650

MRD assessment by Clonoseq

Stratified by MIPI-c (high/high-int vs low/low-int) and induction (intensive vs non-intensive)

Clonal marker present?

Yes

Post-induction restaging, MRD assessment

MRD- CR

MRD+ CR or MRD+/- PR

No

MRD indeterminate

Arm A: **AutoHCT + Rituximab** x 3 y (n = 257)

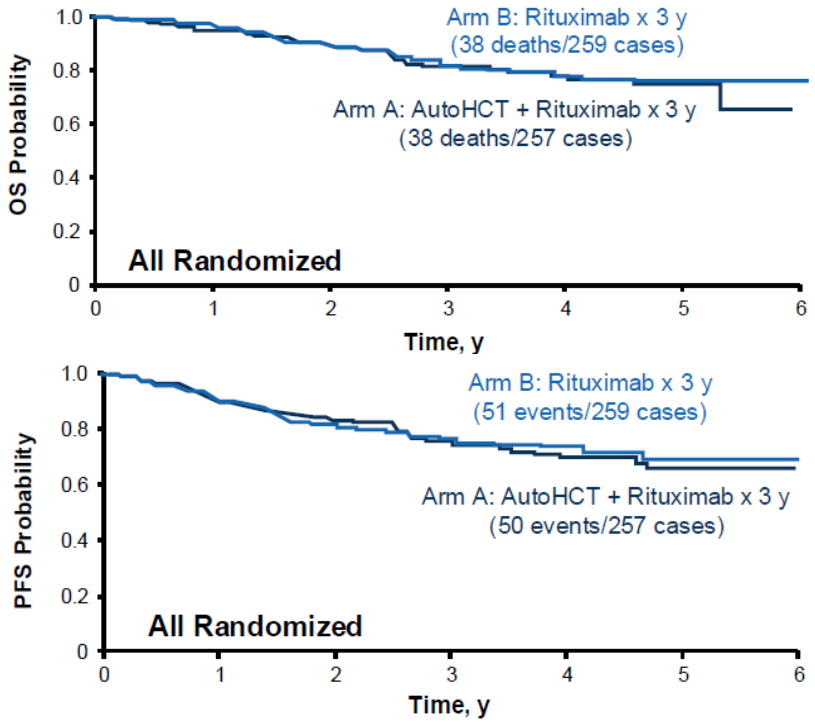
Arm B: **Rituximab** x 3 y (n = 259)

Arm C: **AutoHCT + Rituximab** x 3 y (n = 49)

Arm D: **AutoHCT + Rituximab** x 3 y (n = 85)

Primary endpoint: OS (Arm A vs Arm B)

Key secondary endpoints: PFS (Arm A vs Arm B), PFS (Arms C and D), MRD conversion rate post autoHCT, and safety



Conclusions

- In this initial analysis, in the era of highly effective induction and maintenance regimens, **MCL pts in first CR with uMRD did not benefit from consolidative auto-HCT.**
- Pts who remain MRD+ after induction may benefit from auto-HCT. **MRD+ patients (high risk?) who converted to uMRD6 post auto-HCT appeared to have improved OS and PFS**.

Fenske TS et al. ASH 2024. Abstract LBA-6.

MCL Treatment: The Horizon for Older MCL

Trials of relevance for an elderly population

SHINE trial: BR + ibrutinib until PD

ECHO: BR + acalabrutinib until PD

ENRICH: Ibrutinib-R vs BR/R-CHOP

FIL_VR-BAC: venetoclax consolidation after R-BAC

PUBLISHED RESULTS

MANGROVE: Zanubrutinib-R vs. BR

PENDING RESULTS

VIRAL / MCL Elderly III / GLA 2022-3:
VR+ibrutinib vs R-benda+ibrutinib

ONGOING TRIAL

Phase 3 SHINE Trial: Adding Ibrutinib to Upfront CIT Prolonged PFS…. however, No Improvement in OS

Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II-IV disease
- No planned stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

Enrolled between May 2013 and November 2014 at 183 sites

N = 523

R 1:1

BR induction for 6 cycles → if CR or PR → Rituximab maintenance every 8 weeks for 12 cycles

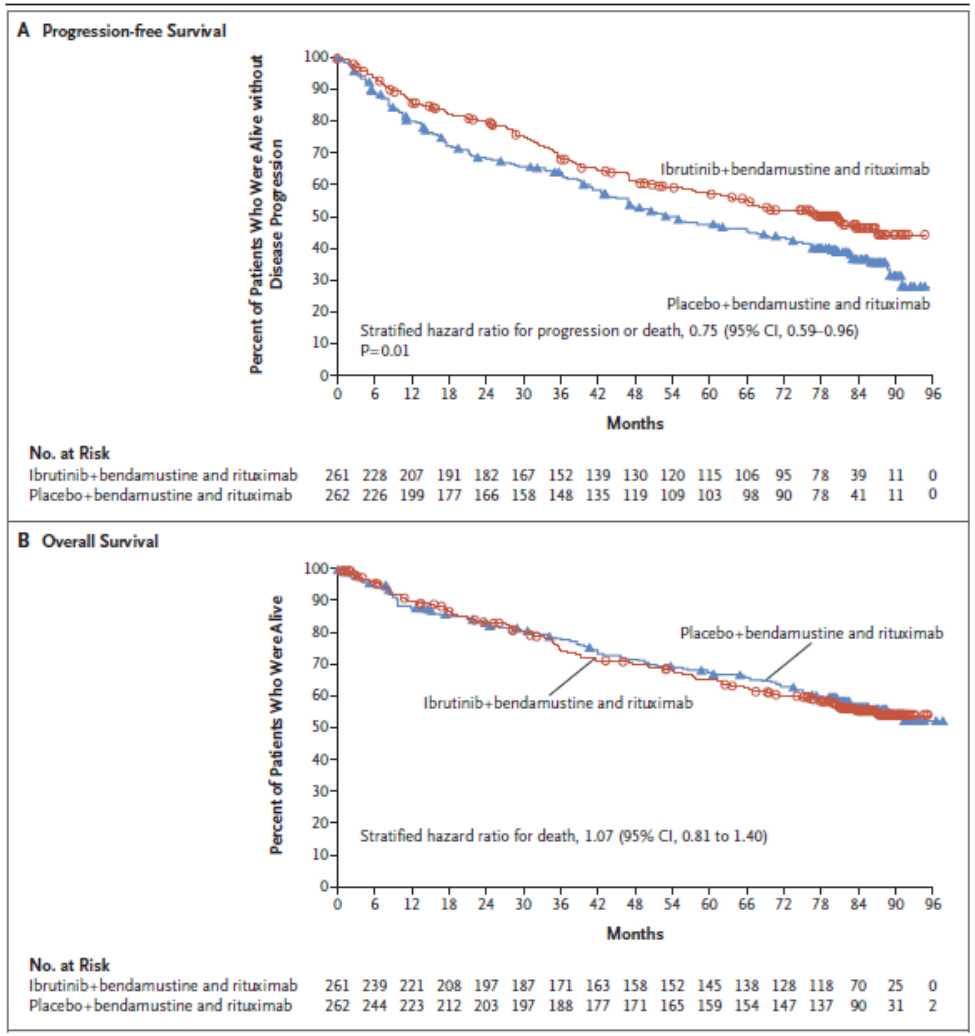
Ibrutinib 560 mg (4 capsules daily) until PD or unacceptable toxicity

BR induction for 6 cycles → if CR or PR → Rituximab maintenance every 8 weeks for 12 cycles

Placebo (4 capsules daily) until PD or unacceptable toxicity

Primary end point: PFS (investigator-assessed) in the ITT population

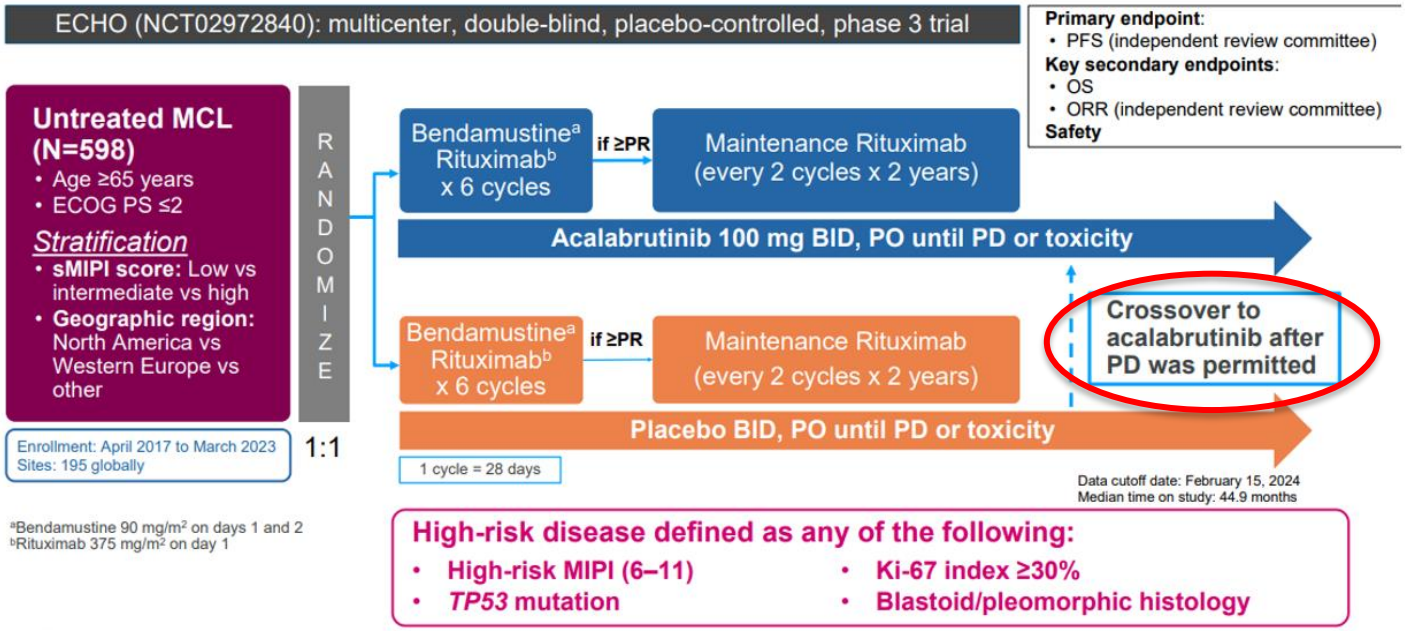
Key secondary end points: response rate, time to next treatment, overall survival, safety



Wang ML et al. N Engl J Med. 2022

ECHO Trial

Study design



Demographic and baseline characteristics

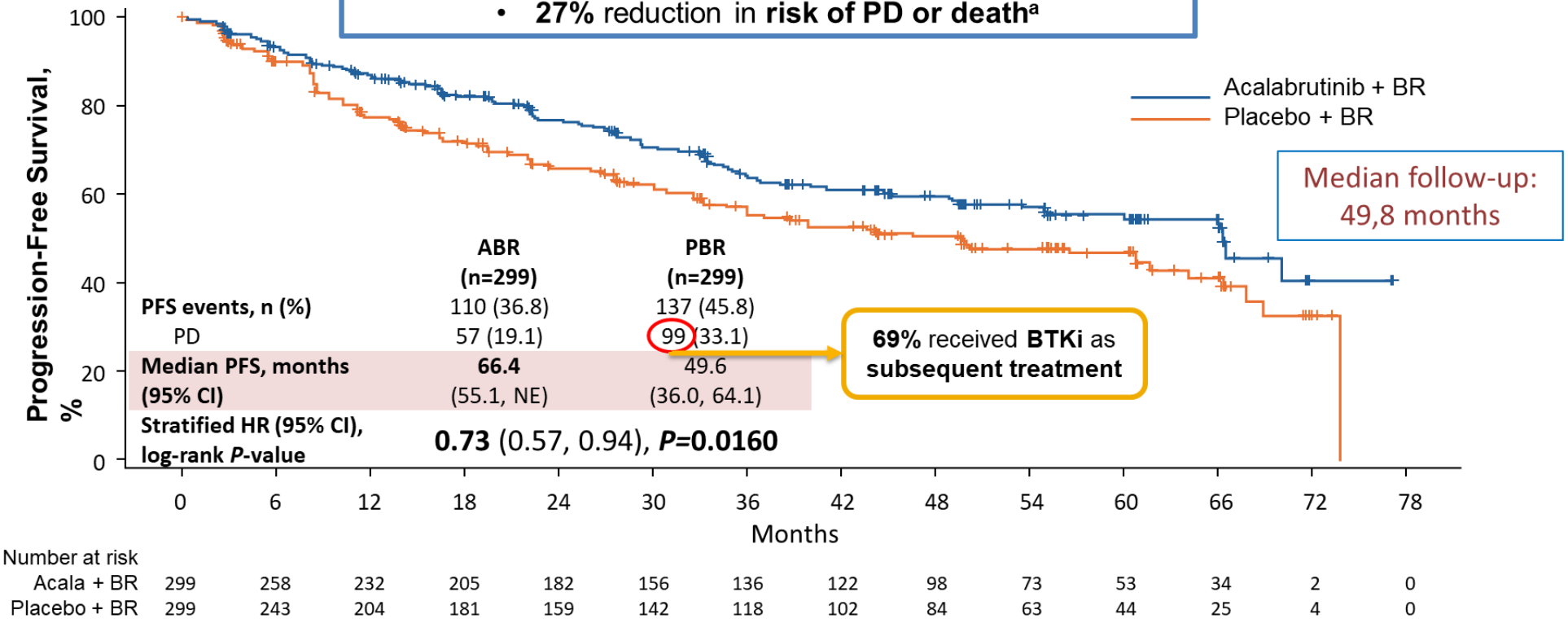
	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, n (%)	41 (13.7)	38 (12.7)
Simplified MIPI score, n (%)		
Low risk	99 (33.1)	101 (33.8)
Intermediate risk	128 (42.8)	125 (41.8)
High risk	72 (24.1)	73 (24.4)
Extranodal disease, n (%)	264 (88.3)	277 (92.6)
TP53 status, n (%)[a]		
Mutated	22 (7.4)	29 (9.7)
Unmutated	97 (32.4)	83 (27.8)
Ki-67, n (%)		
<30%	133 (44.5)	126 (42.1)
≥30%	139 (46.5)	147 (49.2)

Wang M. er al – EHA 2024

50-months follow-up efficacy

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR

- **Significant improvement in median PFS by ~17 mo**
- **27%** reduction in **risk of PD or death**[a]



	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	**66.4** (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

69% received **BTKi** as **subsequent treatment**

[a]At a median follow-up of 45 months.

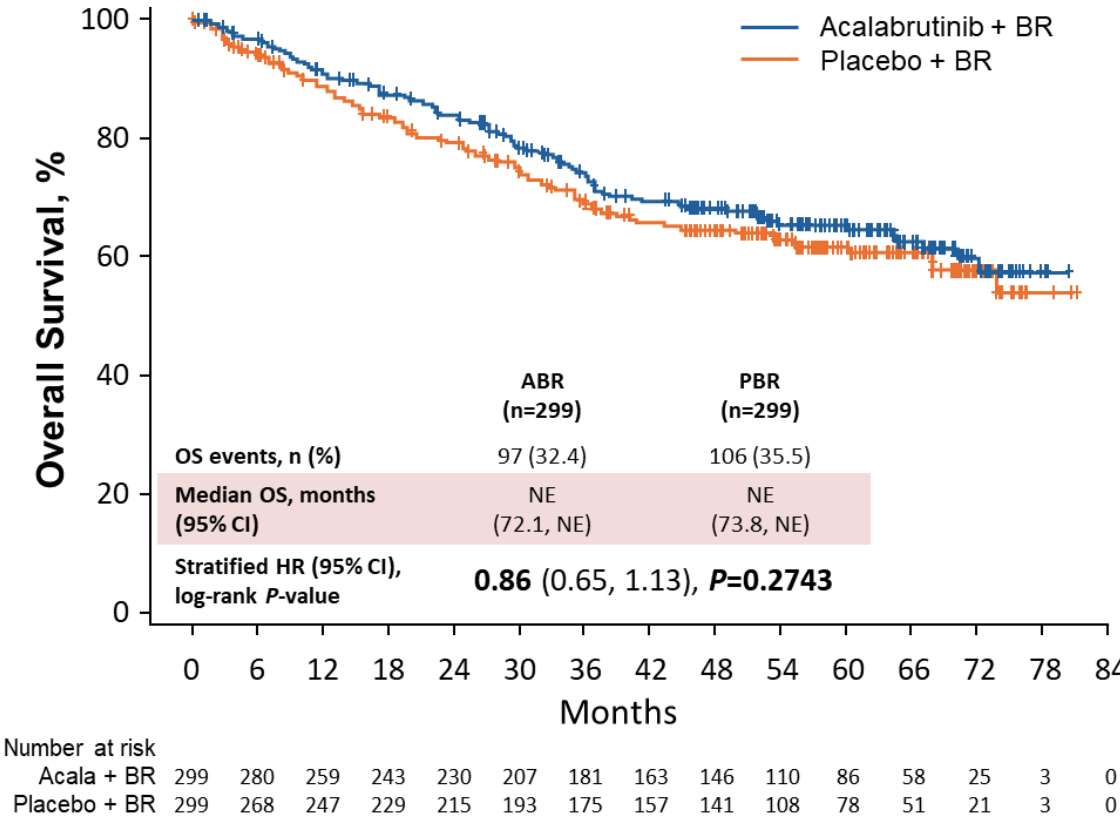
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

Wang M, et al. J Clin Oncol. 2025

50-months follow-up efficacy

OS With and Without COVID-19 Deaths: Prespecified Sensitivity Analysis

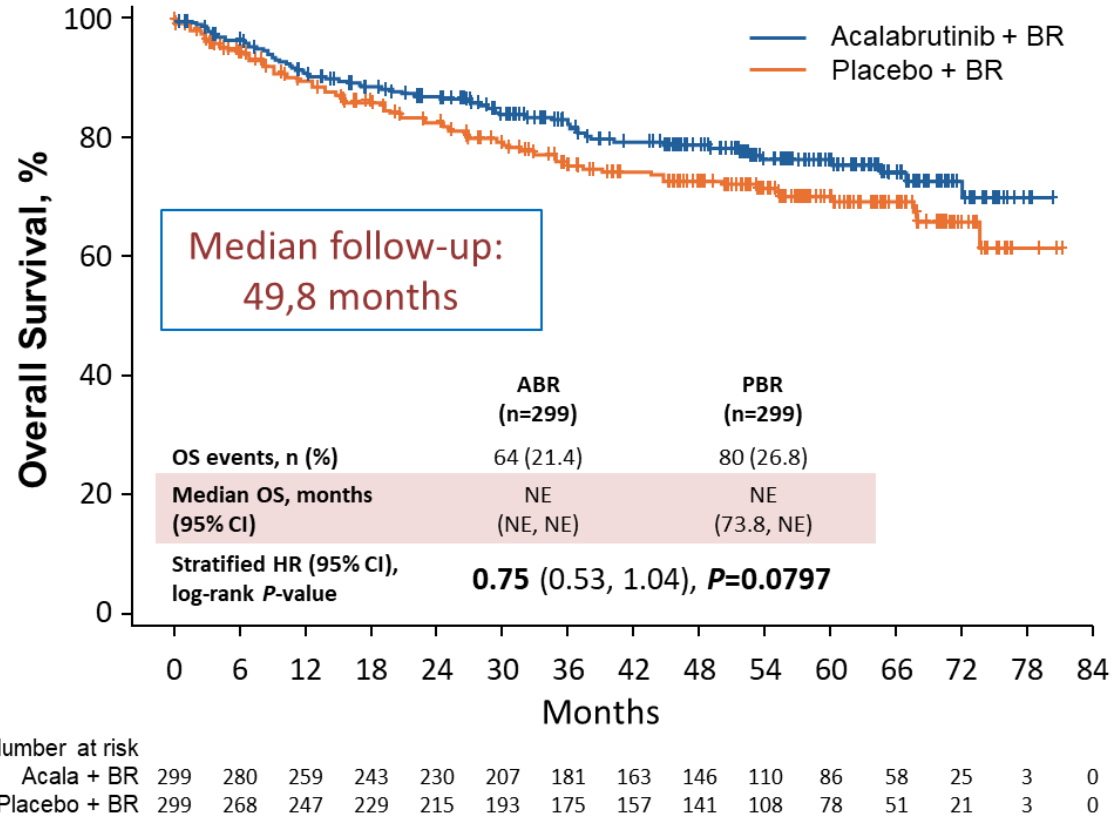
Full analysis population (including crossover)



	ABR (n=299)	PBR (n=299)
OS events, n (%)	97 (32.4)	106 (35.5)
Median OS, months (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.86** (0.65, 1.13), ***P*=0.2743**	

Number at risk															
Acala + BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo + BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

COVID-19 deaths censored



Median follow-up: 49,8 months

	ABR (n=299)	PBR (n=299)
OS events, n (%)	64 (21.4)	80 (26.8)
Median OS, months (95% CI)	NE (NE, NE)	NE (73.8, NE)
Stratified HR (95% CI), log-rank *P*-value	**0.75** (0.53, 1.04), ***P*=0.0797**	

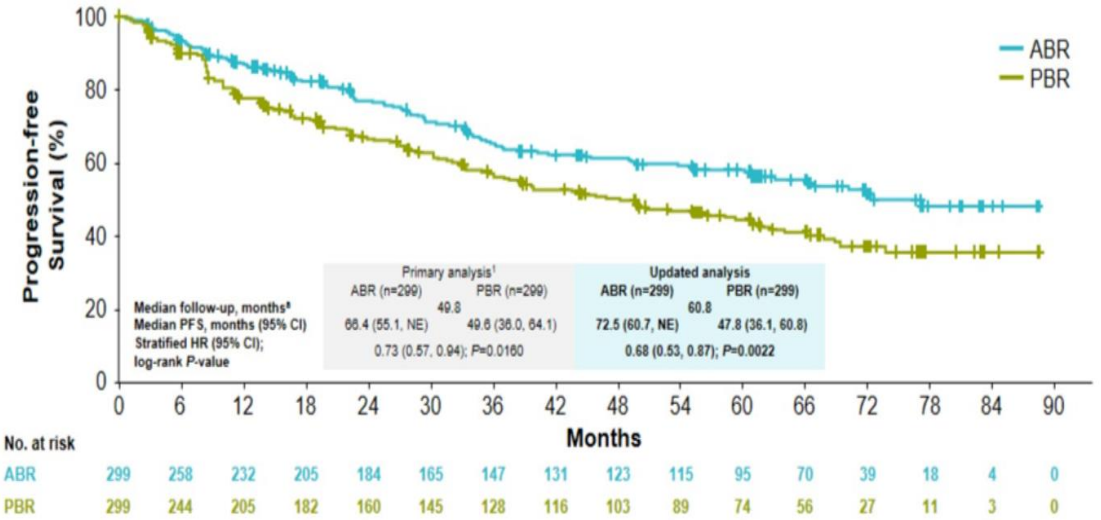
Number at risk															
Acala + BR	299	280	259	243	230	207	181	163	146	110	86	58	25	3	0
Placebo + BR	299	268	247	229	215	193	175	157	141	108	78	51	21	3	0

ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

Wang M, et al. J Clin Oncol. 2025

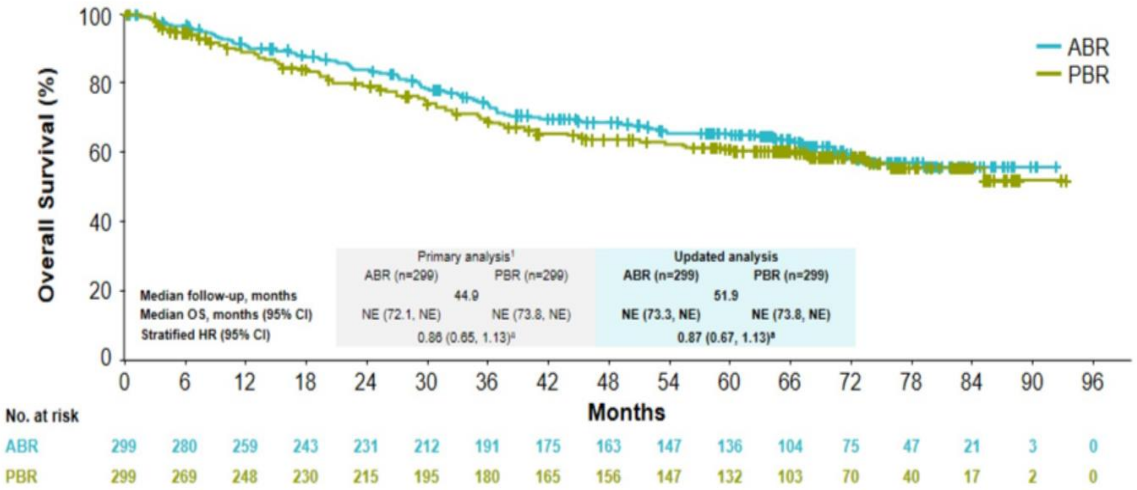
60.8 months of follow-up

PFS further improved with ABR vs PBR



- PFS risk reduction with ABR vs PBR increased from 27% (primary analysis) to 32% (updated analysis)
- Median PFS was longer with ABR vs PBR (6 years vs 4 years)

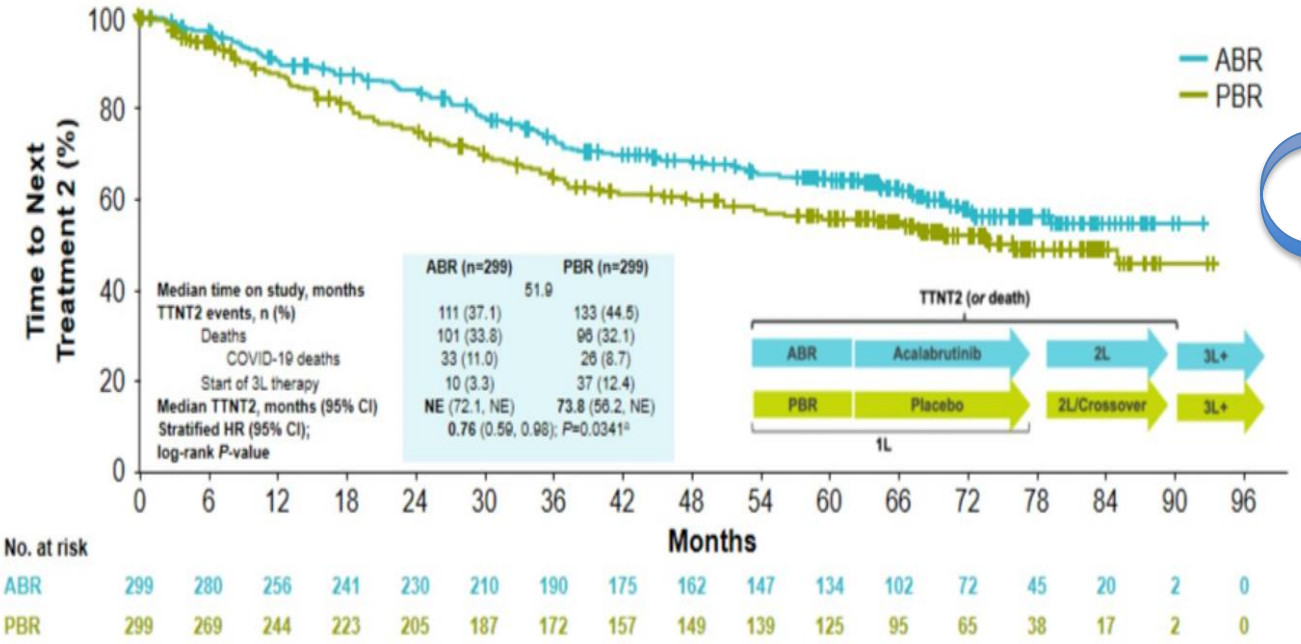
OS results were consistent with the previous analysis



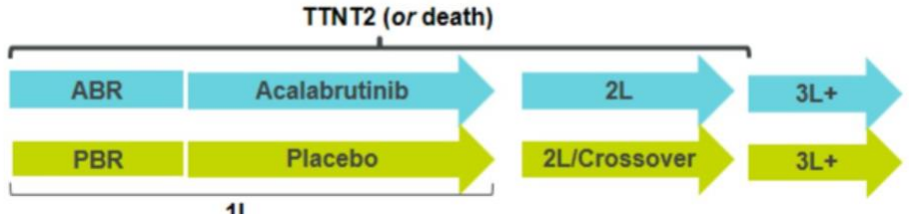
- Although the study was not powered for OS, results were consistent with those reported previously; maturity (number of patients with event) at this timepoint remained low (~38%)
- Censoring beyond median time on study of 52 months was high

Wang M, et al. ASH 2025

60.8 months of follow-up



- At 48 months, the rate of patients who had not yet initiated 3L therapy or had not died was 67.6% for ABR vs 59.2% for PBR



- **TTNT2** was defined as the time from randomization to either the start of 3L antilymphoma treatment after discontinuation of randomized treatment or death

Subsequent therapy was required by 11% with ABR vs 33% with PBR

Number of Patients	ABR (n=299)	PBR (n=299)
≥1 subsequent anticancer therapy	33	100
2L anticancer therapy[a,b]	**33**	**100**
BTKi	12	79
Chemotherapy	11	13
Non-BTKi targeted therapy[c]	9	6[e]
Others[d]	1	3[e]
3L anticancer therapy[a,b]	**10**	**37**
BTKi	3	7
Chemotherapy	4	19
Non-BTKi targeted therapy[c]	3	11
4L+ anticancer therapy[a,b]	**3**	**14**
BTKi	0	5
Chemotherapy	2	7
Non-BTKi targeted therapy[c]	1	7

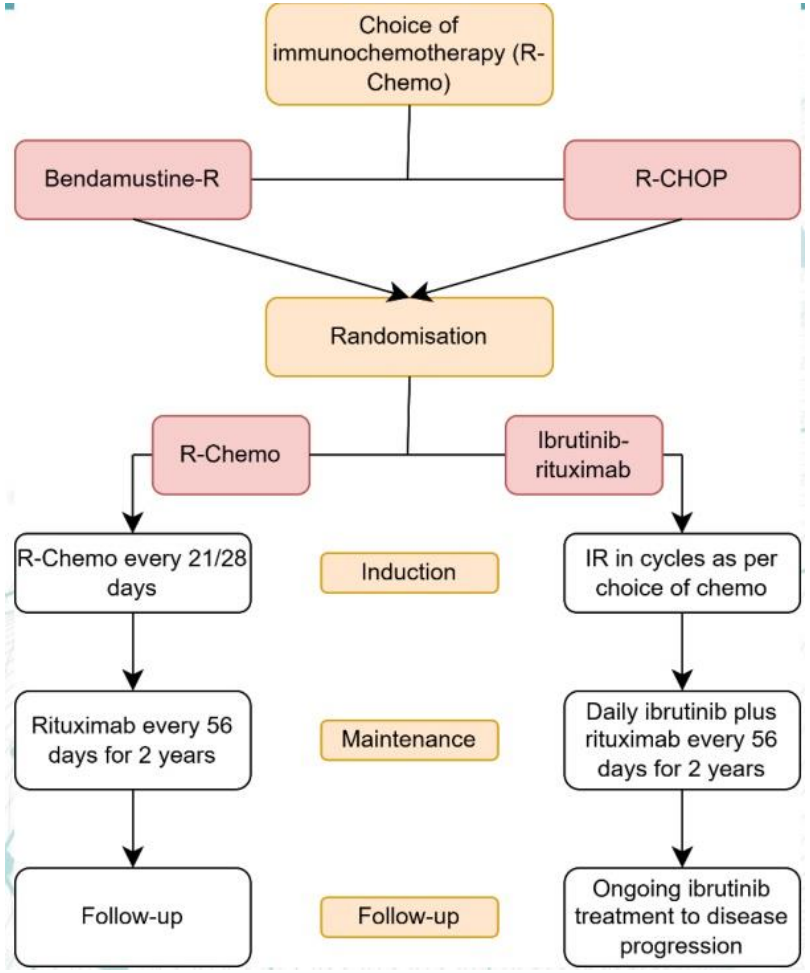
- 57 of 79 patients in the PBR arm who received BTKis in 2L received acalabrutinib on study as crossover

Need for subsequent anticancer therapy was 3-fold higher with PBR: These results emphasize the benefits of acalabrutinib plus BR as a 1L treatment approach, **improving PFS and delaying need of subsequent therapies in patients with TN (treatment-naïve) MCL**.

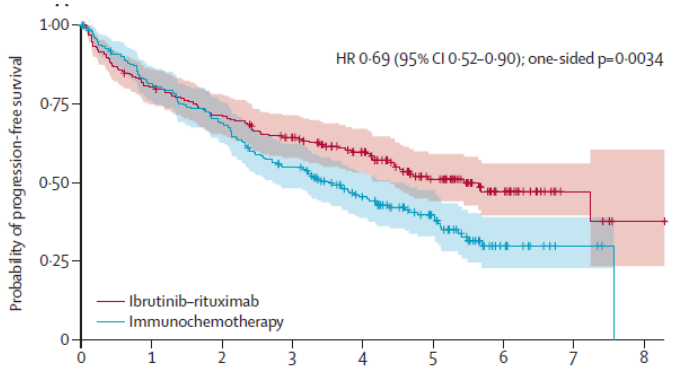
Wang M, et al. ASH 2025

ENRICH

Ibrutinib and rituximab versus immunochemotherapy in patients with previously untreated mantle cell lymphoma *patients 60 years and older*

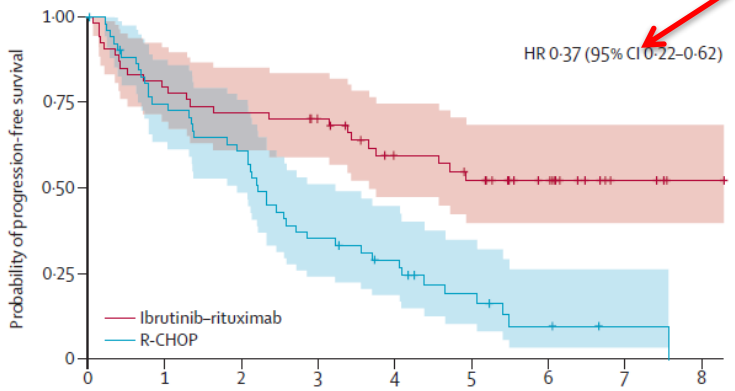


Significant improvement in PFS for ibrutinib–rituximab compared to immunochemotherapy (particularly to R-CHOP).



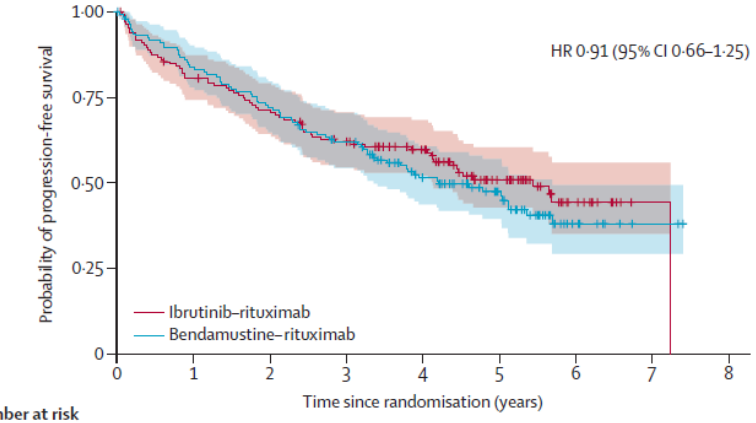
Number at risk (censored)

Ibrutinib–rituximab	199 (0)	158 (2)	140 (3)	120 (9)	94 (27)	58 (51)	27 (79)	5 (101)	1 (104)
Immunochemotherapy	198 (0)	157 (5)	133 (5)	103 (8)	70 (25)	44 (43)	12 (66)	3 (75)	0 (77)



Number at risk (censored)

Ibrutinib–rituximab	54 (0)	43 (0)	39 (0)	35 (3)	25 (8)	21 (9)	14 (16)	4 (26)	1 (29)
R-CHOP	53 (0)	38 (2)	31 (2)	18 (2)	13 (4)	7 (6)	3 (7)	1 (9)	0 (9)



Number at risk (censored)

Ibrutinib–rituximab	145 (0)	115 (2)	101 (3)	85 (6)	69 (19)	37 (42)	13 (63)	1 (75)	0 (75)
Bendamustine–rituximab	145 (0)	119 (3)	102 (3)	85 (6)	57 (21)	37 (37)	9 (59)	2 (66)	0 (68)

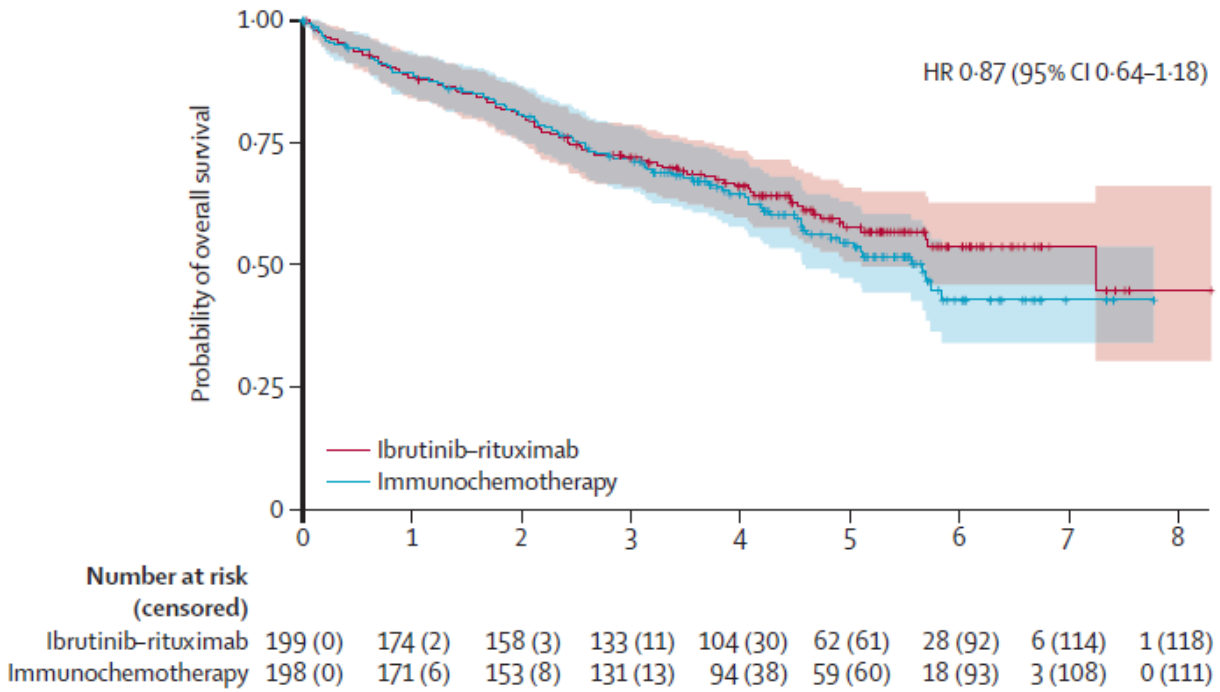
PFS median (95% CI)

IR: 65.3 mo (52.7 to not evaluable)

R-chemo: 42.4 mo (32.7 to 55.3)

David J Lewis, et al – Lancet 2025

ENRICH



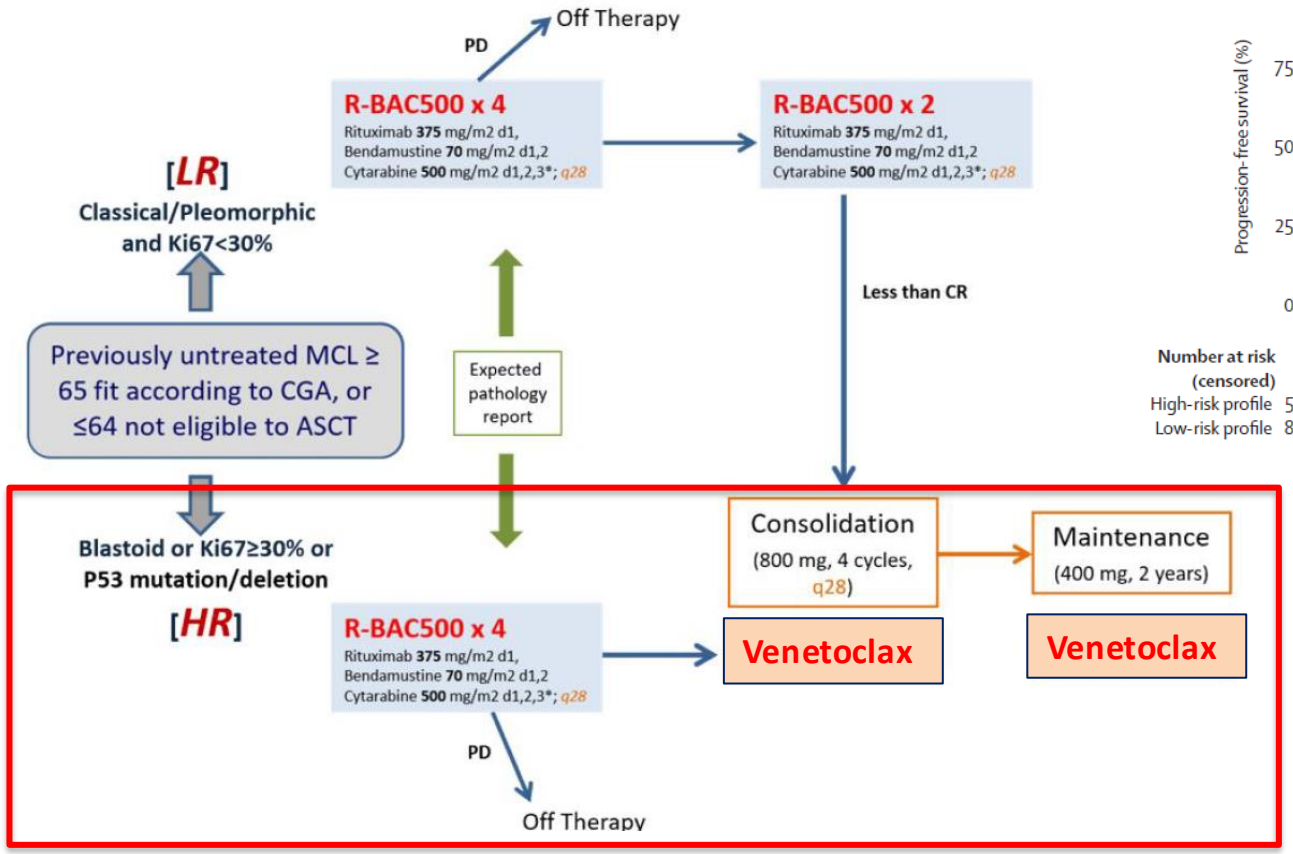
5-year OS (95% CI)

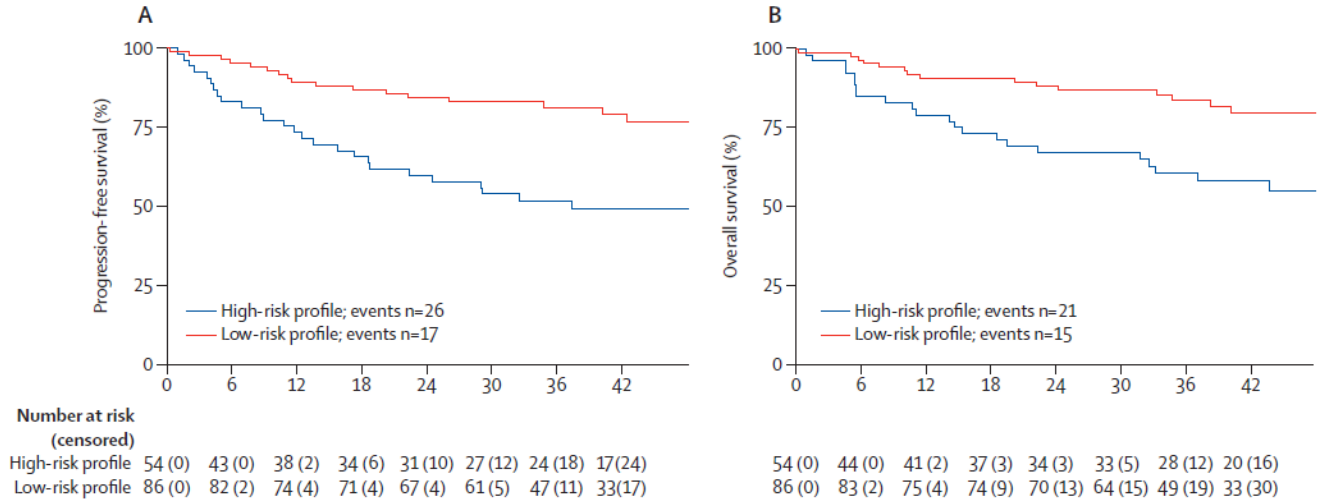
IR: 57.7% (50.6% to 65.7%)

R-Chemo: 54.5% (47.3% to 62.8%)

David J Lewis, et al – Lancet 2025

FIL_V-RBAC : Rituximab, bendamustine, and cytarabine followed by venetoclax in older patients with high-risk mantle cell lymphoma

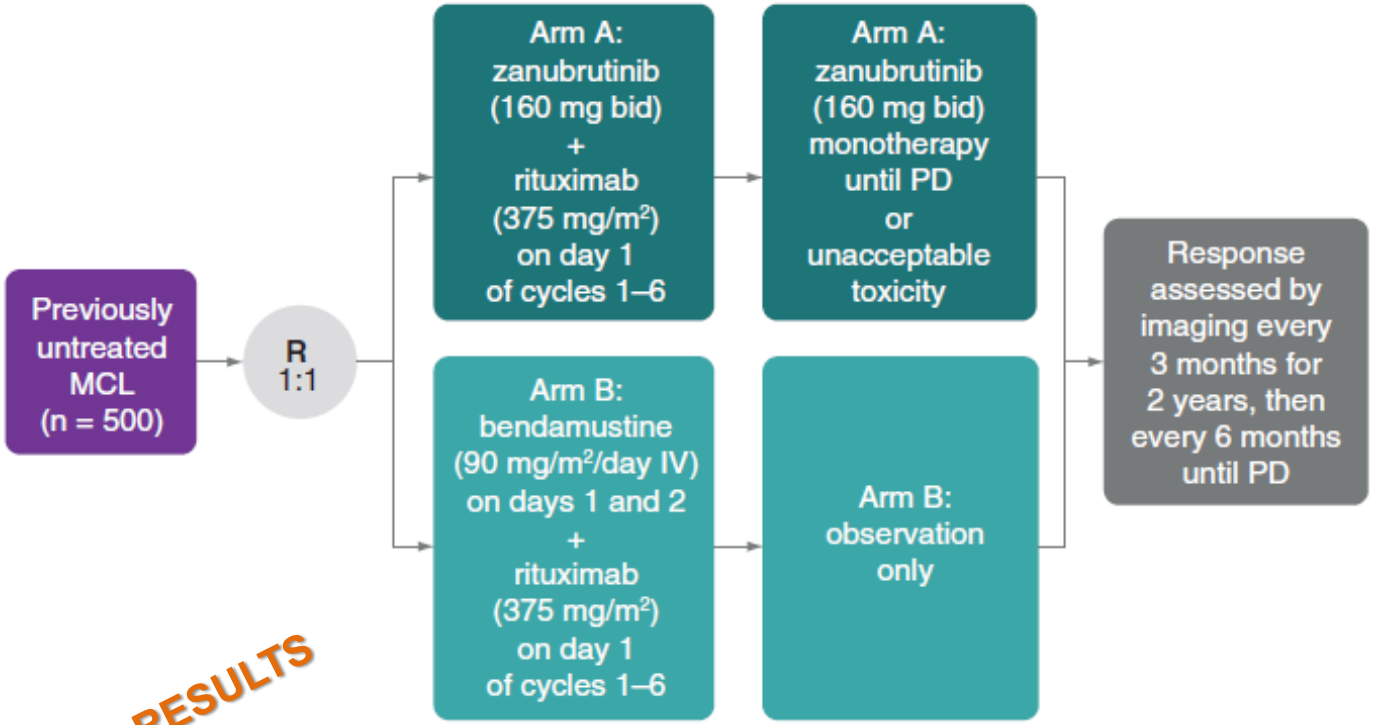




The addition of fixed-duration venetoclax improves the performance of RBAC in patients with a high-risk disease profile.

Visco C., et al – Lancet Hem 2025

MANGROVE: A Phase III Study of Zanubrutinib Plus Rituximab vs Bendamustine Plus Rituximab in Transplant-Ineligible, Untreated Mantle Cell Lymphoma



PENDING RESULTS

Preliminary results:

This chemotherapy-free regimen led to a ***43% reduction in the risk of progression or death*** (HR=0.57; [95% CI, 0.43, 0.76]; p<0.0001).

Dreyling M - Clinical Trial: NCT04002297

Novel chemo-free approachs and TP53 mutation

Chemofree 1L Triplets

BOVen: Zanubrutinib, obinutuzumab, and venetoclax (MCL with a TP53 mutation)

OASIS II : Ibrutinib, Venetoclax Plus CD20 Monoclonal Ab

TrAVeRse: AVR (acalabrutinib, venetoclax e rituximab)

MCL ELDERLY III – GLA 2022-3: venetoclax, ibrutinib and rituximab vs bendamustine, ibrutinib and rituximab

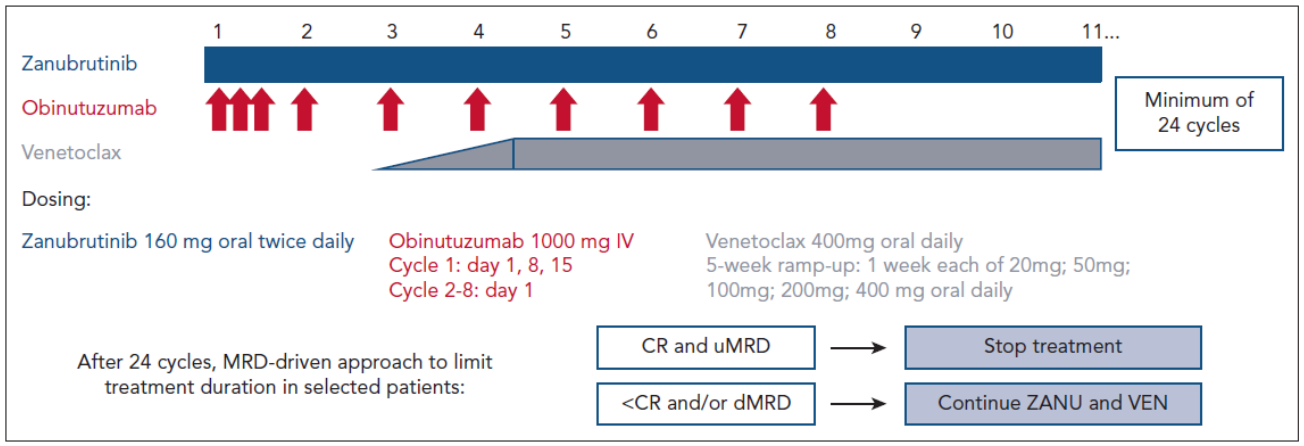
BOVen: Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a TP53 mutation

Study Design

- Open-label, multicenter, single-arm phase II trial (median follow-up : 23.3 mo)



- **Primary endpoint:** 2-yr PFS
  - Treatment considered effective if ≥11 patients are progression-free at 2 yr



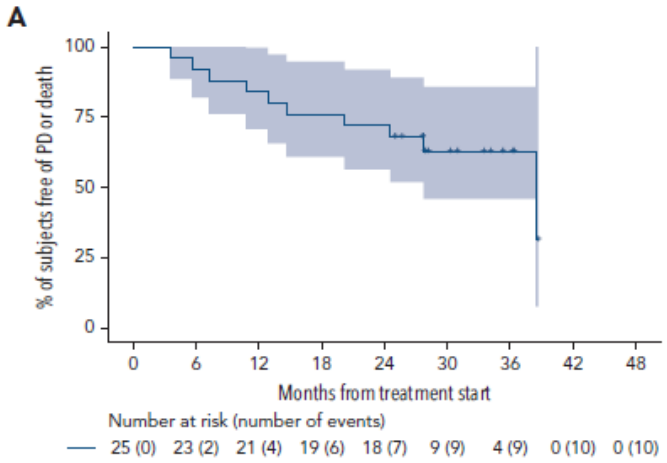
Baseline characteristics

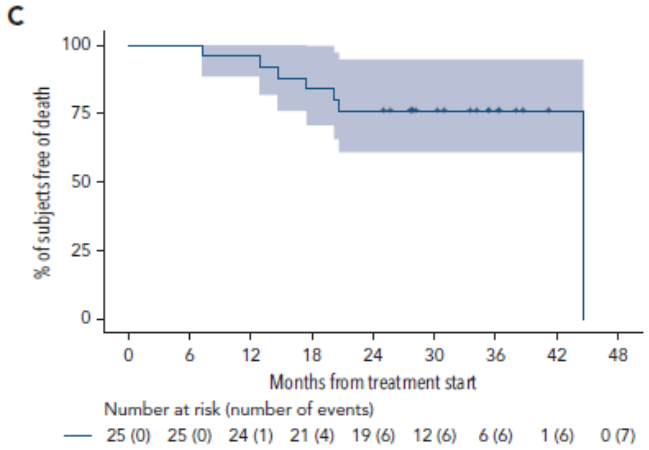
Characteristic	All Patients (N = 25)
Enrollment site, n (%)	
▪ MSKCC	13 (52)
▪ MGH	12 (48)
Median age, yr (range)	68 (60-73)
Male, n (%)	19 (76)
MCL histology, n (%)	
▪ Classical	15 (60)
▪ Non-nodal leukemic	5 (20)
▪ Blastic/blastoid	2 (8)
▪ Pleomorphic	3 (12)
Stage IV, n (%)	25 (100)
Ki-67 proliferation rate, n (%)	
▪ <30%	8 (38)
▪ ≥30% and <50%	6 (29)
▪ ≥50%	7 (33)
▪ Unknown	4

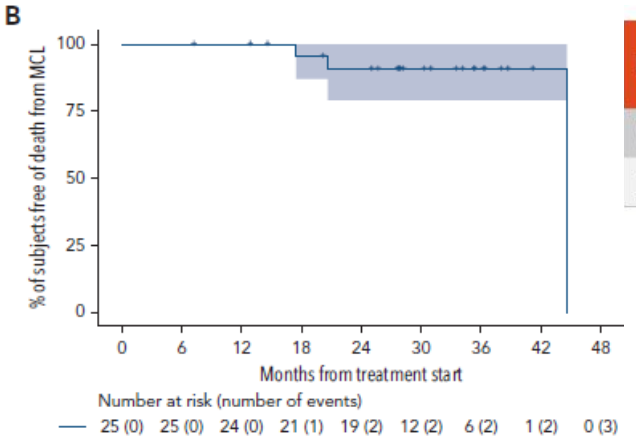
Characteristic	All Patients (N = 25)
MIPI classification, n (%)	
▪ Low	1 (4)
▪ Intermediate	7 (28)
▪ High	17 (68)
Bone marrow involvement, n (%)	22 (88)
Peripheral blood involvement,* n (%)	20 (80)
GI involvement,† n (%)	8 (32)
TP53 overexpression by IHC,‡ n (%)	
▪ Positive	18 (86)
▪ Negative	3 (14)
▪ Unknown	4
IgHV mutation, n (%)	
▪ Mutated	5 (28)
▪ Unmutated	13 (72)
▪ Unknown	7
17p deletion by FISH/SNP array	11 (44)

Kumar. A et al ASH 2023. Abstr 738 and Blood 2025.

BOVen: Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a TP53 mutation







Serious AE, n (%)	All Patients (N = 25)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall
COVID-19 infection	-	**3 (12)**	-	-	**2 (8)**	**5 (20)**
Atrial fibrillation	-	-	1 (4)	-	-	1 (4)
Fever	1 (4)	-	-	-	-	1 (4)
Lung infection	-	-	1 (4)	-	-	1 (4)
Nocardia	-	1 (4)	-	-	-	1 (4)
Organizing pneumonia	-	1 (4)	-	-	-	1 (4)
Maculopapular rash	-	-	1 (4)	-	-	1 (4)
Tumor lysis syndrome	-	-	-	1 (4)	-	1 (4)

Response, %	Complete Metabolic Response	Partial Metabolic Response	Overall
Cycle 3 Day 1	68	8	76
Best overall	88	8	96

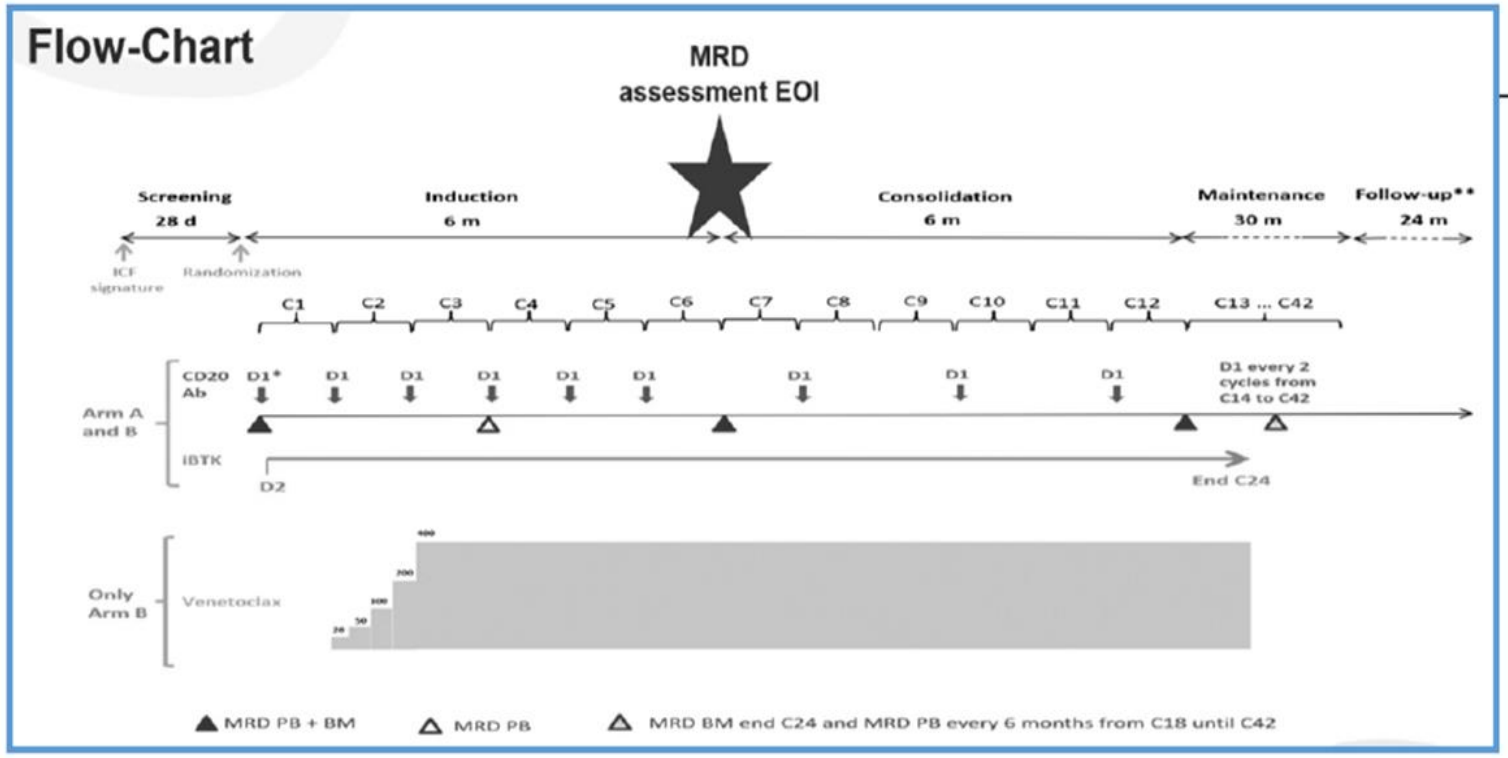
Survival Outcome	All Patients (N = 25)
PFS	
▪ **2-yr, % (95% CI) (Primary Endpoint)**	**72 (56-92)**
▪ Median, mo	NR
OS	
▪ 2-yr, % (95% CI)	75 (58-93)
▪ Median, mo	NR
DFS	
▪ 2-yr, % (95% CI)	88 (76-100)
▪ Median, mo	NR

Conclusions: BOVen was associated with high response rates and a **promising 2-year PFS of 72% in TP53-mutant MCL**. These data support its use and further **evaluation in this high-risk population**.

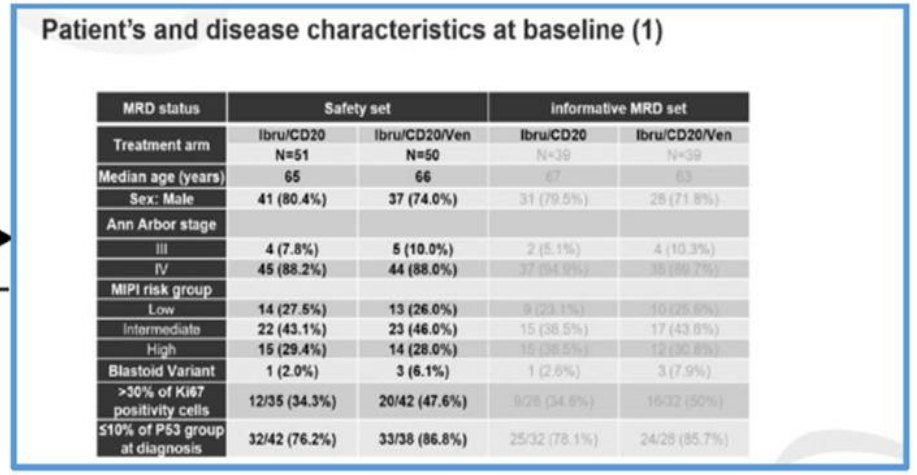
Kumar. A et al ASH 2023. Abstr 738 and Blood 2025.

OASIS II : Ibrutinib, Venetoclax Plus CD20 Monoclonal Ab Provides Very High MRD Negativity in Previously Untreated MCL Patients

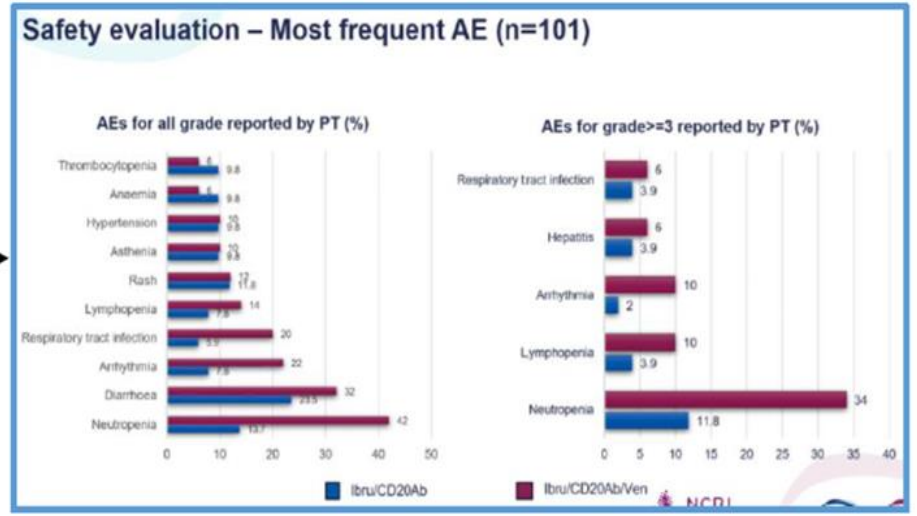
Randomized Phase 2 Trial



Ibrutinib/anti-CD20 vs Ibrutinib/anti-CD20/ Venetoclax



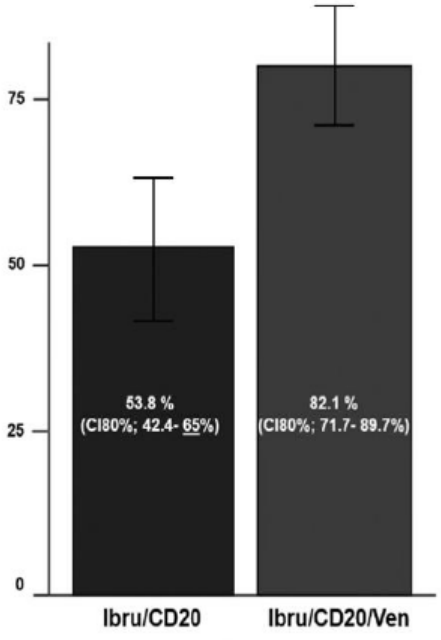
MRD status	Safety set		informative MRD set	
Treatment arm	Ibru/CD20 N=51	Ibru/CD20/Ven N=50	Ibru/CD20 N=39	Ibru/CD20/Ven N=39
Median age (years)	65	66	67	63
Sex: Male	41 (80.4%)	37 (74.0%)	31 (79.5%)	28 (71.8%)
Ann Arbor stage				
III	4 (7.8%)	5 (10.0%)	2 (5.1%)	4 (10.3%)
IV	45 (88.2%)	44 (88.0%)	37 (94.9%)	35 (89.7%)
MIPI risk group				
Low	14 (27.5%)	13 (26.0%)	9 (23.1%)	10 (25.6%)
Intermediate	22 (43.1%)	23 (46.0%)	15 (38.5%)	17 (43.6%)
High	15 (29.4%)	14 (28.0%)	15 (38.5%)	12 (30.8%)
Blastoid Variant	1 (2.0%)	3 (6.1%)	1 (2.6%)	3 (7.9%)
>30% of Ki67 positivity cells	12/35 (34.3%)	20/42 (47.6%)	9/26 (34.6%)	16/32 (50%)
≤10% of P53 group at diagnosis	32/42 (76.2%)	33/38 (86.8%)	25/32 (78.1%)	24/28 (85.7%)



Le Gouill et al. — ASH 2024, ASCO 2025, J Clin Oncol. 2025

MRD Negativity at End of Induction (Primary Efficacy Endpoint) (n=39)

- MRD negativity rate assessed by ddPCR at the end of induction (after C6)
- N=39 in each arms



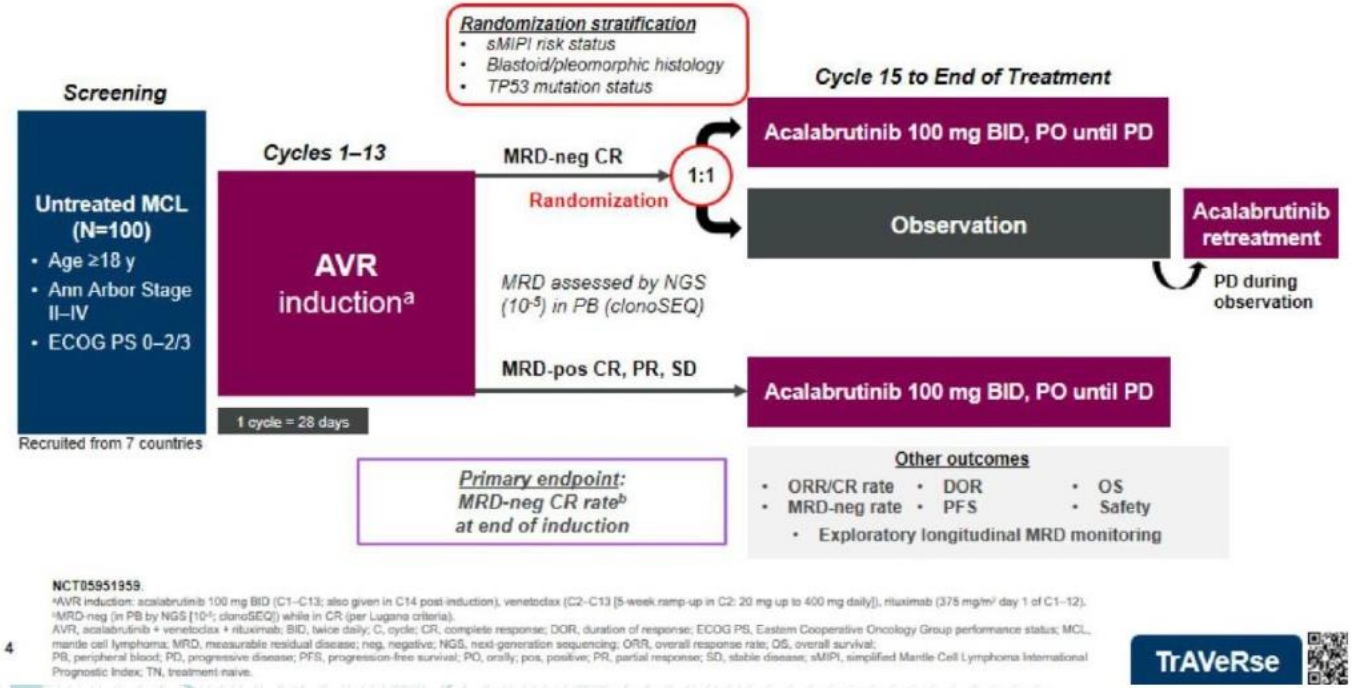
Treatment arm	Ibru/CD20Ab (n=51)	Ibru/CD20Ab/Ven (n=50)	Total (n=101)
CR	29 (56.9%)	32 (64 %)	61 (60.4%)
PR	11 (21.6%)	8 (16 %)	19 (18.8%)
ORR	40 (78.5%)	40 (80%)	80 (79,2%)
SD	2 (3.9%)	0	2 (2%)
PD	1 (2%)	0	1 (1%)
NE	8 (15.7%)	10 (20%)	18 (17.8%)

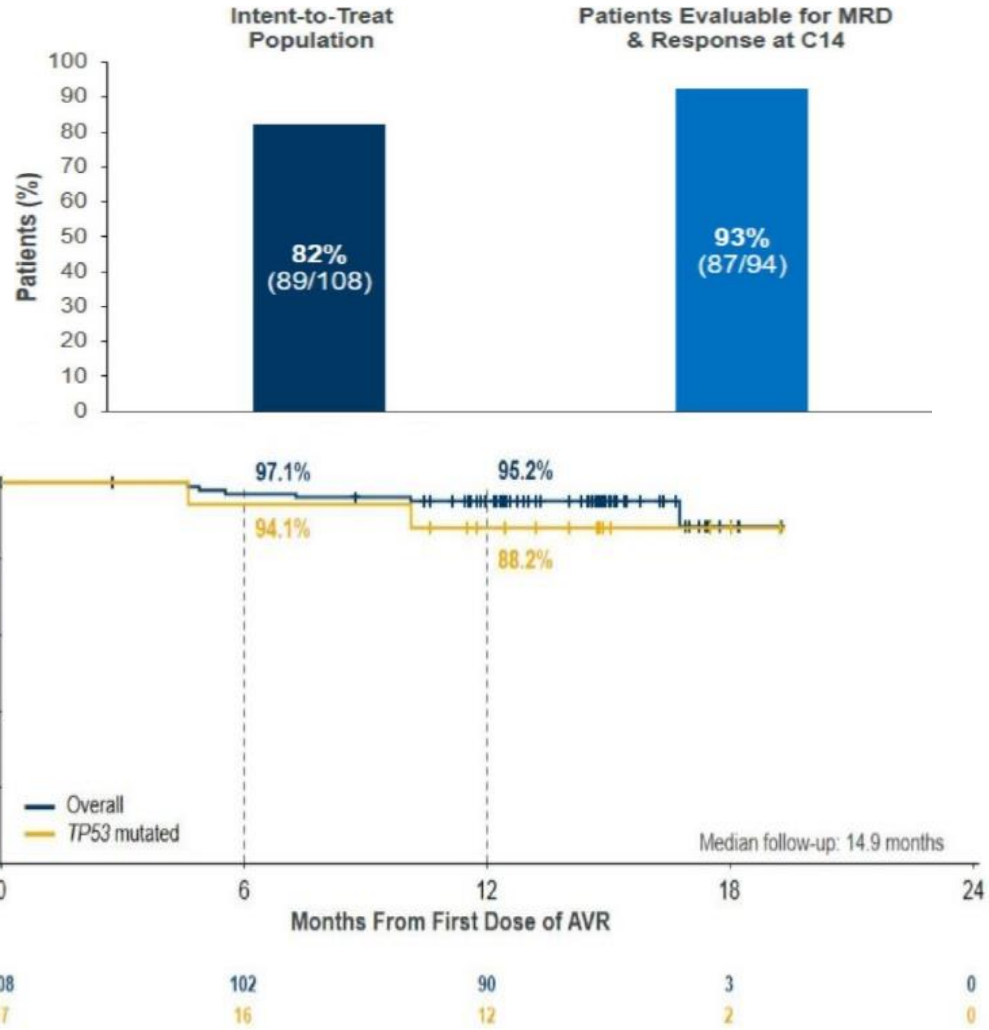
With overall survival (OS) being equal, venetoclax improves the depth of response.

Le Gouill et al. — ASH 2024, ASCO 2025, J Clin Oncol. 2025

TrAVeRse Study: Multicenter, Open-label, Phase 2 Trial

AVR (acalabrutinib, venetoclax e rituximab)



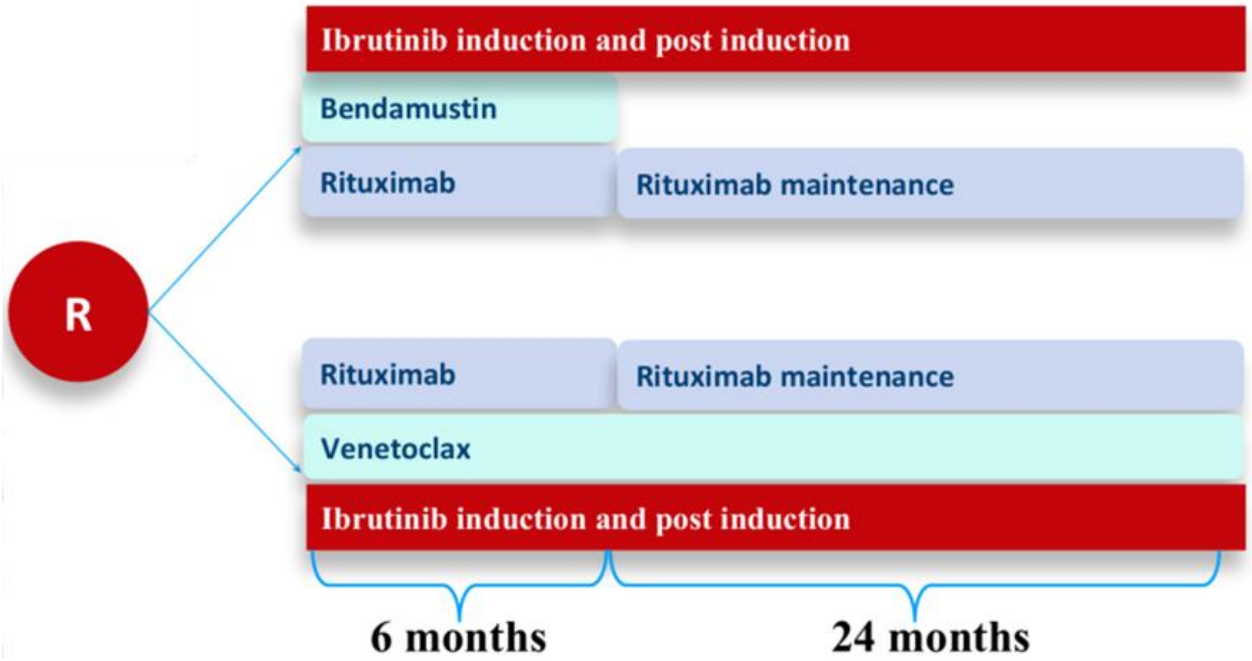


PFS rates were high, regardless of TP53 mutation status

Hawkes et al. ASH 2025

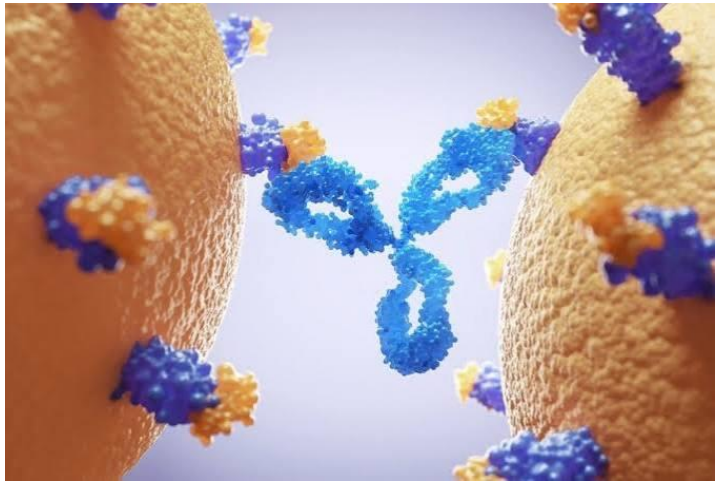
MCL ELDERLY III – GLA 2022-3 (VIRAL)

international, randomized, open-label phase II trial to investigate the combinations of venetoclax, ibrutinib and rituximab or bendamustine, ibrutinib and rituximab in patients with treatment naive mantle cell lymphoma not eligible for dose-intensive treatment



ACTIVE RECRUITING





RECRUITING

Glofitamab With Obinutuzumab, Venetoclax, and Lenalidomide for the Treatment of Patients With Newly Diagnosed High Risk **Mantle** **Cell** **Lymphoma**

ClinicalTrials.gov ID NCT05861050

Sponsor City of Hope Medical Center

NOT YET RECRUITING

Glofitamab Plus Ibrutinib With Obinutuzumab for the Treatment of Patients With **Mantle** **Cell** **Lymphoma**

ClinicalTrials.gov ID NCT06357676

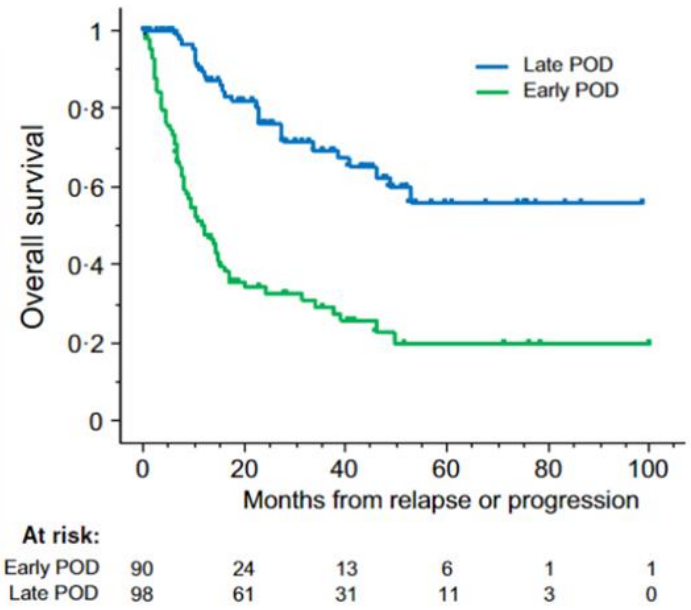
Sponsor OHSU Knight Cancer Institute



How to treat R/R MCL?

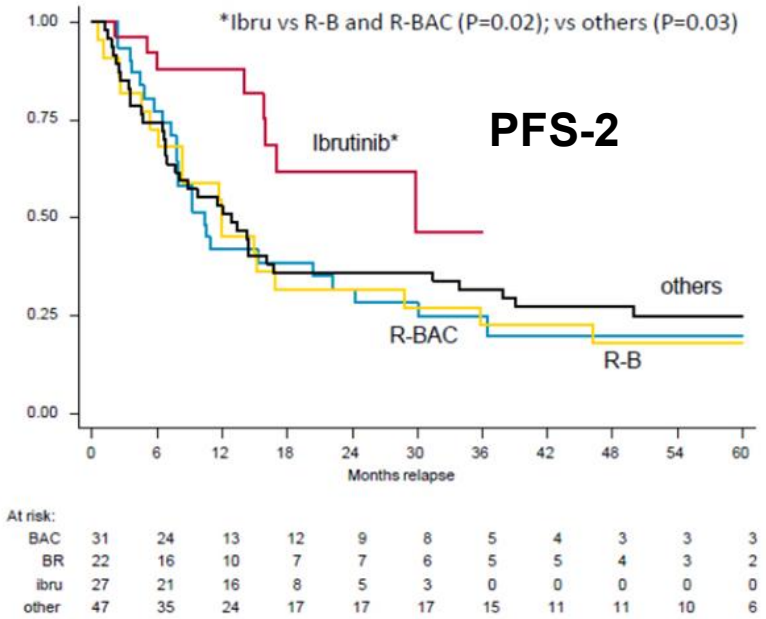
Ibrutinib as standard of care for first relapse: Time to first progression of disease (time to POD)

Ibrutinib 560 mg/die



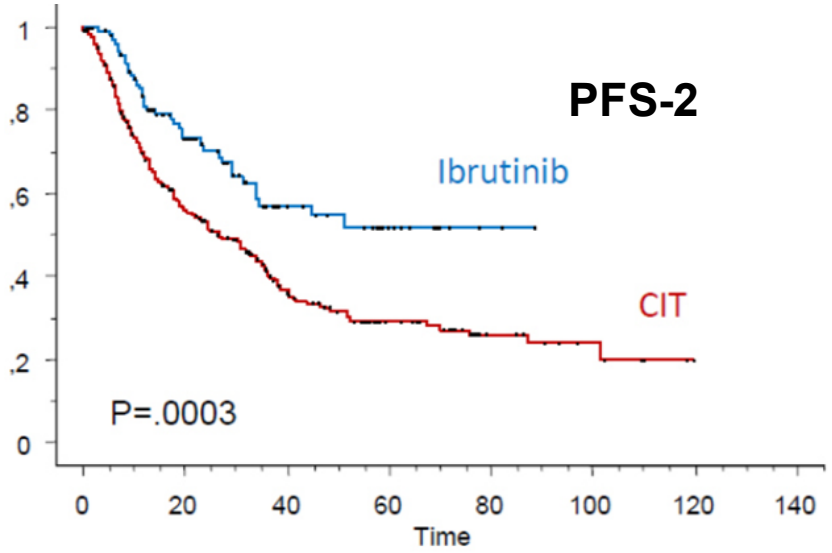
Visco C et al, BJH 2019

Early POD (≤ 24 months)



Visco C et al, Leukemia 2020

Late POD (> 24 months)



Median 26 months for CIT;
NR for Ibrutinib

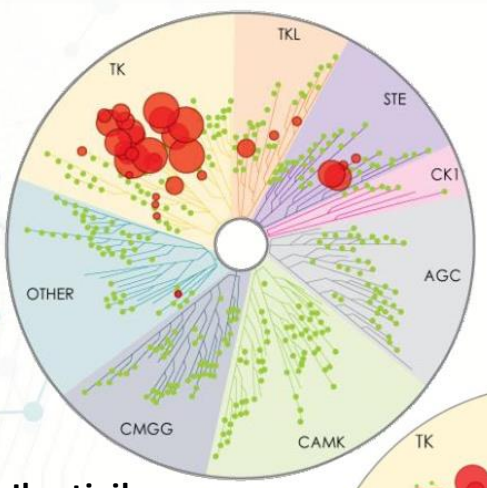
Malinverni C et al, Blood 2024

BTKi as the preferable second-line approach in patients with BTKi-naïve MCL

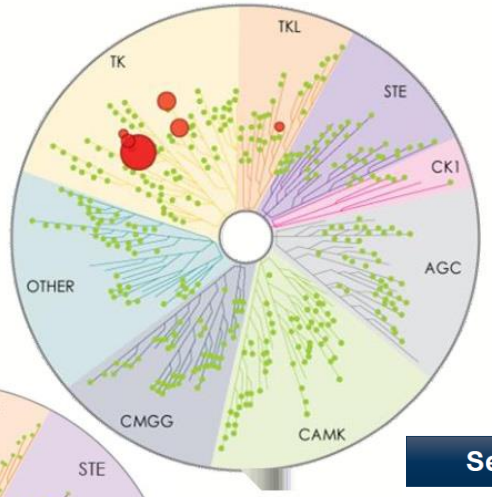
Kinase Selectivity of BTK Inhibitors and toxicities

Kinase	IC_{50}/EC_{50} (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

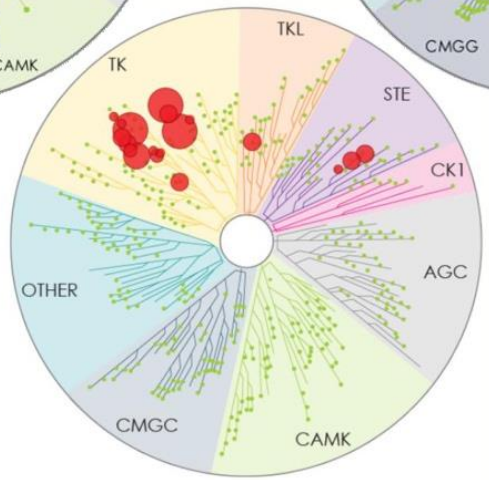
Kinase Selectivity Profiling at 1 μmol/L (in vitro)
Larger red circles represent stronger inhibition



Ibrutinib

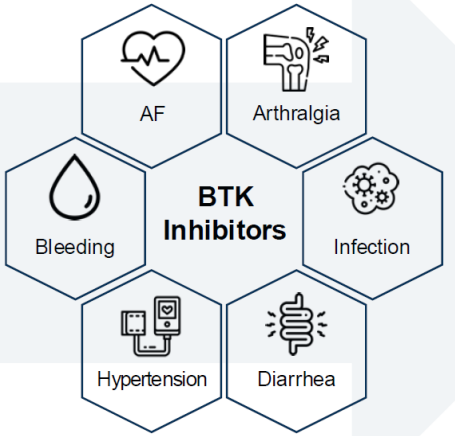


Acalabrutinib
(more selective
Less toxicities,
less off-target)



Zanubrutinib
(more potent)

Selected Toxicities With BTKi

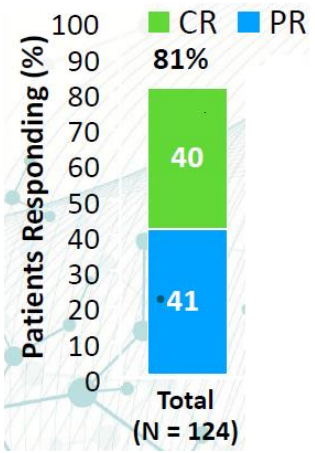


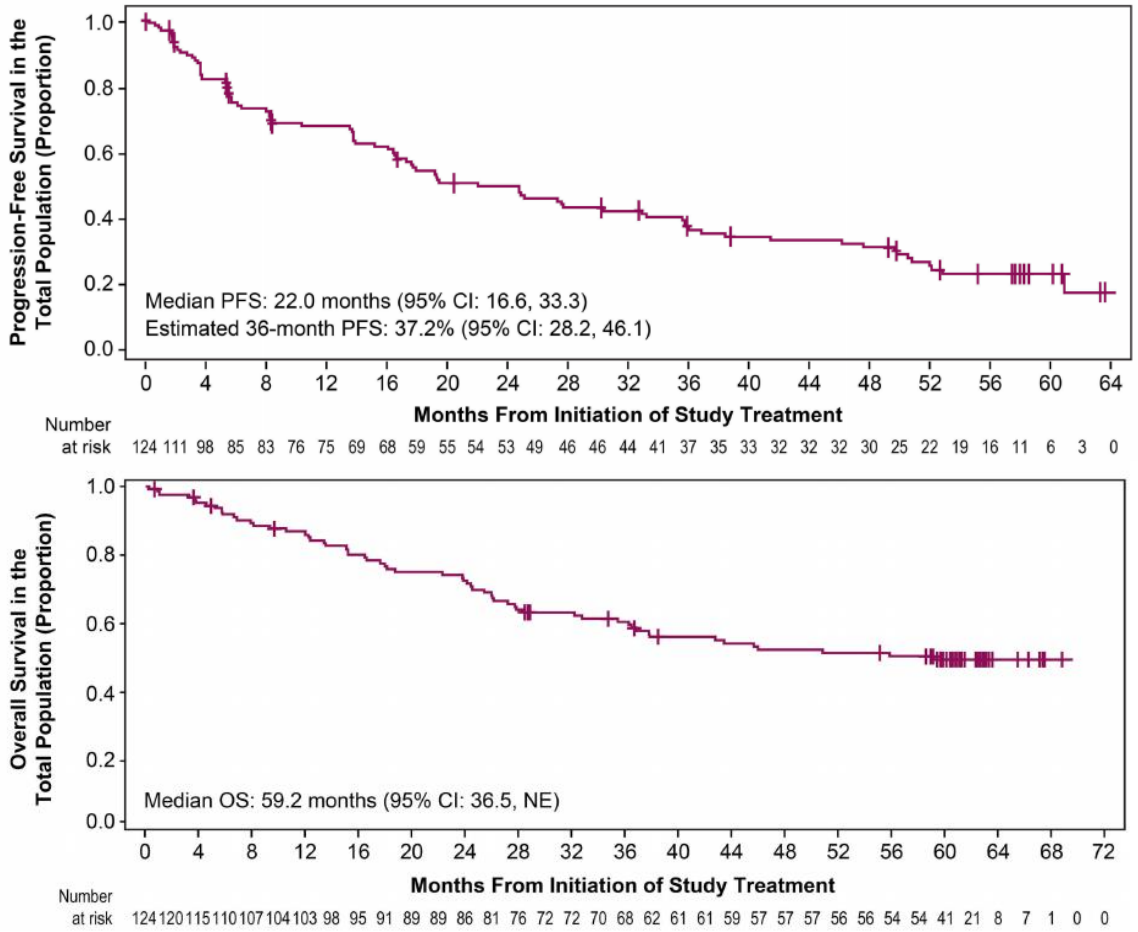
Kaptein. ASH 2018. Abstr 1871.

Phase II ACE-LY-004: Acalabrutinib in Relapsed/Refractory MCL

Acalabrutinib 100 mg PO BID in 28-day cycles (*Until PD*)

- Adult patients with MCL;
- 1-5 prior lines of tx; ECOG PS 0-2; no notable CVD*;
- no concurrent use of warfarin/equivalent vitamin K antagonists,
- no prior BTK inhibitors





- ***Median PFS was 22 months*** *in the overall population*
- ***Median OS was 59.2 months*** *in the overall population*

Wang M. Lancet 2018; Le Gouill S et al. Haematologica. 2024

Phase II ACE-LY-004: Acalabrutinib in Relapsed/Refractory MCL

n (%)	Any Grade	Grade 3/4
Atrial fibrillation	3 (2.4%)	0
Hypertension	5 (4.0%)	2 (1.6%)
Hemorrhage	46 (37.1%)	5 (4.0%)
Infections	84 (67.7%)	21 (16.9%)

n (%)	Acalabrutinib
Discontinuations for PD	77 (62.1%)
Discontinuations for AEs	**15 (12.1%)**
Patients on treatment at data cut-off	18 (14.5%)
Median duration of treatment (range)	17.5 months (0.1–65.3)

- ***Patients discontinue primarily due to disease progression, not because of toxicity.***
- *43.5% of patients continued acalabrutinib for more than 24 months, including 11.3% who continued therapy for more than 60 months.*

Le Gouill S et al. Haematologica. 2024

Zanubrutinib in Relapsed/Refractory MCL

Zanubrutinib 160 mg PO BID

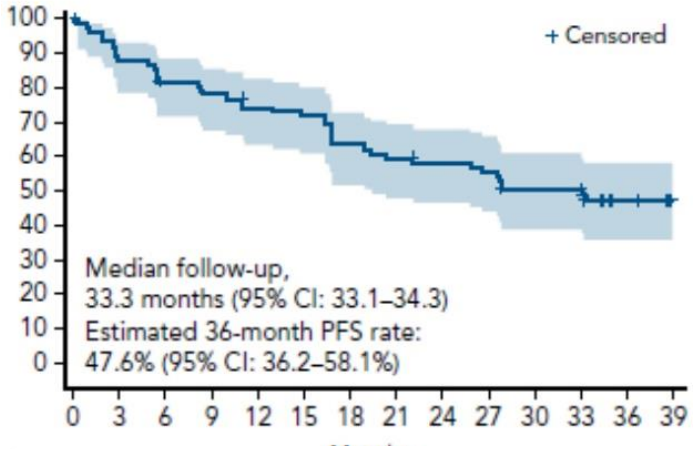
Zanubrutinib monotherapy demonstrates durable clinical benefit in the long-term follow-up of patients with relapsed/refractory MCL

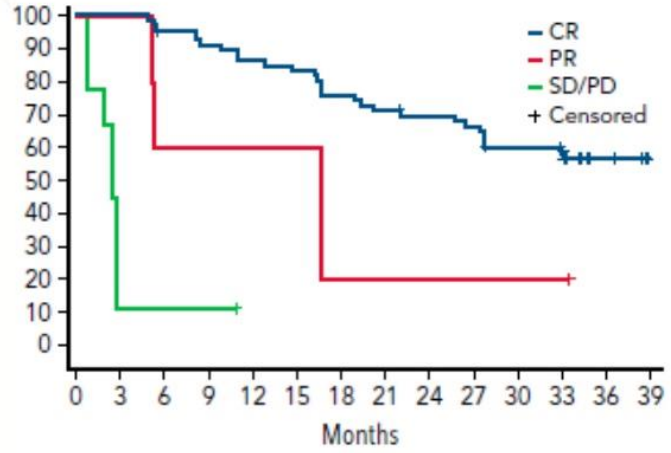
	Response	PFS 2 years	PFS 3 years
Phase 2 86 Patients with R/R MCL Median follow-up **35.3 months**	ORR 84% CR 78%	58%	48%
	Median DOR	**OS 2 years**	**OS 3 years**
	Not reached (95% CI: 24.9 months to NE)	80%	75%

Zanubrutinib was well tolerated

- Few discontinuations (9.3%) due to AEs
- Majority of AEs: low-grade severity
- No atrial fibrillation/flutter
- No second primary malignancies

PFS 36-months follow up



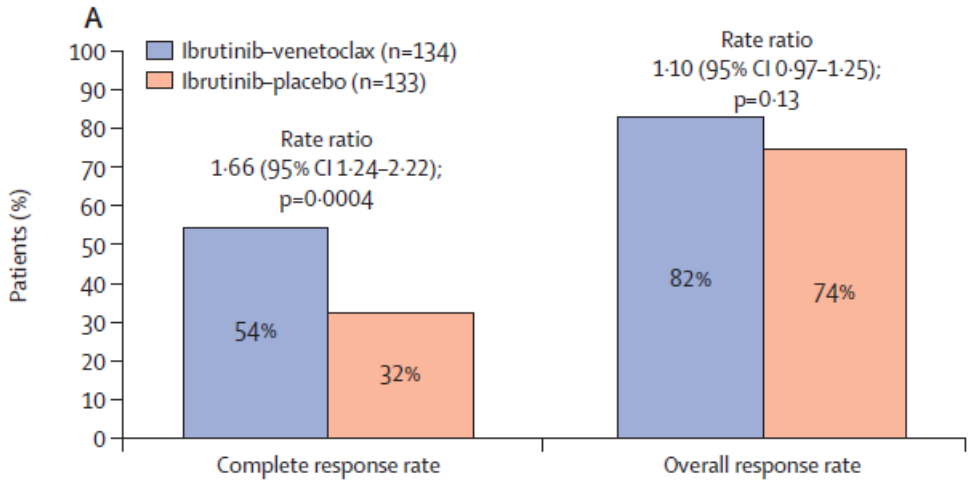


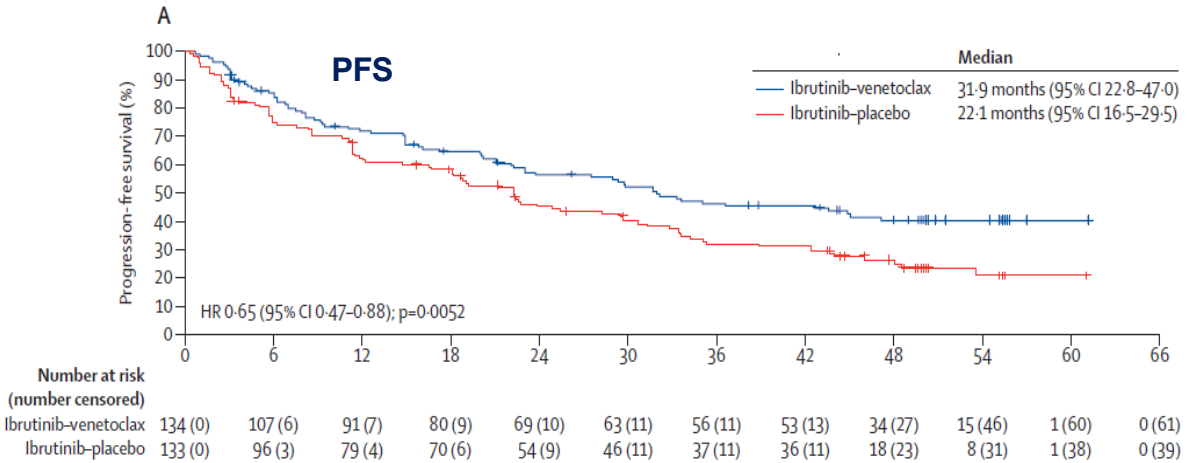
Song Y. et al . Blood . 2022; 139:3149

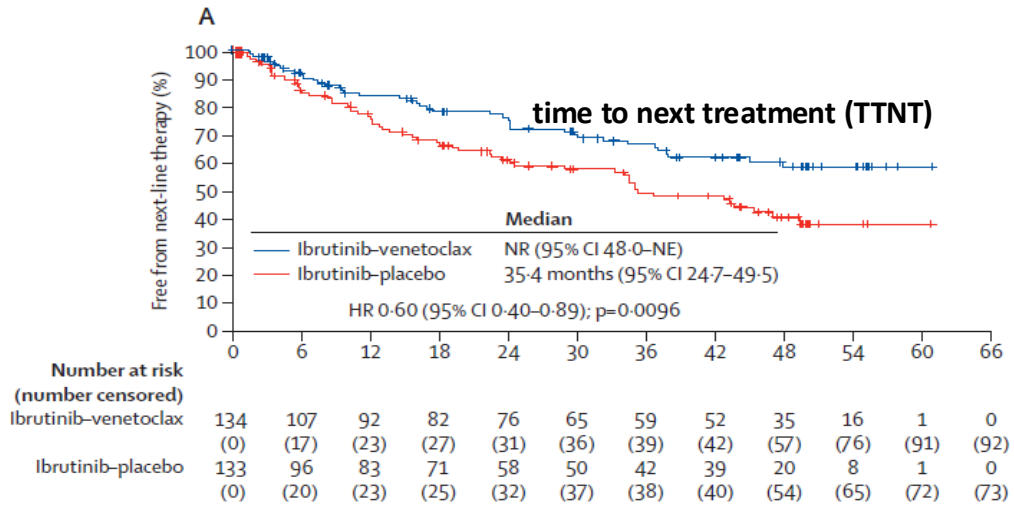
Adverse Events of Available BTK Inhibitors in MCL

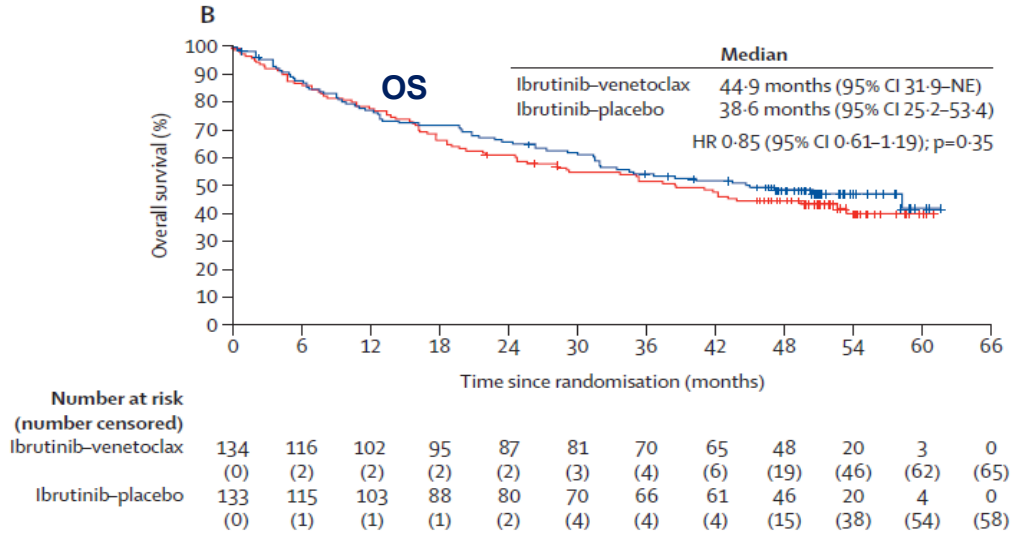
Ibrutinib	Acalabrutinib	Zanubrutinib
Gastrointestinal	**Gastrointestinal**	**Gastrointestinal**
Diarrhea: 51% (grade ≥3: 5%) Nausea: 31% (grade ≥3: 0%)	Diarrhea: 31% (grade ≥3: 3.2%) Nausea: 19% (grade ≥3: 0.8%)	Diarrhea: 23% (grade ≥3: 0.8%) Nausea: NR
Musculoskeletal	**Musculoskeletal**	**Musculoskeletal**
Includes pain, arthralgias, muscle spasms 11% to 37% of patients (grade ≥3: up to 1%	Includes myalgia 21% of patients (grade ≥3: 0.8%)	Includes pain, discomfort, myalgia, back pain, arthralgia, arthritis 14% of patients (grade ≥3: 3.4%)
Other common AEs	**Other common AEs**	**Other common AEs**
Rash: 25% (grade ≥3: 3%) Fatigue: 41% (grade ≥3: 5%) Headache: 13% (grade ≥3: 0%)	Rash: 18% (grade ≥3: 0.8%) Fatigue: 28% (grade ≥3: 0.8%) Headache: 39% (grade ≥3: 1.6%)	Rash: 36% (grade ≥3: 0%) Fatigue: 11% Headache: 4.2%

SYMPATICO : Ibrutinib plus venetoclax in R/R MCL: a multicentre, randomised, double-blind, placebo-controlled, phase 3 study





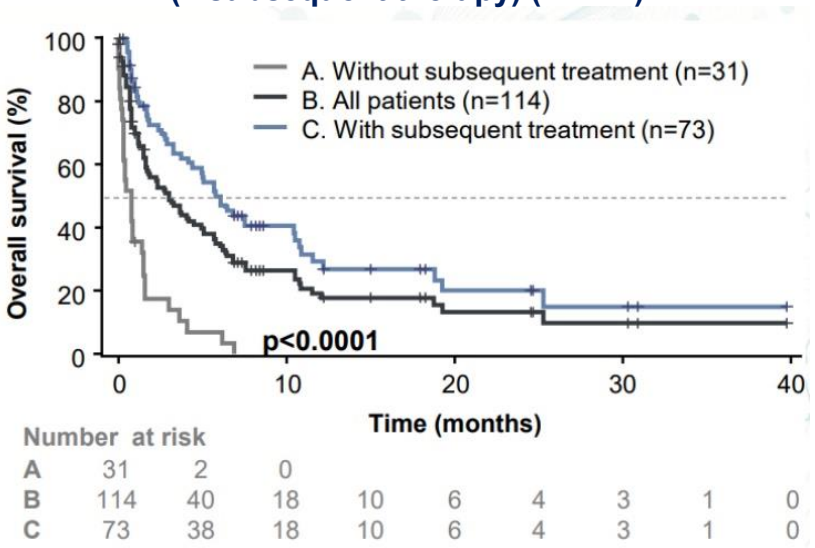




Wang M et al. Lancet Oncology 2025

Outcome in MCL is Poor Following Covalent BTK Inhibitor Progression

OS of patients with MCL after ibrutinib cessation (± subsequent therapy) (N=114)



Adapted form Martin P, et al. Blood 2016

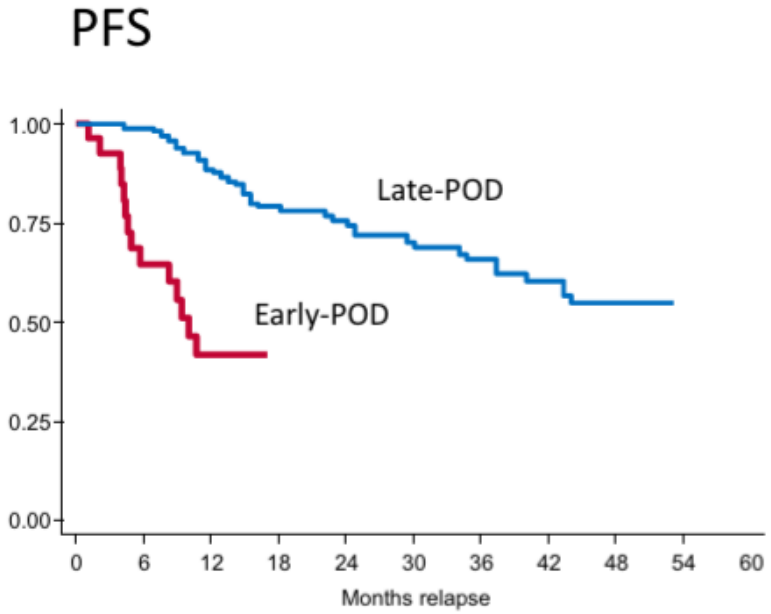
Median OS all patients: 2.9 months

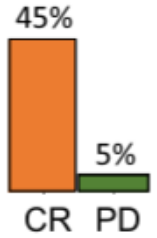
- The **main cause of discontinuation** is **disease progression**
- Acquired resistance appeares to be universal
- **Primary resistance to ibrutinib occurs in 1/3 patient**
- **Lower activity of ibrutinib in high-risk MCL**
- **(**Blastoid, TP53, ki67≥ 50%)

Unmet medical needs

Martin P, et al. Blood 2016; Jain P, et al. Br J Haematol 2018

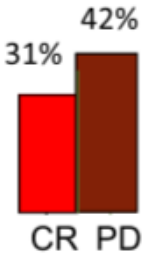
Ibrutinib at first relapse and CAR-T





Late-POD

Standard approach during BTKi
Refer to CAR-T centre if suboptimal response or high-risk features (i.e. TP53 mutation)



Early-POD

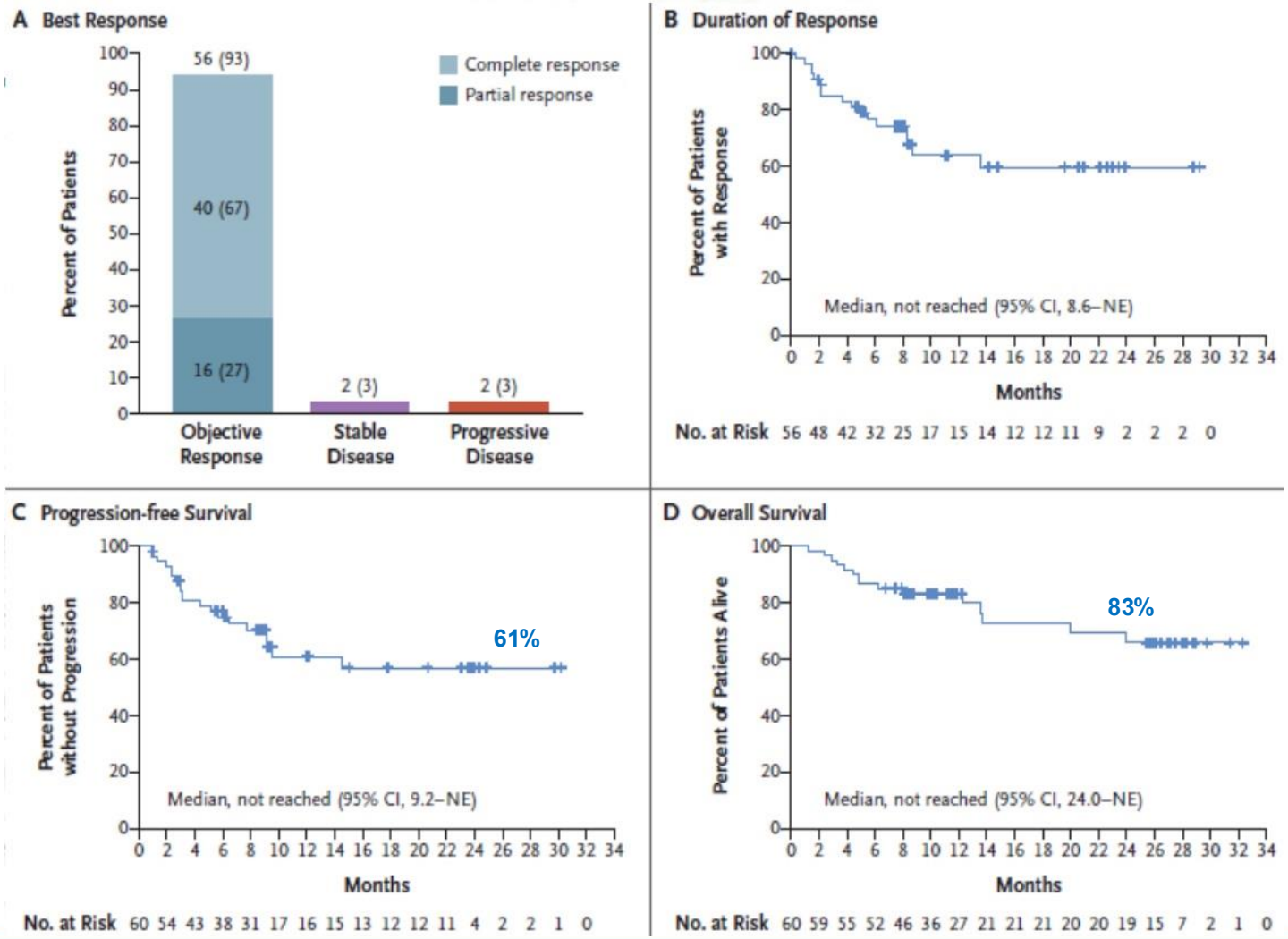
Refer to CAR-T centre at start of therapy
Close clinical monitoring
Restage 8-12 weeks

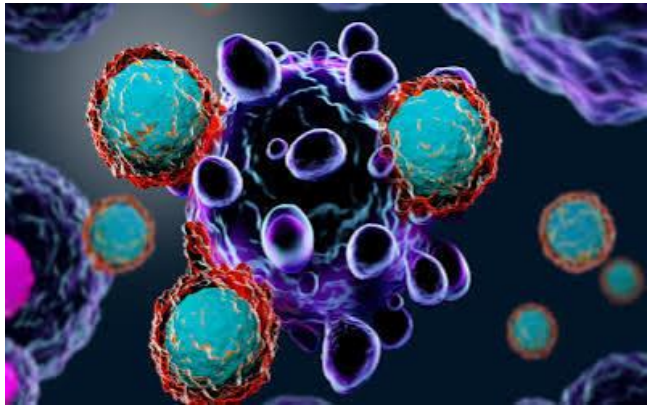
Patient identification at first relapse (before starting 2L):
High risk patients:

- **Blastoid/pleomorfic morphology**
- **TP53 mut (including high expression of p53 with immunohistochemistry)**
- **Ki 67 > 50%**
- **Bulky > 5 cm**
- **POD24**
- **sMIPI high score (≥ 6,2)**

Visco, BJH 2023; Eyre BJH 2023

CART- Brexucel: ZUMA 2: phase 2 study





Median follow up: 12.3 months

74 patients enrolled

Median age 65 (38-79)

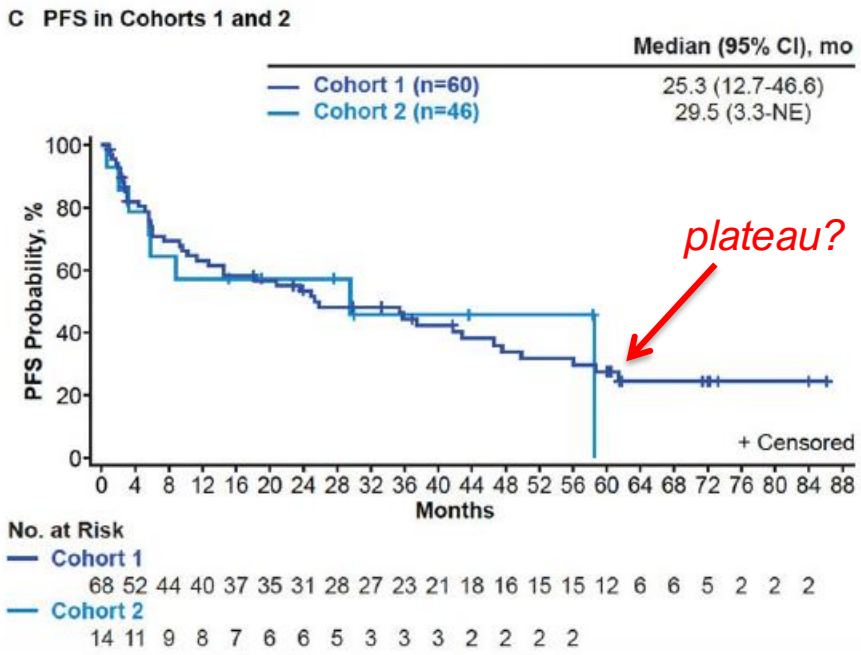
Wang M, et al. N Engl J Med 2020

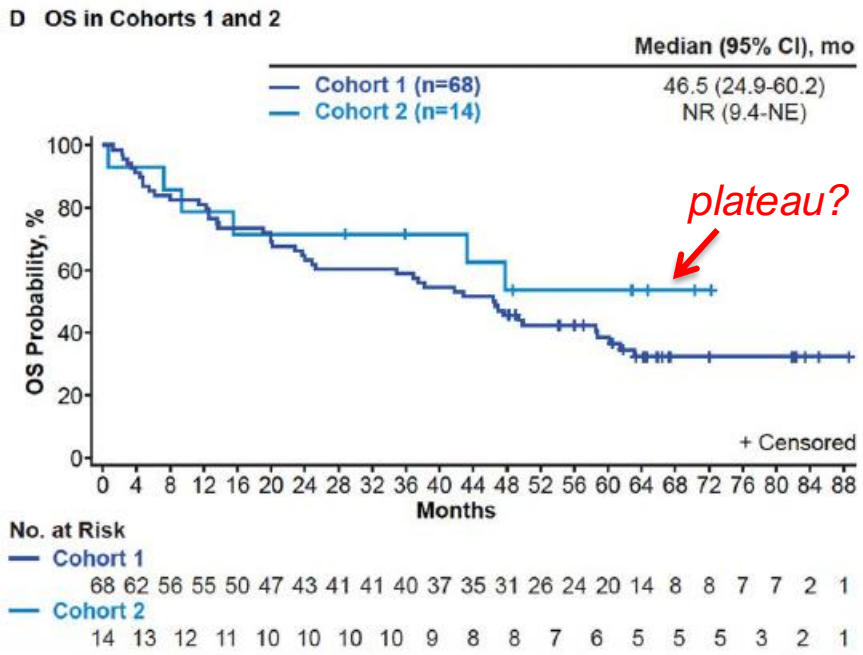
ZUMA-2 Study: Comparison of the Three Cohorts

Characteristic	Cohort 1	Cohort 2	Cohort 3
Patient population	R/R MCL	R/R MCL	R/R MCL
Prior BTKi exposure	Yes	Yes	No (BTKi-naive)
CAR-T therapy	Brexu-cel	Brexu-cel	Brexu-cel
CAR-T dose (cells/kg)	2×10^6	0.5×10^6	2×10^6
Patients treated (n)	68	14	86
Overall response rate (ORR)	93%*	93%	91%
Complete response (CR) rate	67%*	64%	73%

Wang M et al, ASH 2024 ; Munoz J – Journal of Hematology & Oncology 2026

Patient disposition for ZUMA-2 Cohorts 1 and 2: follow up 5-years





- ❑ **ORR 93%**
- ❑ **CR rate 64%**

Median follow-up of 5 years

- ❑ Late-onset toxicities were infrequent;
- ❑ only 3% of treatment-emergent adverse events of interest in ZUMA-2 occurred during this longer follow-up.

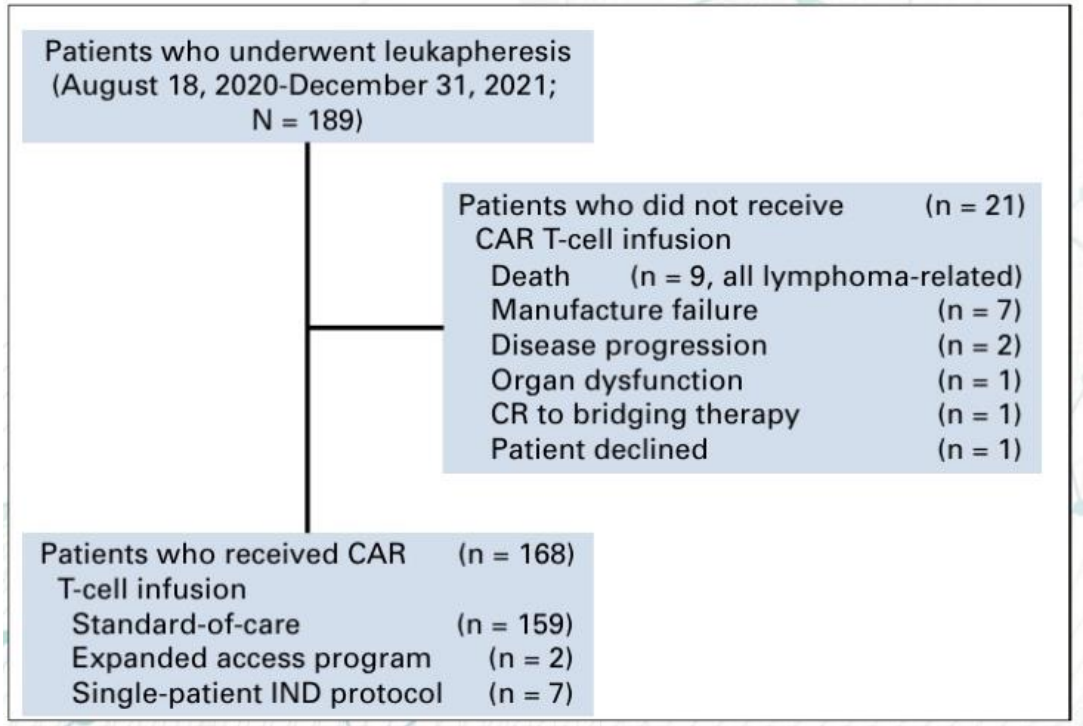
• Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month **PFS rate was 32%** (95% CI, 20.0-44.2) **in Cohort 1.**
• In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month **PFS rate was 46%** (17.3-70.5; N=14).

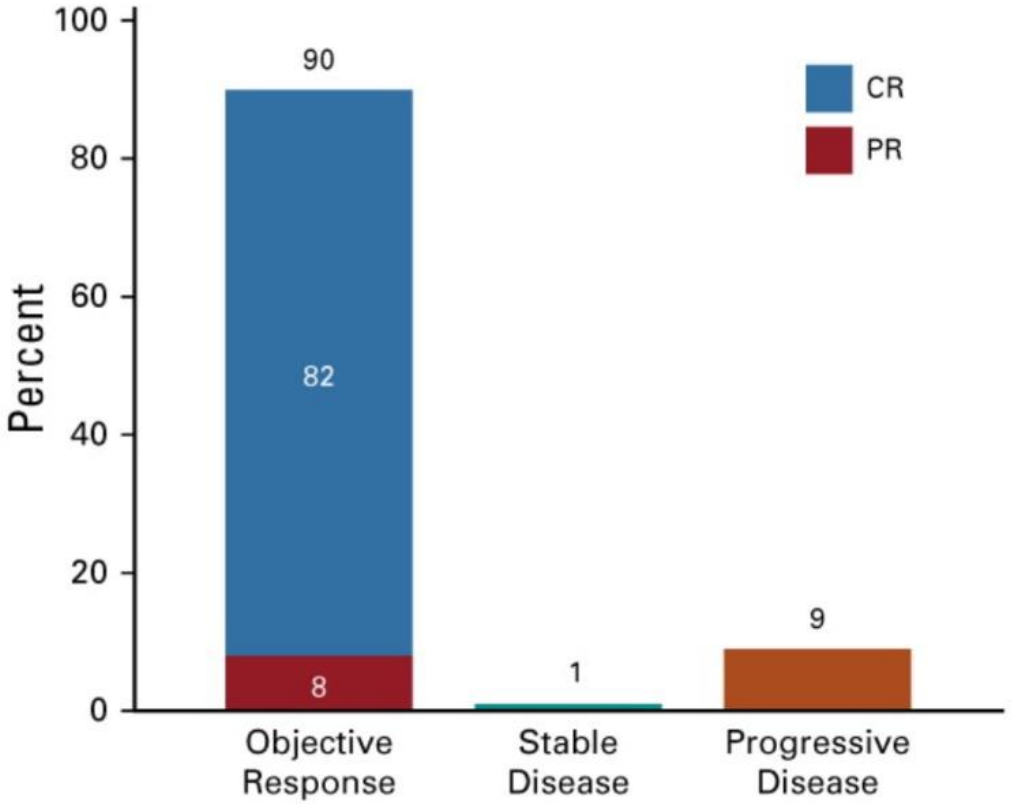
In **Cohort 1**, the median OS was 46.5 months (95% CI, 24.9–60.2; Fig. 1D) and the 60-month OS rate was **38%** (95% CI, 26.7–50.1).
In **Cohort 2**, median OS was not reached (NR; 95% CI, 9.4-NE; *N* = 14) and the 60-month **OS rate was 54%** (95% CI, 23.8–76.2; Fig. 1D).

Wang M et al, ASH 2024 ; Munoz J – Journal of Hematology & Oncology 2026

Brexu-cel for R/R MCL in Standard of Care Practice: results from the US consortium

US Lymphoma CAR-T Consortium: retrospective, multicenter study in patients receiving KTE-X19 (n= 189)



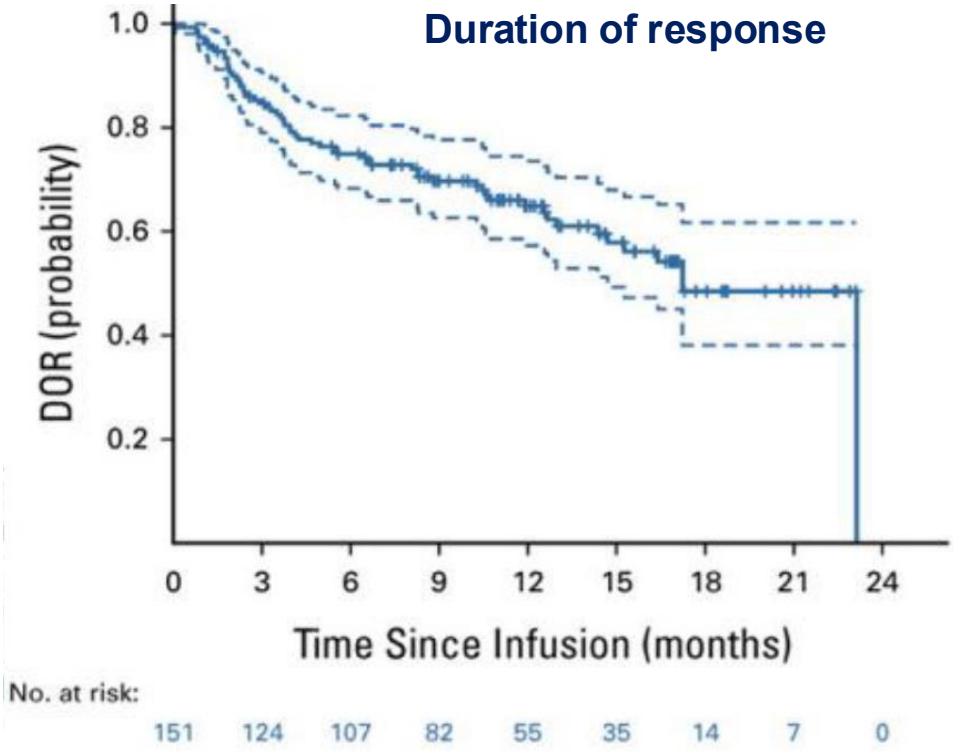


Wang Y, et al. JCO 2023

Brexu-cel for R/R MCL in Standard-of-Care Practice

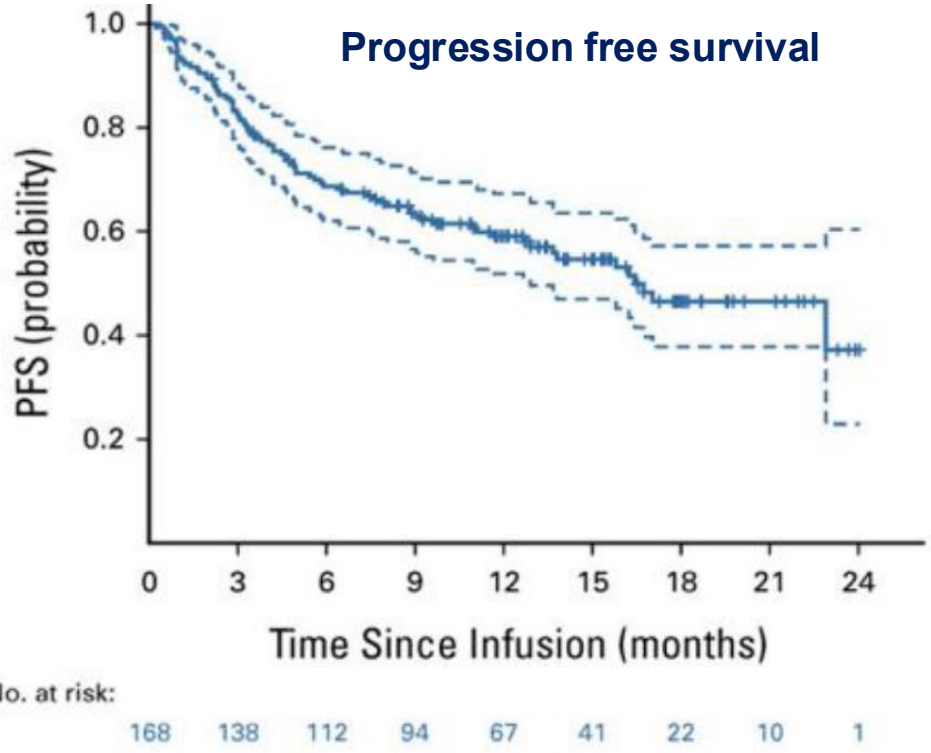
median follow-up time after infusion was 14.3 months

Duration of response



The rate of continuous response at 12 months was 65%.

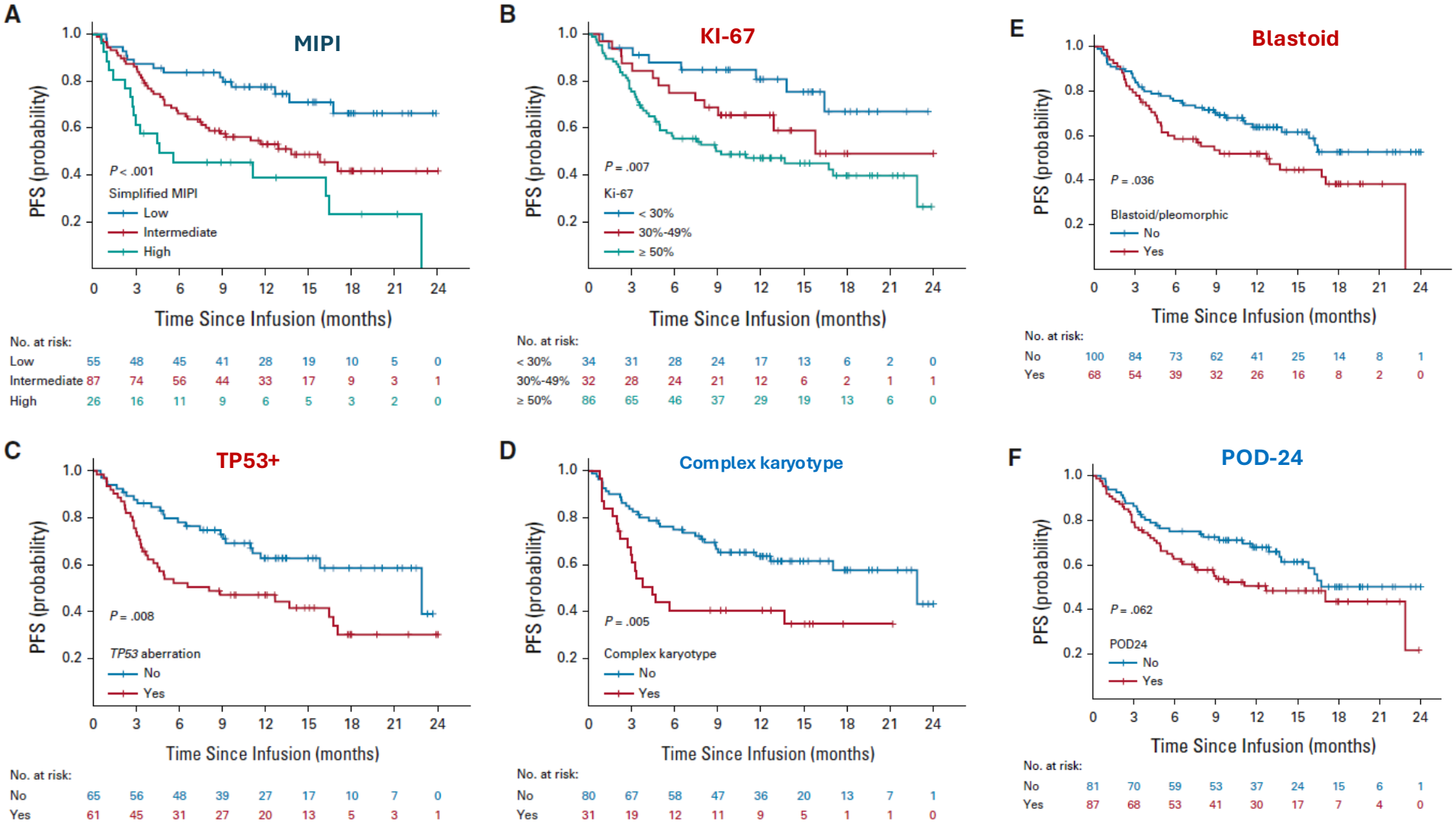
Progression free survival



The 12-month PFS rate was 59%

Wang Y, et al. JCO 2023

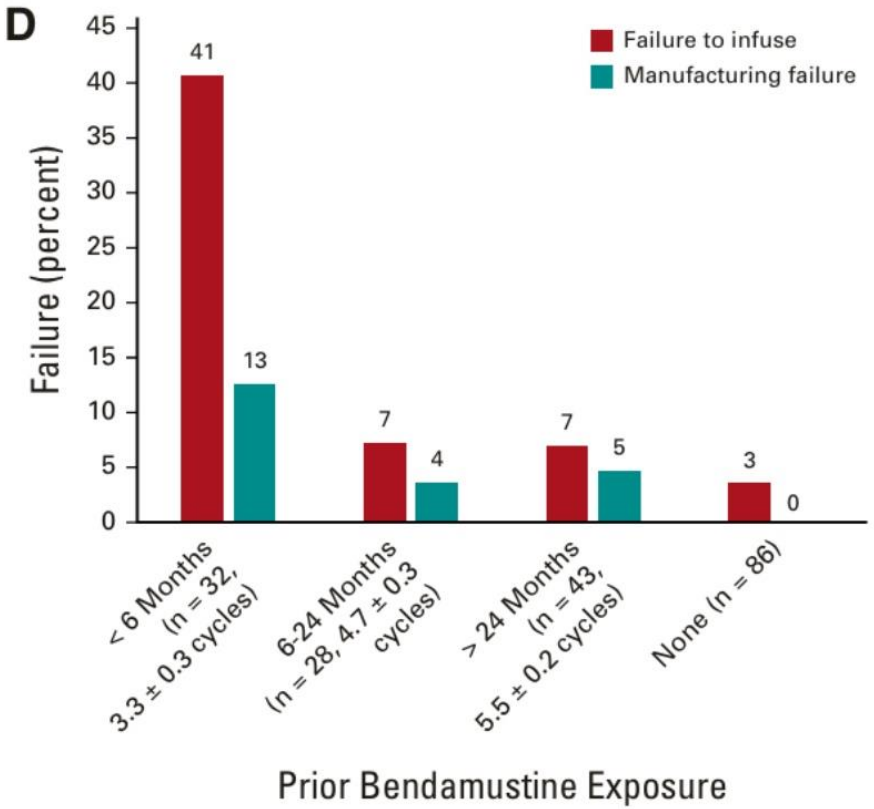
Brexu-cel for R/R MCL in Standard-of-Care Practice in different risk patients

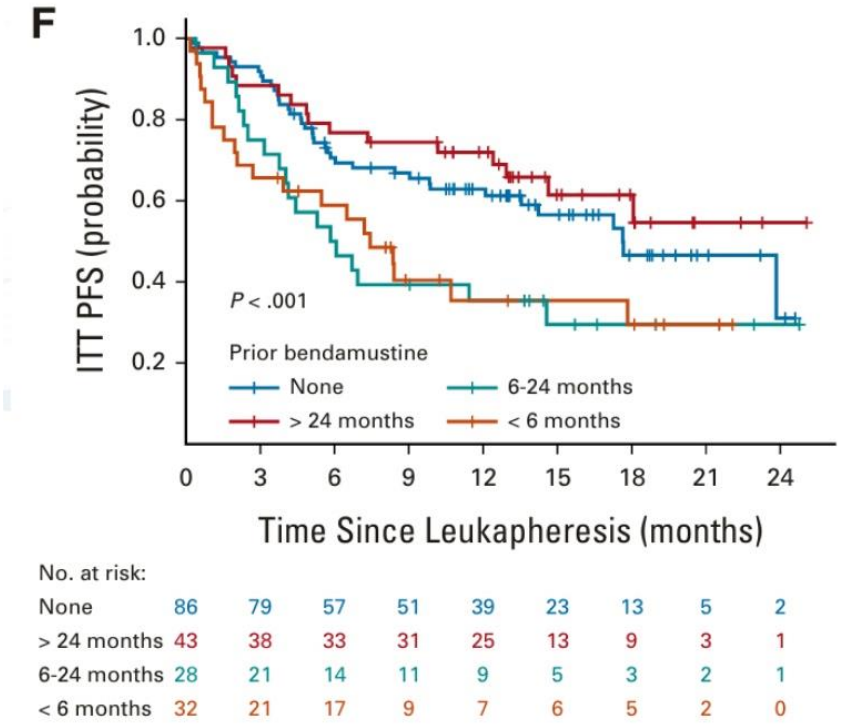


Wang Y, et al. JCO 2023

Prior Bendamustine exposure and outcomes

103/189 patients received prior bendamustine





No. at risk:

None	86	79	57	51	39	23	13	5	2
> 24 months	43	38	33	31	25	13	9	3	1
6-24 months	28	21	14	11	9	5	3	2	1
< 6 months	32	21	17	9	7	6	5	2	0

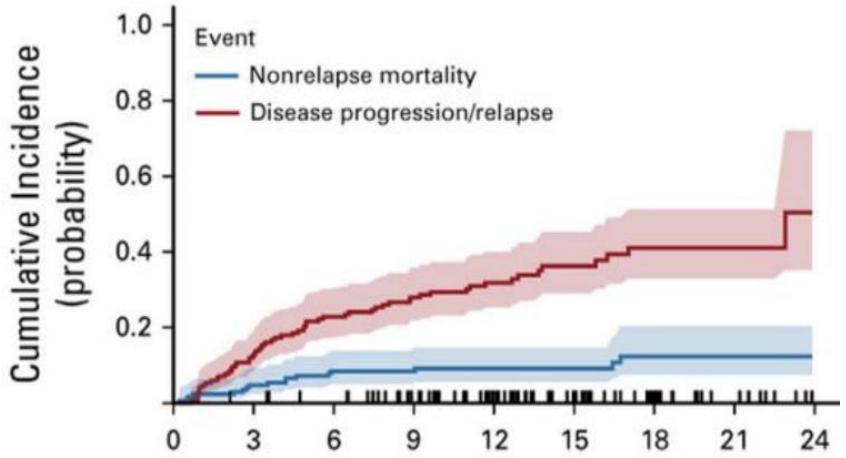
Wang Y, et al. JCO 2023

Short term and long term toxicity

- The incidences of CRS and ICANS were comparable to those reported in ZUMA-2
- Tocilizumab and corticosteroids use appeared to be more frequent in this Consortium study cohort

- The non relapse mortality was 9.1% at 1 year, primarily because of infections.

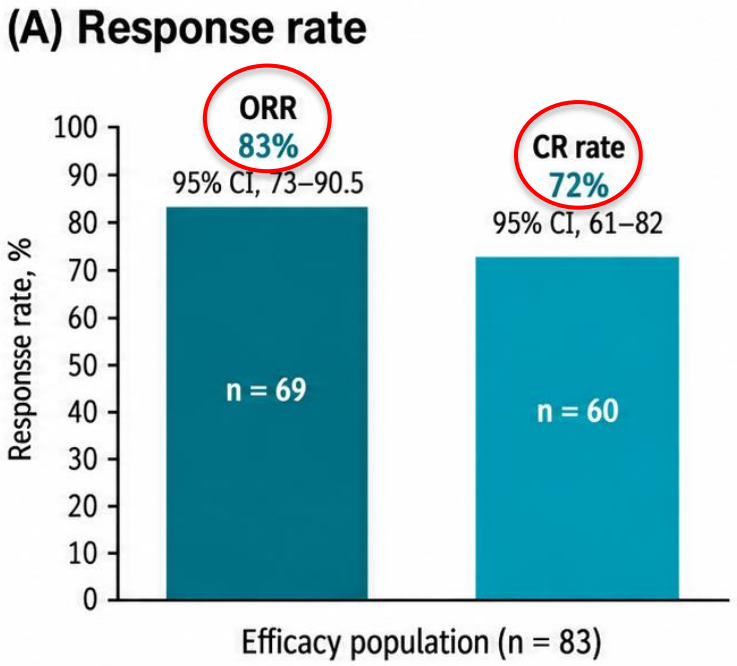
	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	86 (91%)	57 (60%)	91%	63%
Max Grade*				
1-2	78 (82%)	24 (25%)	76%	32%
3-4	8 (8%)	33 (35%)	15%	31%
Days to onset	4 (0-11)	6 (1-15)	2 (1-13)	7
Days to max Grade	5 (0-7)	7 (3-15)	-	-
Duration	5 (1-33+)	6 (2-144+)	11	12

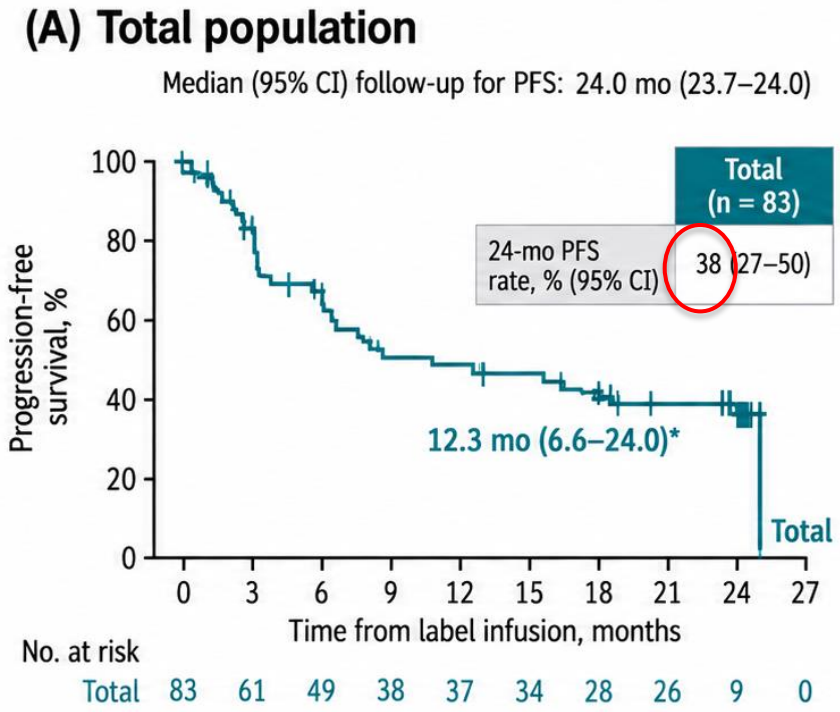


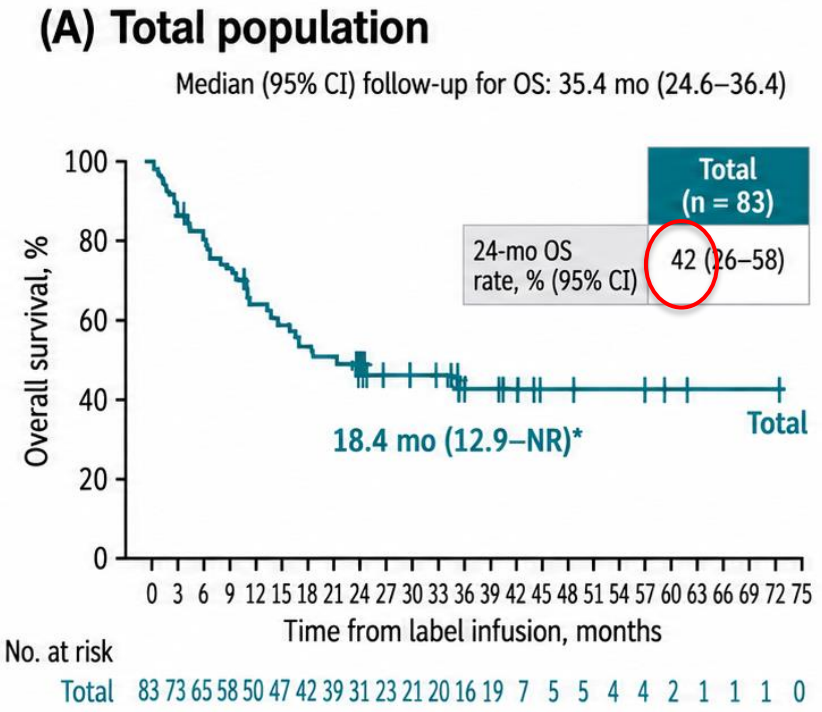
CRS = Cytokine Release Syndrome
NE = Neurologic Events
ICANS= (Immune Effector Cell-Associated Neurotoxicity Syndrome)

Wang Y, et al. JCO 2023

CAR-T: TRANSCEND NHL 001 study, Liso-Cel







CRS any grade: 61% **CRS grade 3-4:** 1%

NEs any grade: 31% **NEs grade 3-4:** 9%

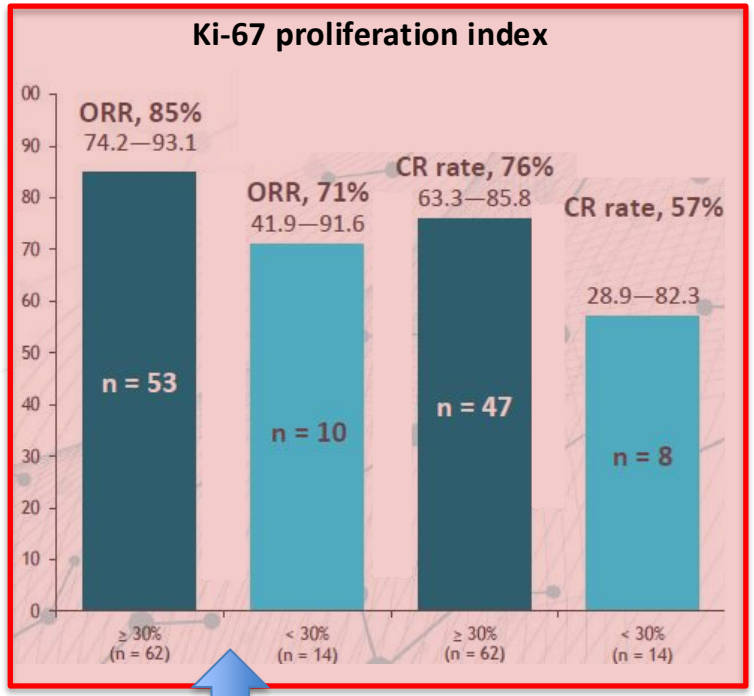
No grade 5 CRS or Neurological Events (NEs)

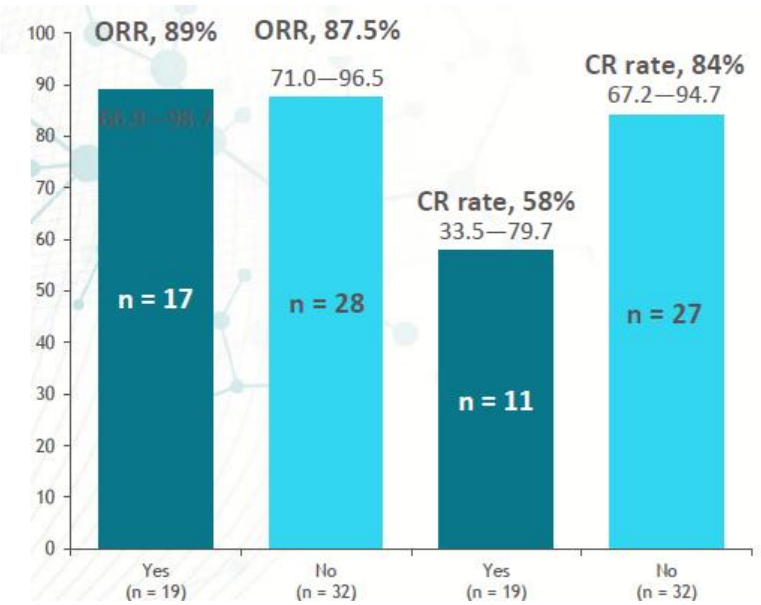
Wang et al, JCO 2024

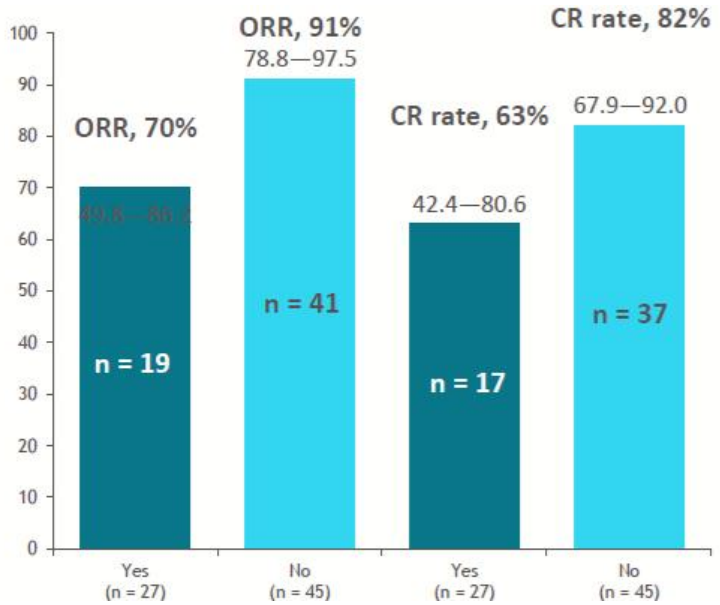
CAR-T: TRANSCEND NHL 001 study, Liso-Cel

ORR and CR rate by high-risk disease feature subgroup (efficacy set)

High risk MCL







In the total of 83 pts (efficacy set) ORR was 83.1% and CR was 72.3%

Wang et al, JCO 2024

Efficacy | CAR T-cell therapy in R/R MCL

	LISO-CEL · TRANSCEND NHL 001 (n = 83)	BREXU-CEL · ZUMA-2 (n = 68)
ENDPOINT	**TRANSCEND NHL 001**	**ZUMA-2**
Overall response rate (ORR)	**83.1%**	**91%**
Complete response (CR)	**72.3%**	**68%**
Median duration of response	**15.7 months**	**28.2 months**
Median PFS	**15.3 months**	**25.8 months**
Median OS	**18.2 months**	**46.6 months**
Median follow-up	**16.1 months**	**35.6 months**

Wang M et al. J Clin Oncol. 2024;42:1146–1157 (TRANSCEND); Wang M et al. J Clin Oncol. 2023;41:555–567 (ZUMA-2).

Safety | CRS and neurological toxicity

	TRANSCEND NHL 001	ZUMA-2
ADVERSE EVENT	**LISO-CEL**	**BREXU-CEL**
Cytokine release syndrome (CRS) Any grade	**61%**	**91%**
Cytokine release syndrome (CRS) **Grade ≥3**	**1%**	**15%**
Neurological events Any grade	**31%**	**63%**
Neurological events **Grade ≥3**	**9%**	**31%**

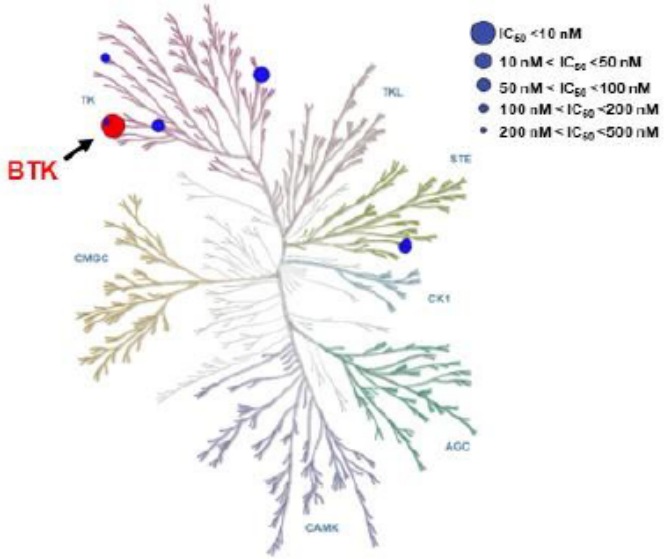
CRS and ICANS management optimization

Costimulatory domain:
- ❑ **Brexu-cel = CD28**
- ❑ **Liso-cel = 4-1BB**

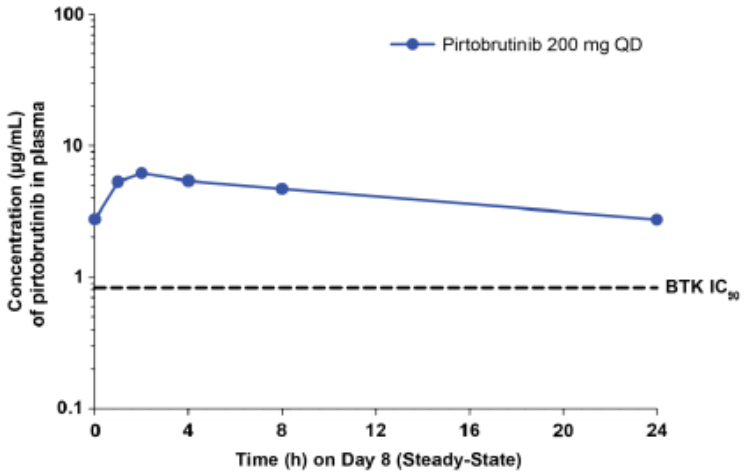
Wang M et al. J Clin Oncol. 2024;42:1146–1157 (TRANSCEND); Wang M et al. J Clin Oncol. 2023;41:555–567 (ZUMA-2).

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

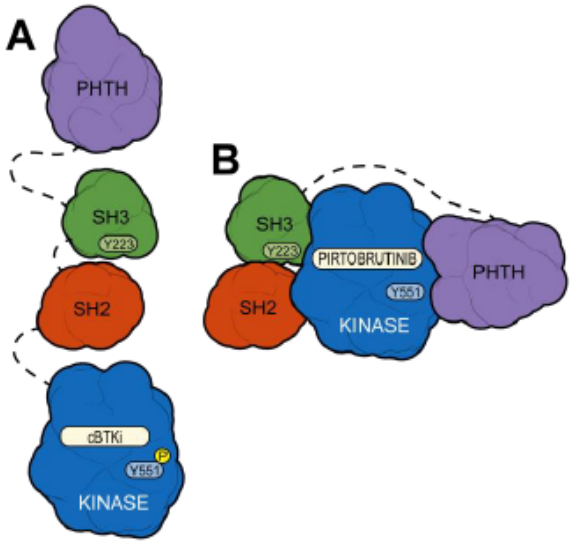
Kinome selectivity
Highly Selective for BTK[1,2]



Plasma Exposures Exceeded BTK Throughout Dosing Interval



Pirtobrutinib May Stabilize/Maintain BTK in a Closed Inactive Conformation[3]

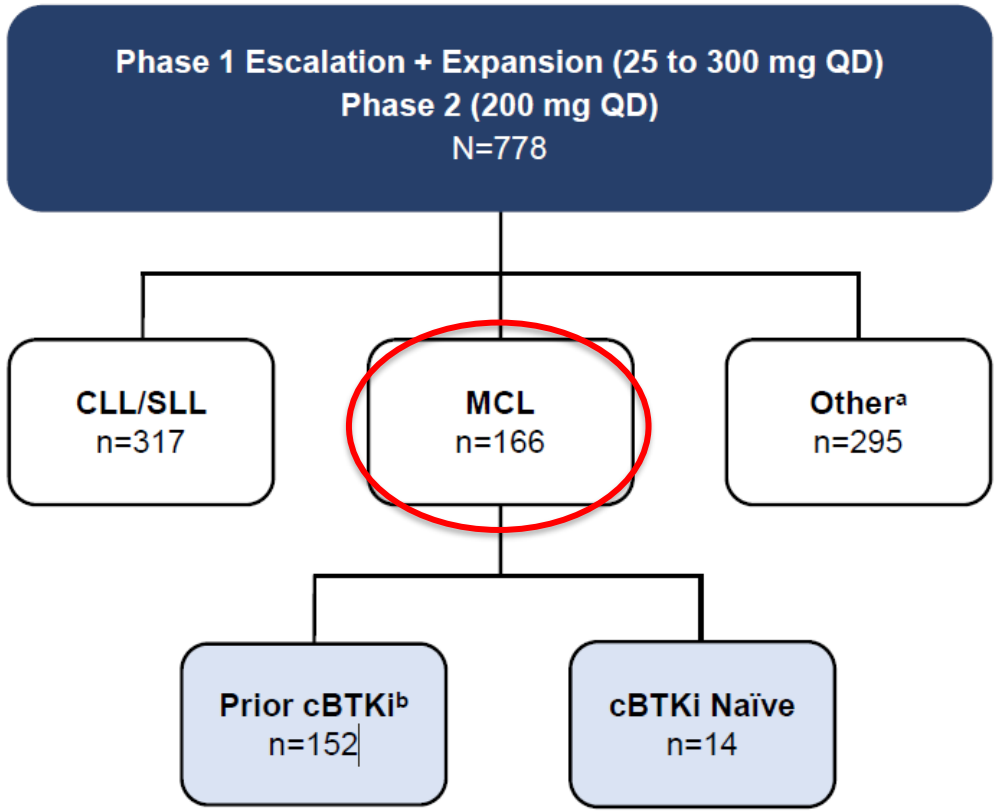


- **Inhibits both wild-type and C481-mutant BTK** with equal low-nanomolar potency [3]
- Steady-state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours [3]
- In contrast to cBTKi (**A**), pirtobrutinib (**B**) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling [3]

1 Mato AR, et al. Lancet. 2021; 2 Brandhuber B, et al. Clin Lymphoma Myeloma Leuk. 2018; 3 Gomez EB, et al. Blood. 2023. Wang, et al.; ASH 2025

Phase 1/2 BRUIN Study: Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL)

Study design



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

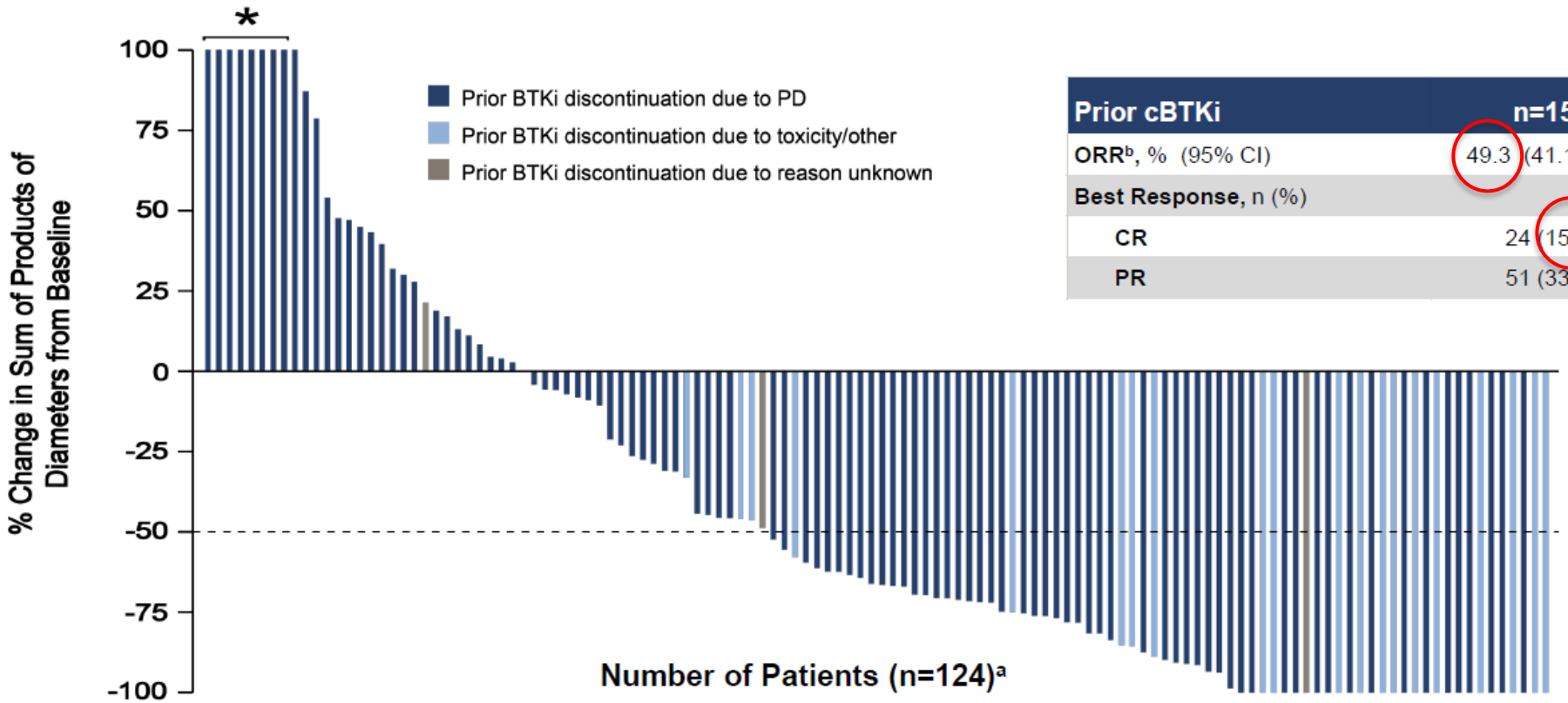
Data cutoff of 05 May 2023 (NCT03740529).

a Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformations.

b Prior cBTKiincludes Primary Analysis Set (PAS) n=90 and Supplemental Cohort n=62. The PAS comprised the first 90 patients enrolled and served as the primary efficacy population for regulatory interactions and met the following criteria:; had measurable disease, had received a prior cBTKi containing regimen, had no known central nervous system involvement.

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

Pirtobrutinib phase 1/2 BRUIN Study: outcomes in Prior cBTKi pts with MCL



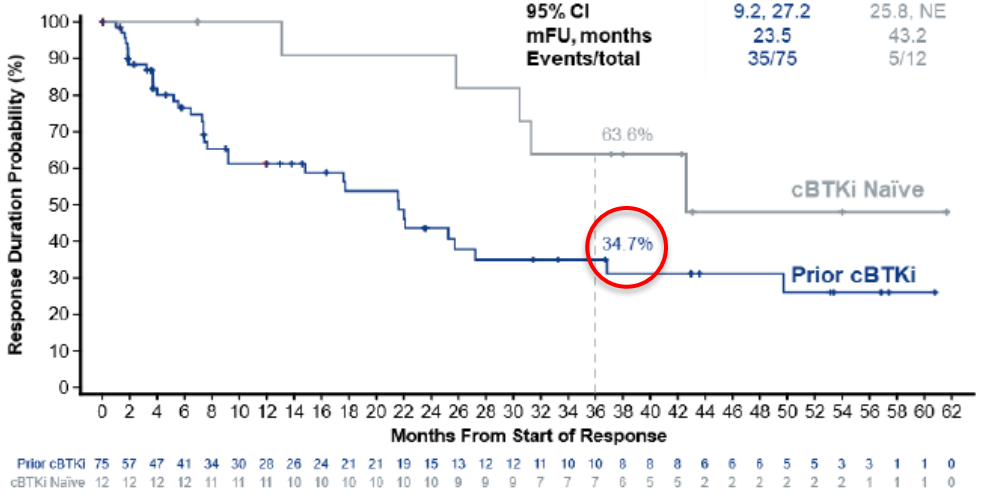
Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Median Time to First Response was 1.8 months (range: 0.8-13.8)

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

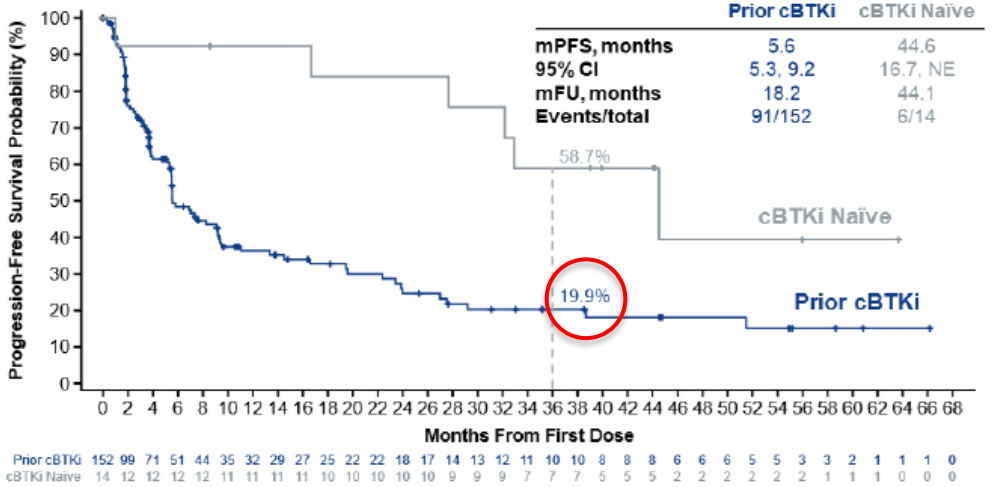
Pirtobrutinib phase 1/2 BRUIN Study: outcomes in Prior cBTKi and cBTKi Naïve pts with MCL

Duration of Response

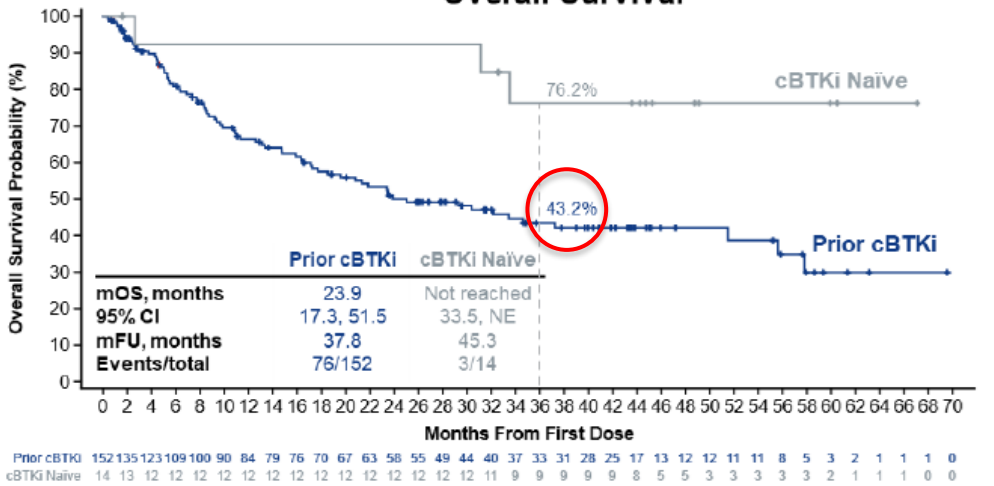


Outcome by Reason of Discontinuation From Prior BTKi	PD	Toxicity/Other
mDoR, months 95% CI	14.8 4.0, 27.2	25.3 7.5, NE
mPFS, months 95% CI	5.5 3.8, 7.4	27.0 9.3, NE
mOS, months 95% CI	18.5 11.3, 33.5	57.8 32.2, NE

Progression-Free Survival



Overall Survival

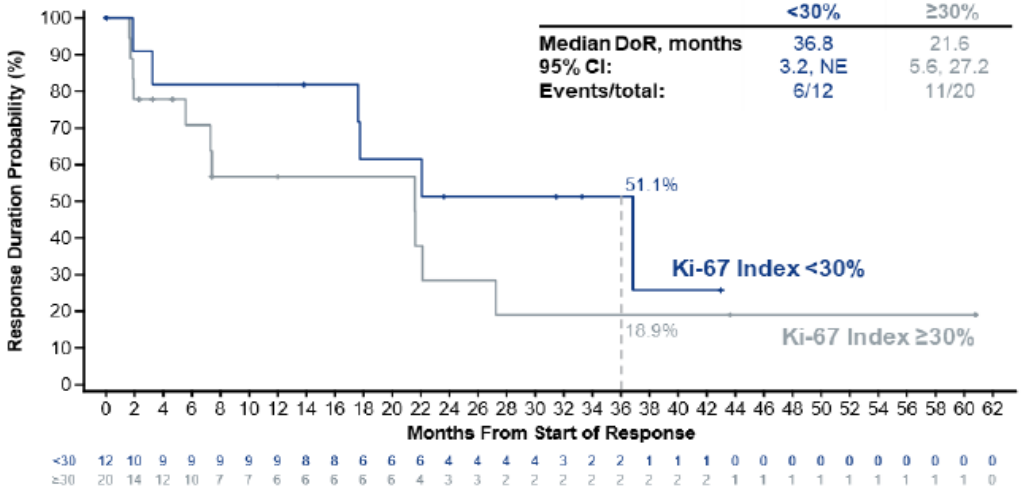


Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent BTKi; CI, confidence interval; MCL, mantle cell lymphoma; mDoR, median duration of response; mFU, median follow-up; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; PD, progressive disease.

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

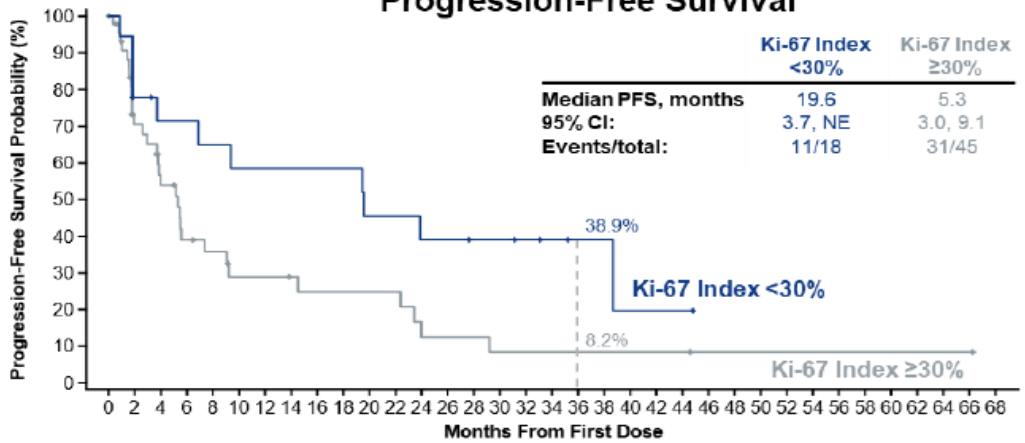
Pirtobrutinib Outcomes in Prior cBTKi Patients With MCL by High-Risk Subgroups: Ki-67 Index

Duration of Response



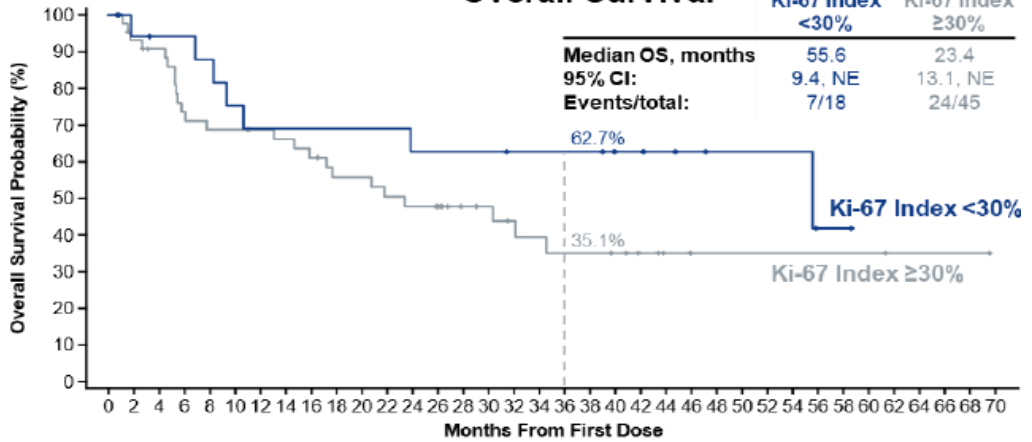
	Ki-67 Index <30%	Ki-67 Index ≥30%
Median DoR, months	36.8	21.6
95% CI:	3.2, NE	5.6, 27.2
Events/total:	6/12	11/20

Progression-Free Survival



	Ki-67 Index <30%	Ki-67 Index ≥30%
Median PFS, months	19.6	5.3
95% CI:	3.7, NE	3.0, 9.1
Events/total:	11/18	31/45

Overall Survival

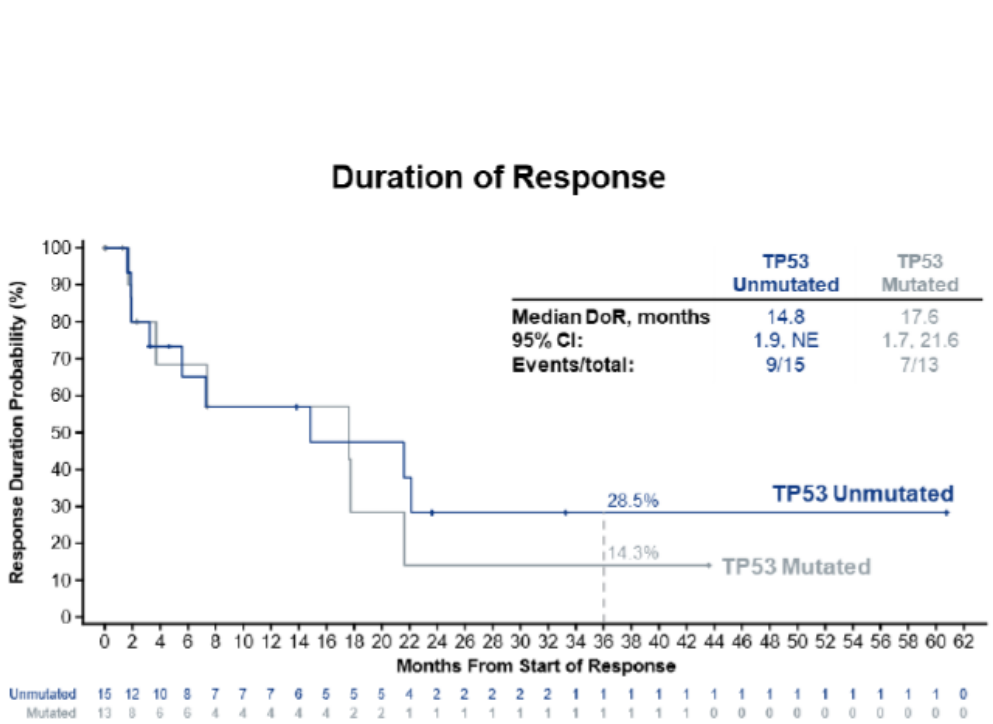


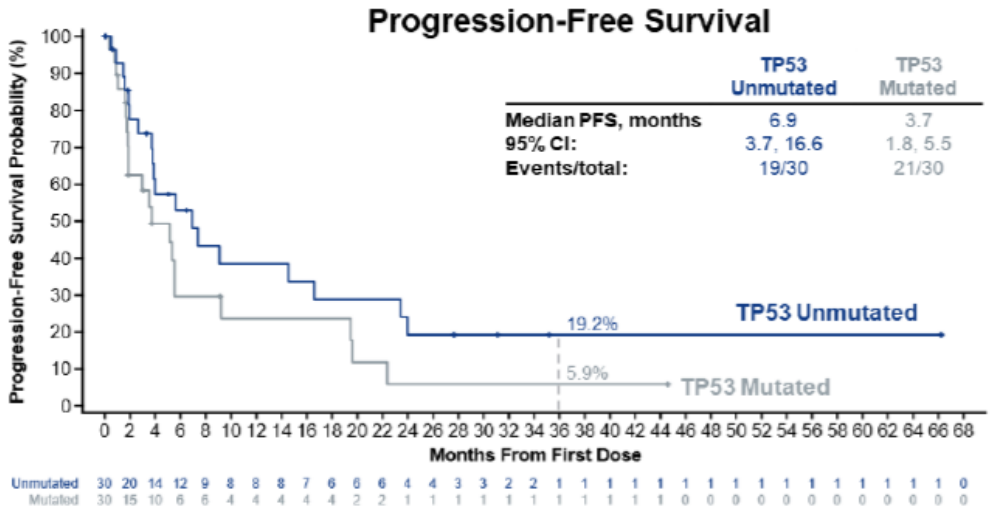
	Ki-67 Index <30%	Ki-67 Index ≥30%
Median OS, months	55.6	23.4
95% CI:	9.4, NE	13.1, NE
Events/total:	7/18	24/45

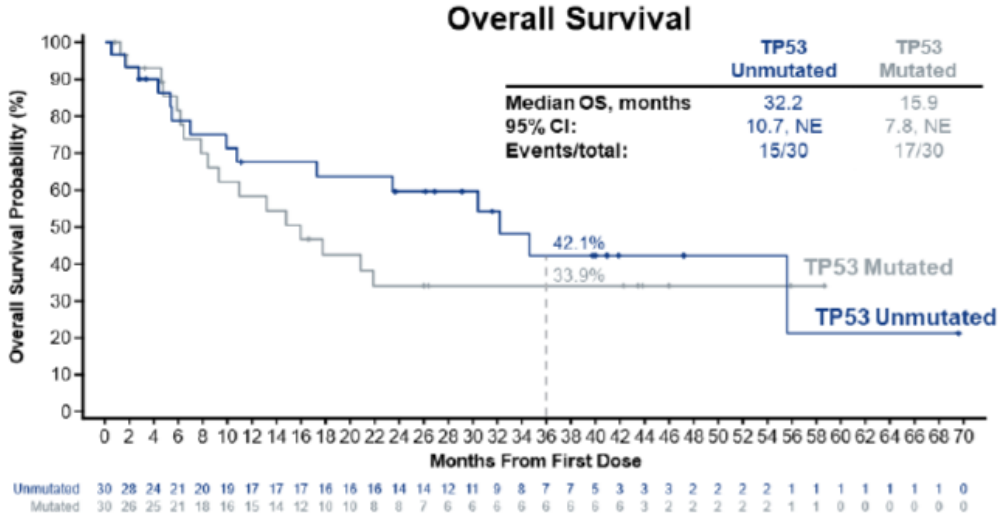
Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; DoR, duration of response; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

Pirtobrutinib Outcomes in Prior cBTKi Patients With MCL by High-Risk Subgroups: TP53 Status







Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; DoR, duration of response; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

Pirtobrutinib Safety Profile

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Platelet Count Decreased	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

No DLTs (dose-limiting toxicities) reported and MTD (Maximum Tolerated Dose) not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D (Recommended Phase 2 Dose) of 200 mg daily
3,6% (n=6) of patients permanently discontinued due to treatment-related AEs

Cohen ASH 2023 - Wang M.L et al.; ASH 2025

The Phase 3 BRUIN MCL-321 Trial Will Assess the Efficacy of Pirtobrutinib vs Covalent BTKi in R/R MCL



Key Inclusion Criteria

- MCL previously treated with ≥1 prior line of systemic therapy
- Measurable disease per Lugano criteria
- ECOG PS of 0-2
- ANC ≥0.75 × 10^9/L without GCSF within 7 days of screening
- Hb ≥8 g/dL and PLT ≥50 x 10^9/L not requiring transfusion support or growth factors within 7 days of screening
- AST and ALT ≤3.0 x ULN; total bilirubin ≤1.5 x ULN
- CrCl ≥30 mL/min

Stratification

- sMIPI risk group (low/intermediate vs high)
- Intended comparator BTKi (ibrutinib vs acalabrutinib/ zanubrutinib)
- Number of prior lines of therapy (1 vs ≥2)

Primary endpoint:
progression-free survival

1:1

R

Pirtobrutinib

Investigator's choice BTKi (ibrutinib, acalabrutinib, or zanubrutinib)

https://clinicaltrials.gov/ct2/show/NCT04662255.
Eyre T et al. ASH 2021. Abstract 2422.
Ghia P et al. EHA 2022. Abstract P1101.

Treatment R/R Mantle Cell Lymphoma

The next future……



- ✓ Bispecific T-cell Engager (BiTE)
- ✓ Antibody-drug conjugate (ADC)
- ✓ Novel BCL2 inhibitor
- ✓ Novel BCL2 inhibitor + cBTKi
- ✓ BTK degrader
- ✓ ……

Phase I/II study of glofitamab in R/R NHL (NP30179): Multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with obinotuzumab (Gpt)

Glofitamab IV administration

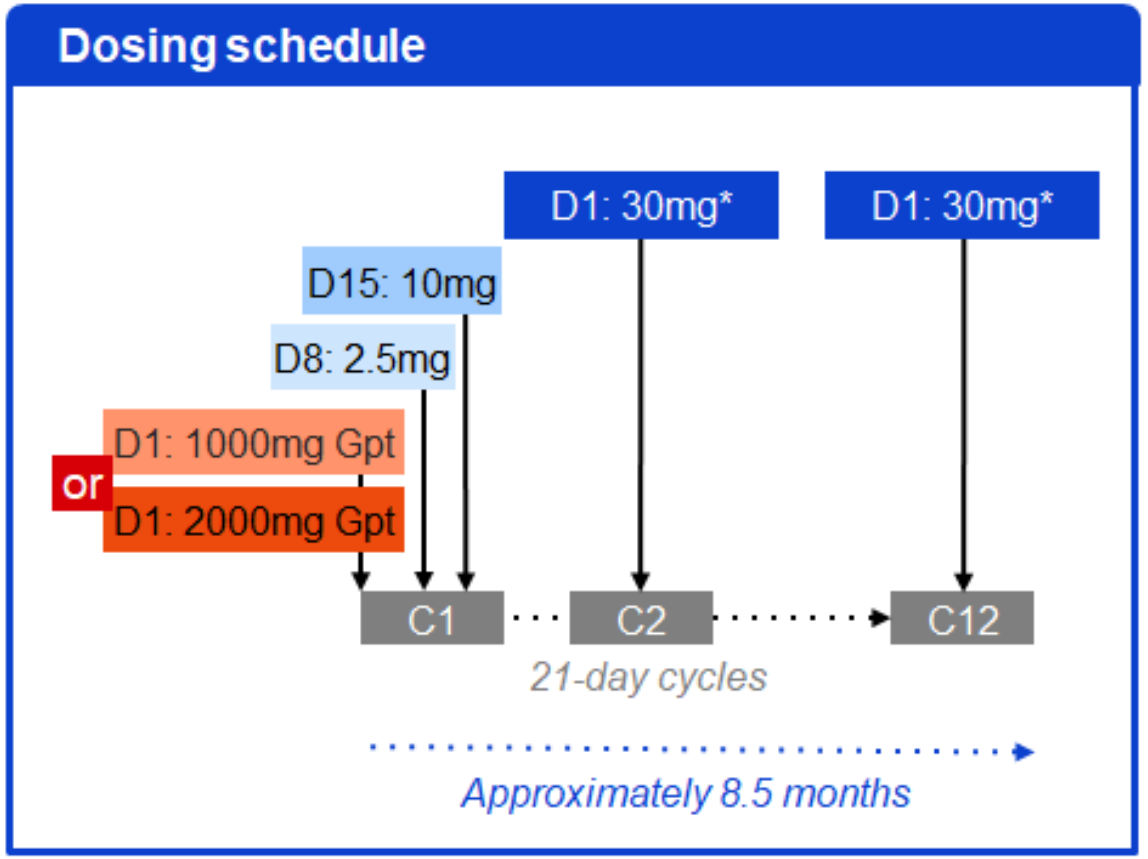
- Fixed-duration treatment: maximum 12 cycles
  - > Fixed dosing: 0.6mg, 16mg or 25mg Q3W*[1]
  - > Step-up dosing: target dose 30mg Q3W†

Population characteristics

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS 0 or 1

CRS mitigation

- Obinutuzumab pretreatment (1000mg or 2000mg);
- (2000mg option with step-up dosing only)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

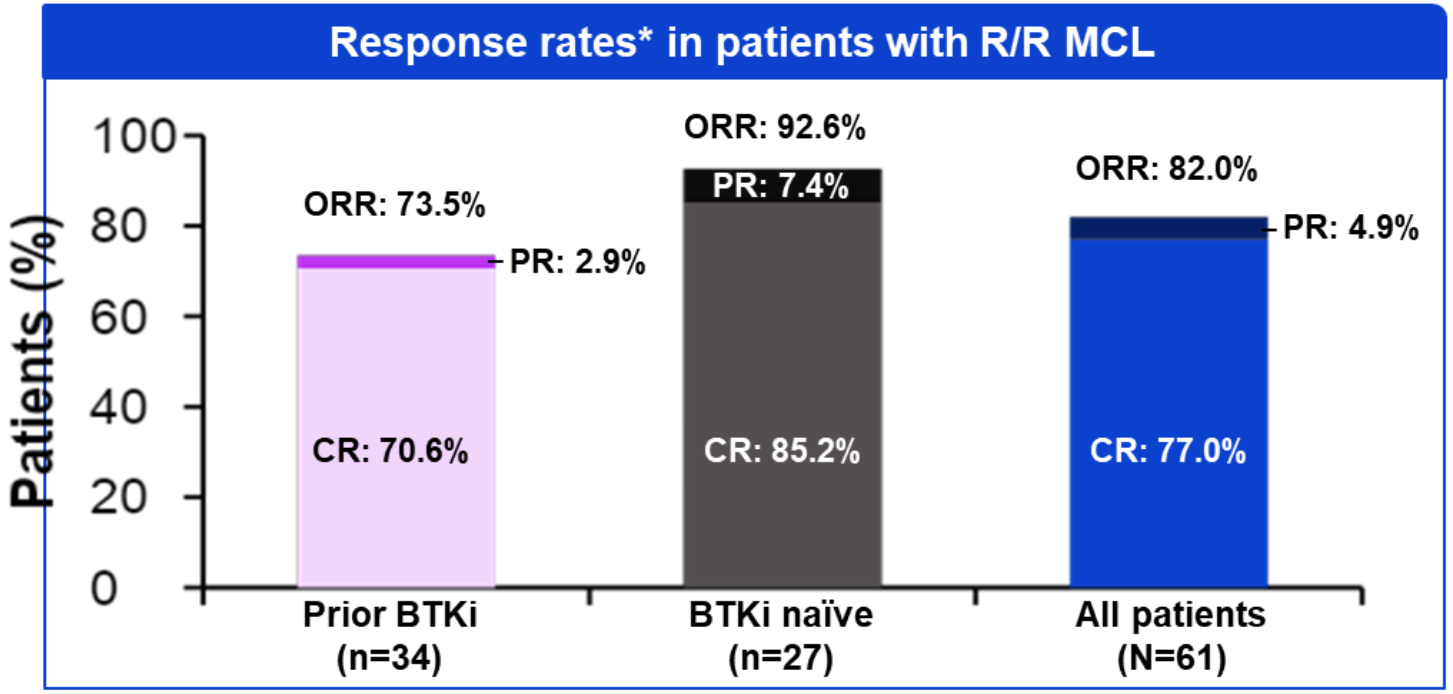
Baseline characteristics

n (%), unless otherwise specified		Prior BTKi (n=34)	BTKi naïve (n=27)	All patients (N=61)*
Median age, years (range)		71 (41–84)	72 (52–86)	72 (41–86)
Male		25 (73.5)	20 (74.1)	45 (73.8)
ECOG PS†	0	14 (41.2)	14 (51.9)	28 (45.9)
	1	19 (55.9)	13 (48.1)	32 (52.5)
Ann Arbor stage III/IV		31 (91.2)	22 (81.5)	53 (86.9)
MIPI score ≥6		9 (26.4)	7 (25.9)	16 (26.3)
Bone marrow involvement‡		19 (55.9)	14 (51.9)	33 (54.1)
Median number of prior lines of therapy (range)		3 (1.0–5.0)	2 (1.0–4.0)	2 (1.0–5.0)
Median time since last prior therapy§, months (range)		1.3 (0.1–53.2)	7.5 (0.1–132.5)	2.4 (0.1–132.5)
Refractory to last prior therapy		30 (88.2)	15 (55.6)	45 (73.8)
Ki67 index†	High (≥30%)	23 (67.6)	15 (55.6)	38 (62.3)
	Low (<30%)	5 (14.7)	6 (22.2)	11 (18.0)
***TP53* mutation†**	Mutation abnormality	10 (29.4)	2 (7.4)	12 (19.7)
	Wild type	4 (11.8)	2 (7.4)	6 (9.8)
Blastoid morphology	Yes	5 (14.7)	1 (3.7)	6 (9.8)

Patients with R/R MCL were heavily pretreated
and highly refractory to their last prior therapy, with high-risk features

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up



Median time to first CR (n=47):
45 days (range: 29–234)

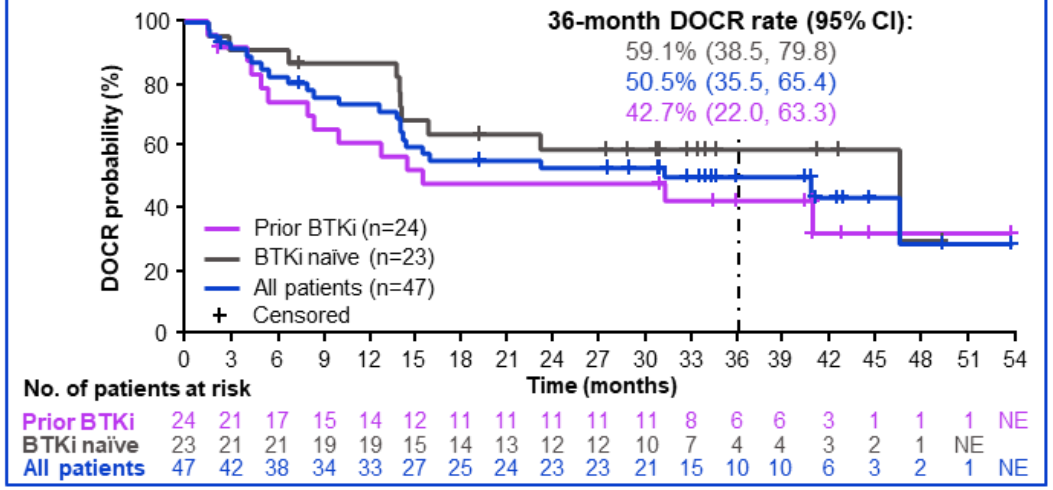
High ORR and CR rates were observed early during glofitamab treatment in both the overall population and patients with prior BTKi and those who were BTKi naïve

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

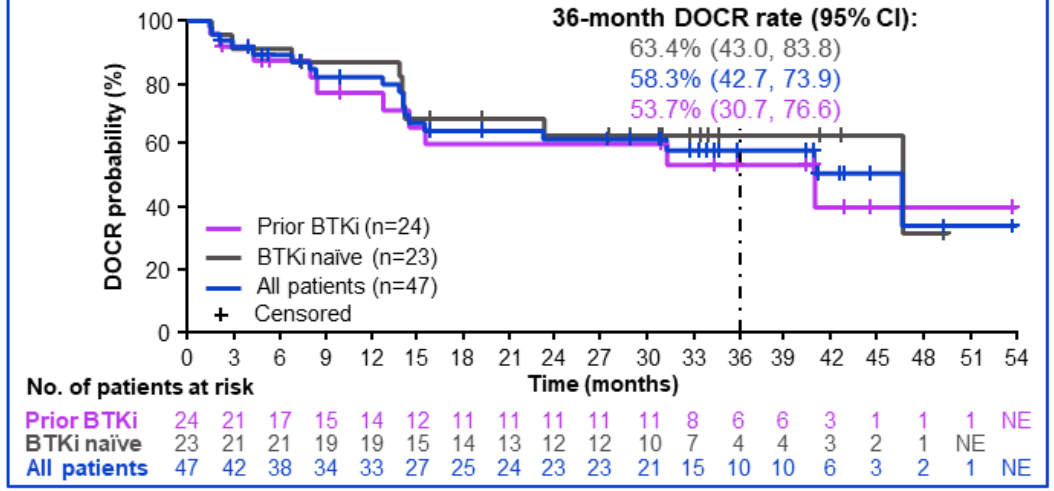
Duration of complete response

DOCR*†



DOCR	Prior BTKi (n=24)	BTKi naive (n=23)	All patients (n=47)
Median DOCR, months (95% CI)	15.4 (8.3, NE)	46.5 (14.1, NE)	40.8 (14.1, NE)

DOCR COVID-19 sensitivity*



DOCR	Prior BTKi (n=24)	BTKi naive (n=23)	All patients (n=47)
Median DOCR, months (95% CI)	40.8 (14.4, NE)	46.5 (14.1, NE)	46.5 (23.1, NE)

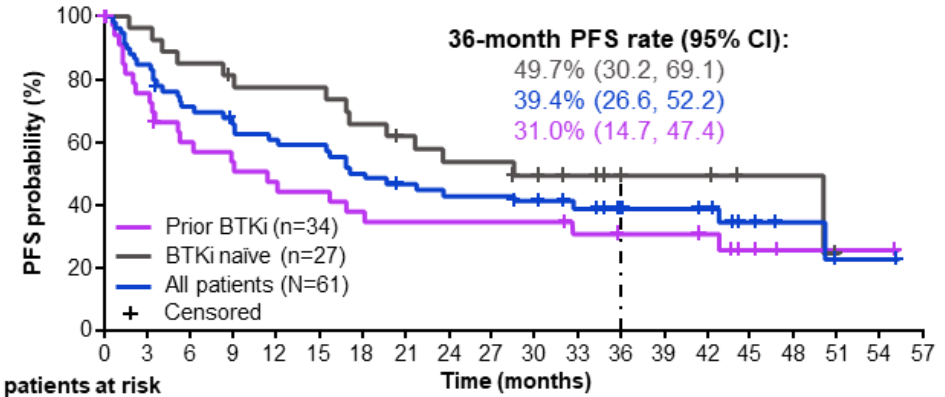
Fixed-duration glofitamab monotherapy achieved durable CRs in patients with prior BTKi and those who were BTKi naïve; COVID-19 censoring further extended the median DOCR

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

Progression-free survival

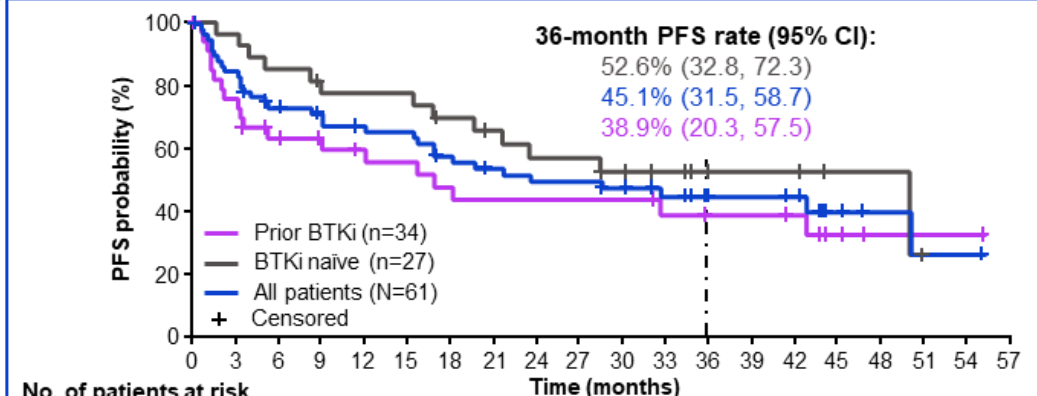
PFS*†



No. of patients at risk

Prior BTKi	34	25	19	16	14	14	12	11	11	11	11	8	7	7	6	3	1	1	1	NE
BTKi naïve	27	26	23	20	20	20	17	15	13	13	11	9	5	4	4	2	2	NE		
All patients	61	51	42	36	34	34	29	26	24	24	22	17	12	11	10	5	3	1	1	NE

PFS COVID-19 sensitivity*



No. of patients at risk

Prior BTKi	34	25	19	16	14	14	12	11	11	11	11	8	7	7	6	3	1	1	1	NE
BTKi naïve	27	26	23	20	20	20	17	15	13	13	11	9	5	4	4	2	2	NE		
All patients	61	51	42	36	34	34	29	26	24	24	22	17	12	11	10	5	3	1	1	NE

PFS	Prior BTKi (n=34)	BTKi naive (n=27)	All patients (N=61)
Median PFS, months (95% CI)	11.3 (5.1, 32.6)	28.5 (17.0, NE)	18.0 (11.3, 42.8)

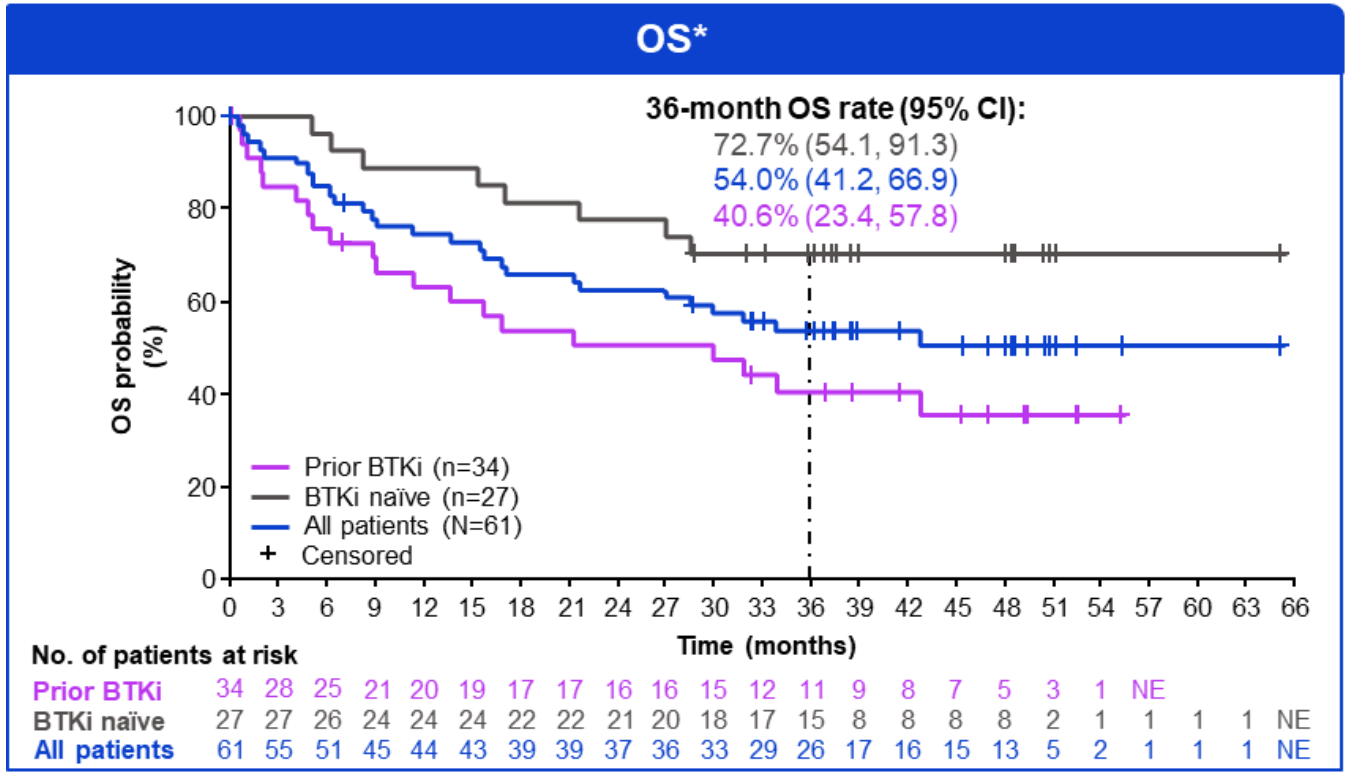
PFS	Prior BTKi (n=34)	BTKi naive (n=27)	All patients (N=61)
Median PFS, months (95% CI)	16.8 (5.2, NE)	50.0 (19.6, NE)	23.5 (15.6, NE)

Clinically meaningful PFS was achieved with glofitamab monotherapy after 3.5 years of follow-up; COVID-19 censoring further extended the median PFS from 18.0 to 23.5 months

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

Overall suvival



OS	Prior BTKi (n=34)	BTKi naive (n=27)	All patients (N=61)
Median OS, months (95% CI)	29.9 (11.3, NE)	NE (NE, NE)	NE (26.9, NE)

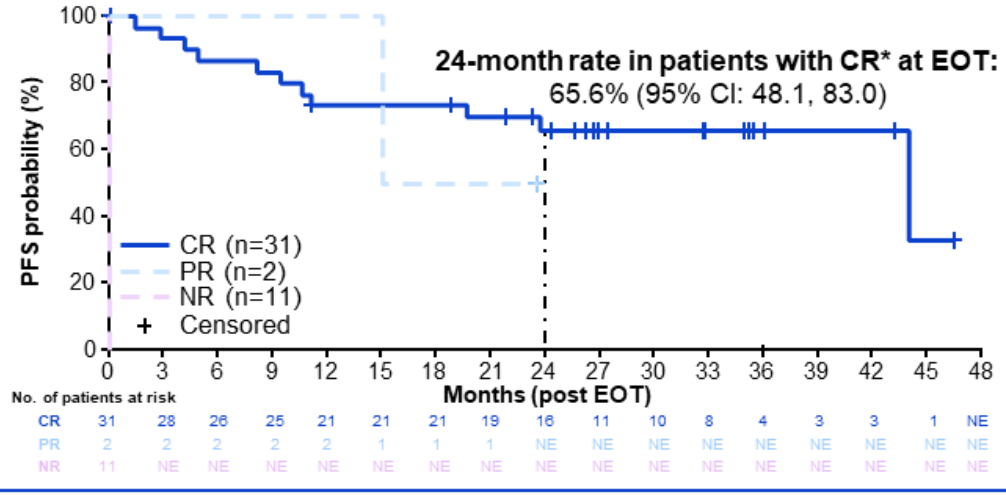
Durable OS was achieved with fixed-duration glofitamab monotherapy in patients with prior BTKi and those who were BTKi naïve

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

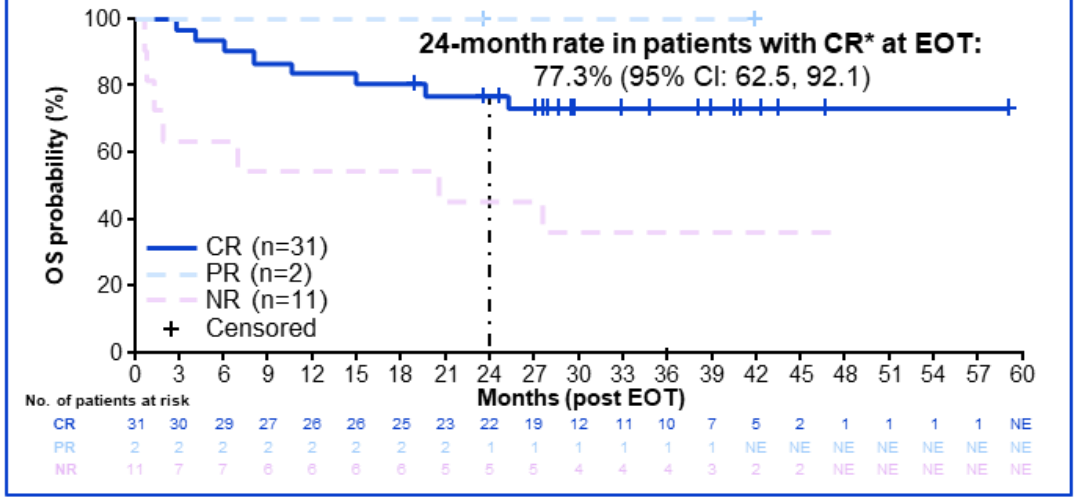
Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

Landmark analyses by response at EOT

PFS* post EOT



OS post EOT



Landmark PFS from EOT in patients with CR* at EOT	All patients N=61
Median PFS, months (95% CI)	44.1 (23.6, NE)

Landmark OS from EOT in patients with CR* at EOT	All patients N=61
Median OS, months (95% CI)	NE (NE, NE)

A large proportion of patients (65.6%) with a CR at EOT remained progression-free and alive 2 years post EOT

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Karimi JH et al, EHA 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

Safety summary

n (%)*	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)†
Any grade AE	16 (100)	44 (100)	60 (100)
Serious AE	15 (93.8)	32 (72.7)	47 (78.3)
Grade 3–5 AE	15 (93.8)	33 (75.0)	48 (80.0)
Grade 5 AE	2 (12.5)	7 (15.9)	9 (15.0)
AE leading to glofitamab discontinuation	2 (12.5)	3 (6.8)	5 (8.3)

Grade 5 AEs were due to COVID-19 pneumonia (n=3), COVID-19 (n=2), and one case each of pneumonia, post-acute COVID-19 syndrome, septic shock, and cardiac arrest

n (%)*	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)†
Infection, any grade	12 (75.0)	32 (72.7)	44 (73.3)
Grade 3–4	4 (25.0)	9 (20.5)	13 (21.7)
Grade 5	2 (12.5)	6 (13.6)	8 (13.3)
COVID-19, any grade	4 (25.0)	15 (34.1)	19 (31.7)
Grade 3–4	2 (12.5)	4 (9.0)	6 (10.0)
Grade 5	0	5 (11.4)	5 (8.3)
COVID-19 pneumonia, any grade	1 (6.3)	5 (11.4)	6 (10.0)
Grade 3–4	1 (6.3)	2 (4.5)	3 (5.0)
Grade 5	0	3 (6.8)	3 (5.0)

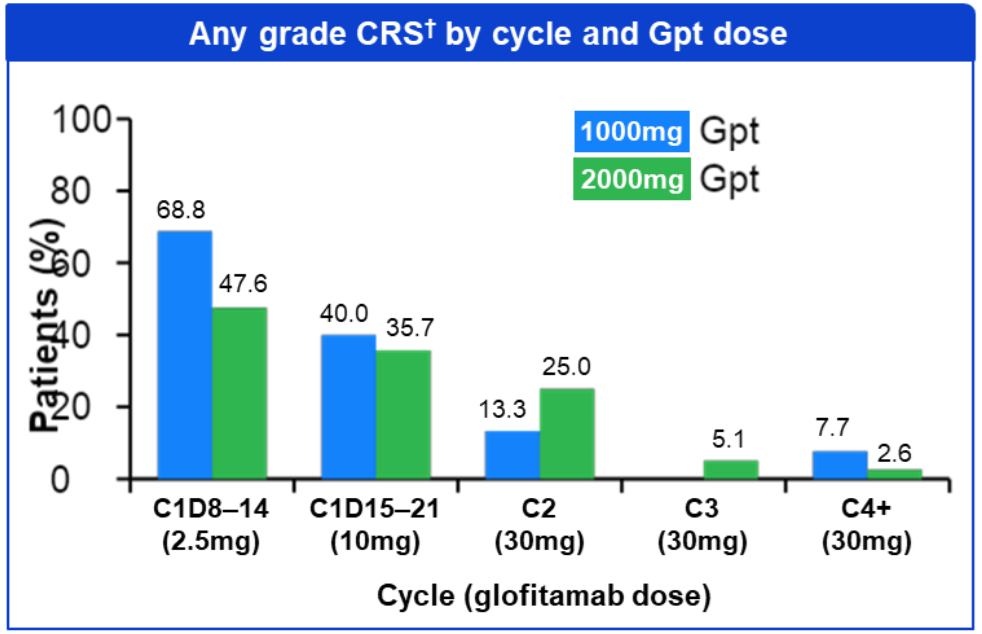
AEs were consistent with the known safety profile of glofitamab,[1] with no new cytopenias or infection events observed since the last analysis;[2] COVID-19 impacted infection prevalence

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Dickinson MJ, et al. N Engl J Med 2022; Phillips TJ, et al. J Clin Oncol 2024; Karimi JH et al, EHA 2026 & ASCO 2026

Phase I/II study of glofitamab in R/R NHL (NP30179): Updated outcomes with 3.5-year follow-up

CRS summary

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)*
Any grade CRS†	14 (87.5)	28 (63.6)	42 (70.0)
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)
Grade 4	2 (12.5)	0	2 (3.3)
CRS management‡			
Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Corticosteroids	8 (50.0)	10 (22.7)	18 (30.0)
ICU admittance	5 (31.3)	4 (9.1)	9 (15.0)



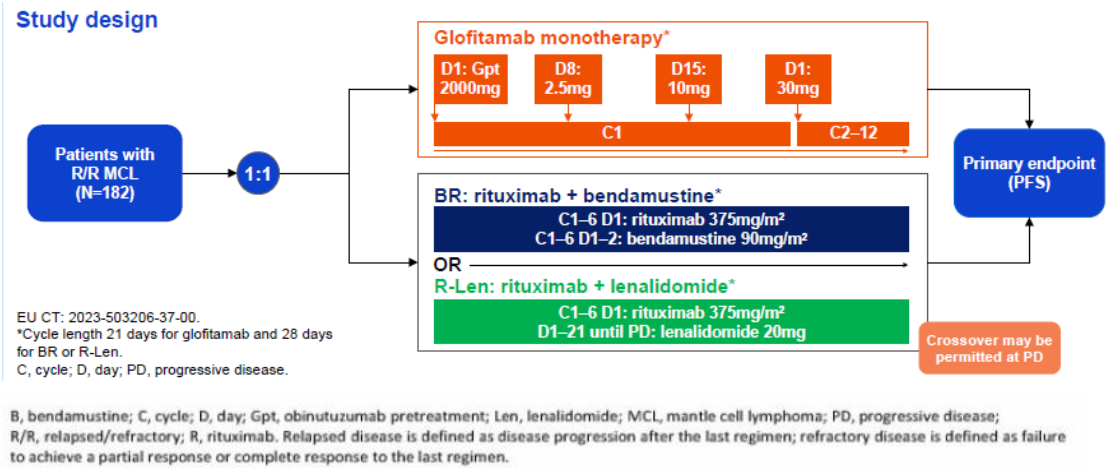
- The majority of CRS events were Grade 1/2
- A lower incidence of CRS was observed in the 2000mg versus 1000mg cohort
- ICANS any grade (3 pts – 5%) – all G1-G2

Phillips T et al, ASH 2021; Phillips T et al, ASH 2022; Phillips T et al, ASCO 2024; Phillips T et al, EHA 2024
Dickinson MJ, et al. N Engl J Med 2022; Phillips TJ, et al. J Clin Oncol 2024; Karimi JH et al, EHA 2026 & ASCO 2026



Future prospectives

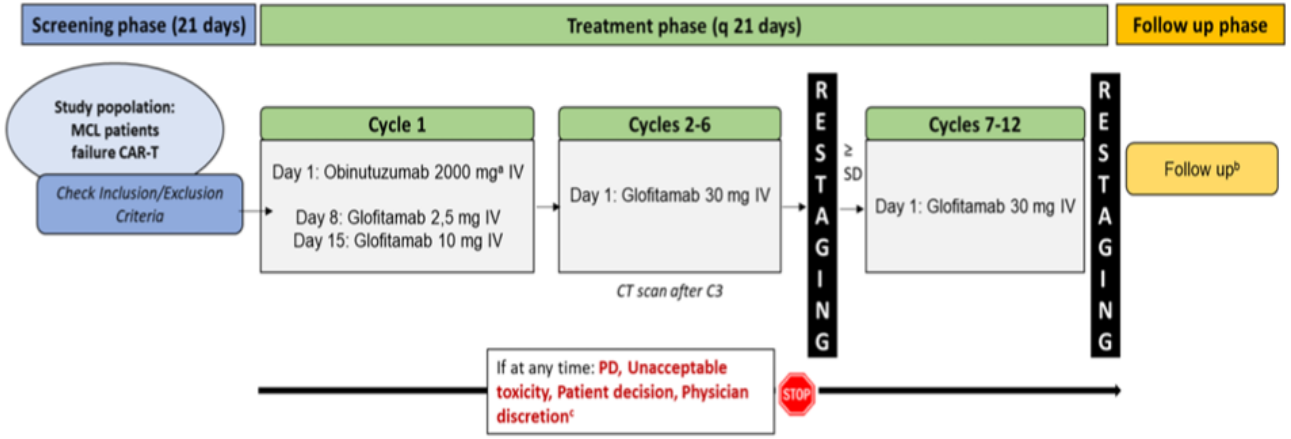
GLOBRYTE (NCT06084936) is a Phase III, open-label, multicenter, randomized, controlled trial in R/R MCL



B, bendamustine; C, cycle; D, day; Gpt, obinutuzumab pretreatment; Len, lenalidomide; MCL, mantle cell lymphoma; PD, progressive disease; R/R, relapsed/refractory; R, rituximab. Relapsed disease is defined as disease progression after the last regimen; refractory disease is defined as failure to achieve a partial response or complete response to the last regimen.

No prior CAR T-cell therapy

A phase II, multicenter study of GlOfitamab in patients with mantle cell Lymphoma and inaDequate response or relapse following CAR T-cell therapy (GOLD)



Post-CAR T-cell therapy (no prior pirtobrutinib treatment)

FONDAZIONE ITALIANA LINFOMI

Bispecific –Phase Ib/II Study– Mosunetuzumab-Polatuzumab in R/R MCL

Patients with Prior-BTKi Treated – Baseline Characteristics

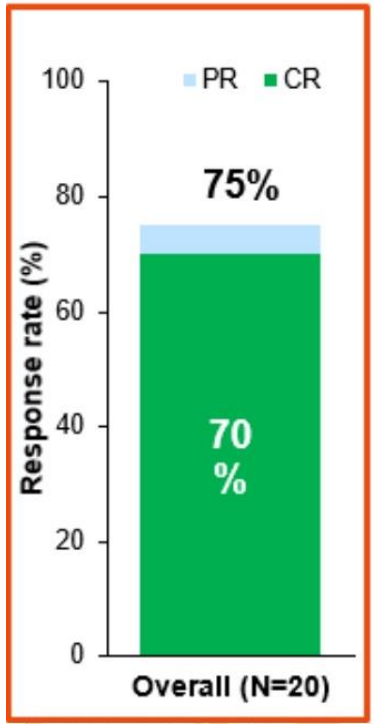
n (%), unless stated	N=20
Median age, years (range)	68 (44–82)
Male sex	15 (75)
ECOG PS score	
0	12 (60)
1	5 (25)
2	3 (15)
Ann Arbor stage III–IV	19 (95)
Extranodal involvement	17 (85)
Elevated LDH	9 (45)
Median lines of prior therapy, n (range)	3 (2–9)
Number of prior lines of therapy	
2	5 (25)
3	6 (30)
≥4	9 (45)

n (%), unless stated	N=20
Prior therapy	
BTKi	20 (100)
CAR T	7 (35)
ASCT	6 (30)
Refractory to last prior therapy	17 (85)
TP53 aberration at study entry	
Mutation/deletion	5/12 (42)*
Wildtype	7/12 (58)
Unknown	8
Ki-67	
≥30%	13 (65)†
≥50%	12 (60)
MIPI score ≥6	8 (40)
Blastoid/pleomorphic	10 (50)
Bone marrow involvement	9 (45)

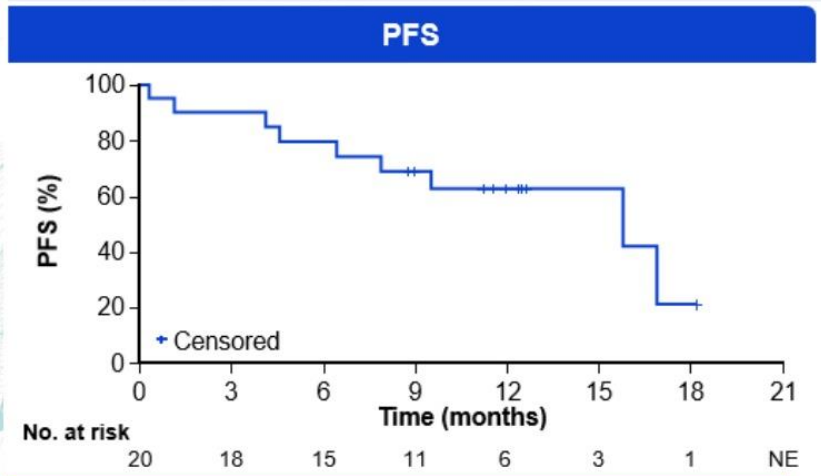
Wang M et al, ASH 2023

Bispecific –Phase Ib/II Study– Mosun-Pola in R/R MCL

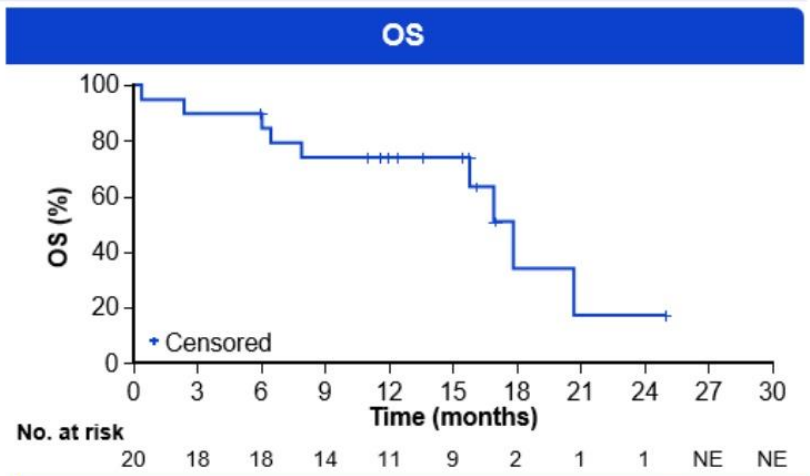
Response and Survival



Median follow-up:15.8 months



	N=20
Median PFS, months (95% CI)	15.8 (8.0–NE)
9-month event-free rate, % (95% CI)	68.8% (48.1–89.6)



	N=20
Median OS, months (95% CI)	17.9 (15.8–20.7)
9-month event-free rate, % (95% CI)	74.1% (54.5–93.7)

Wang M et al, ASH 2023

Sonrotoclax (BGB-11417) monotherapy in R/R MCL previously treated with a BTK inhibitor: early results from a phase 1/2 study

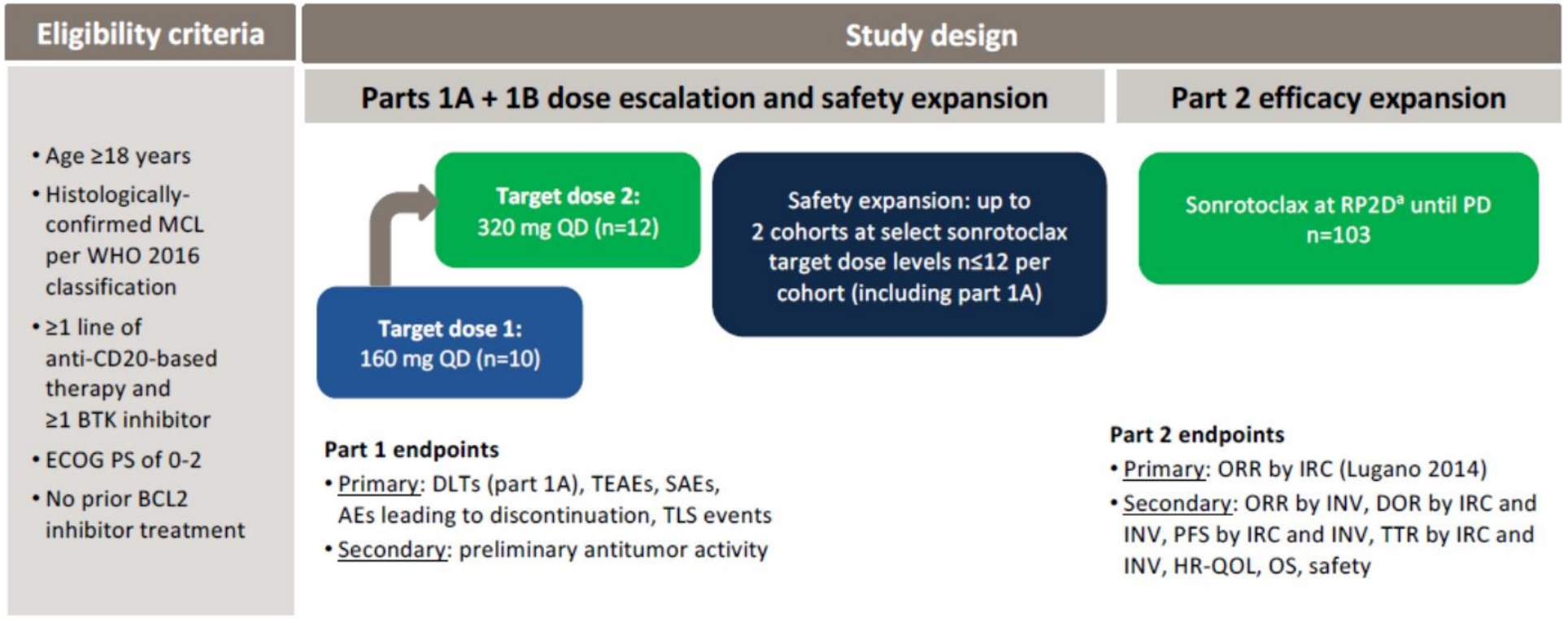
	Sonrotoclax	Venetoclax	Differences in Design
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may potentially lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity
Half-life in humans	≈5 hours[2]	26 hours[3]	Short half-life and no accumulation may potentially result in simplified TLS monitoring during sonrotoclax ramp-up

Sonrotoclax (BGB-11417), a BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation.

In May 2026, sonrotoclax received accelerated approval from the US FDA for patients with R/R MCL who had previously received ≥2 lines of therapy, including a BTK inhibitor

Guo Y, et al. J Med Chem. 2024;67(10):7836-7858.
Liu J, et al. Blood. 2024;143(18):1825-1836.
Wang M et al, ASH 2023

BGB-11417-201 (NCT05471843) study design



Sonrotoclax target doses were achieved after a ~4 week ramp-up that did not require hospitalization or 12- or 24-hour post-dose laboratory monitoring

Wang M et al, ASH 2025

a RP2D: Recommended Phase 2 Dose

Baseline patient demographics and disease characteristics

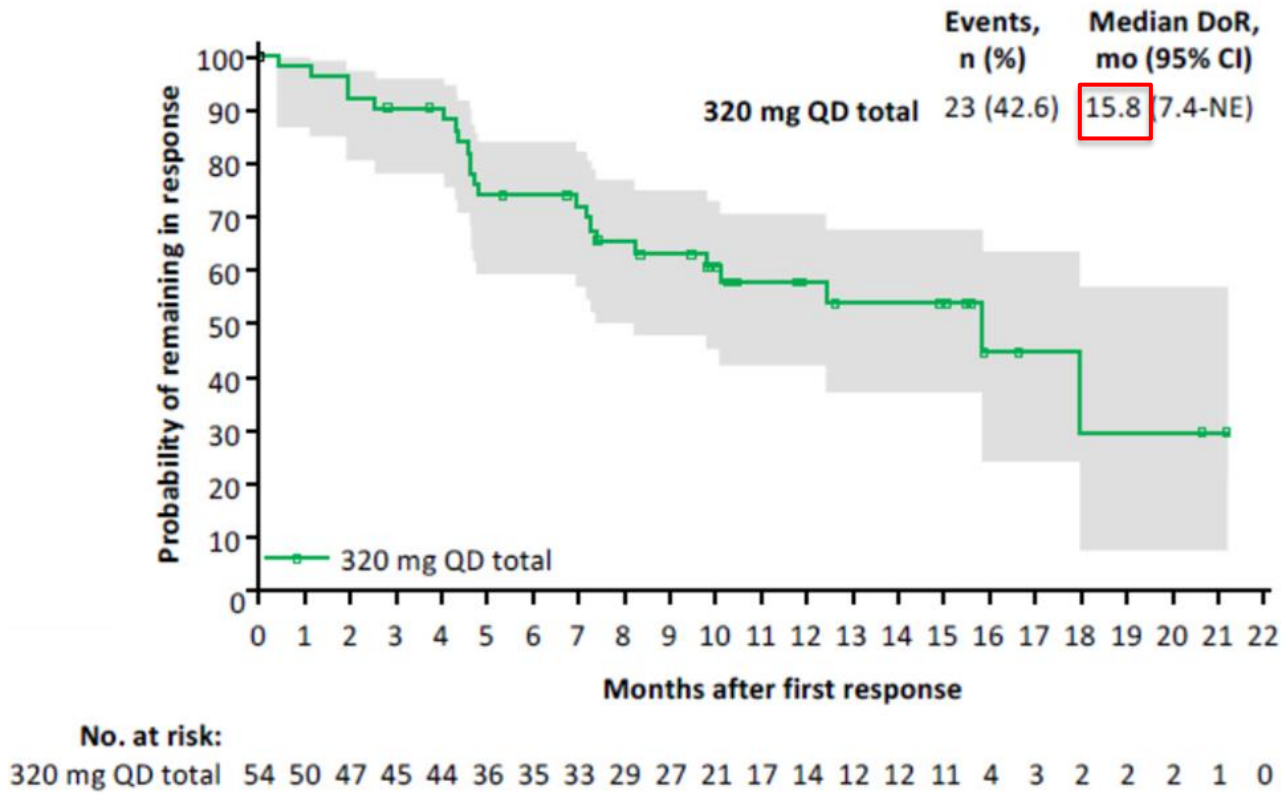
Parameters	Sonrotoclax 320 mg (n=115)
Age, median (range), years	68 (39-85)
≥65 years, n (%)	74 (64.3)
Male, n (%)	87 (75.7)
Race, n (%)	
Asian	45 (39.1)
Black or African American	3 (2.6)
White	61 (53.0)
Other/not reported	6 (5.2)
Ethnicity, n (%)	
Not Hispanic or Latino	87 (75.7)
Hispanic or Latino	25 (21.7)
ECOG performance status, n (%)	
0	34 (29.6)
1	74 (64.3)
2	7 (6.1)
Disease stage at study entry, n (%)	
III	11 (9.6)
IV	90 (78.3)
Disease status to last prior therapy, n (%)	
Refractory[a]	100 (87.0)
Relapsed[b]	14 (12.2)
MIPI, n (%)	
High	39 (33.9)
Intermediate	41 (35.7)

Parameters	Sonrotoclax 320 mg (n=115)
Bulky disease status, n (%)	
LDi ≥5 cm	46 (40.0)
LDi ≥10 cm	12 (10.4)
Bone marrow involvement at baseline, n (%)	58 (50.4)
Ki67 status, n/N with known status (%)	
Positive	92/98 (93.9)
≥30%	41/98 (41.8)
***TP53* mutation, n/N with known status (%)**	27/78 (34.6)
Prior lines of therapy, median (range)	3 (1-8)
≥3 prior lines, n (%)	68 (59.1)
Prior BTK inhibitor treatment, n (%)	115 (100)
≥2 prior BTK inhibitors	22 (19.1)
Prior ASCT, n (%)	17 (14.8)
Prior CAR-T therapy, n (%)	3 (2.6)
Reason for ending last line of anticancer therapy, n (%)	
Progressive disease	79 (68.7)
Treatment completed	17 (14.8)
Toxicity	12 (10.4)
Other	7 (6.1)

Wang M et al, ASH 2025

Efficacy for Sonrotoclax at RP2D 320 mg/die

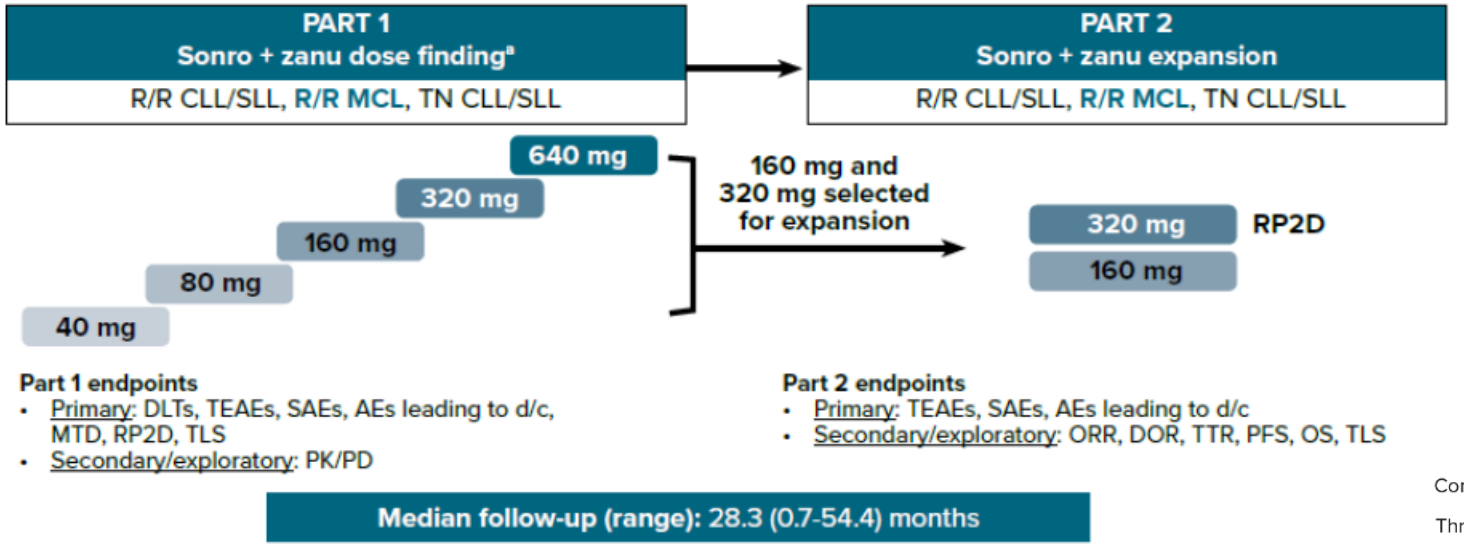
	Part 2: Sonrotoclax 320 mg (n=103)
ORR, n (%)	54 (**52.4**)
95% CI, %	42.4-62.4
CR rate, n (%)	16 (**15.5**)
95% CI, %	9.1-24.0
TTR, median (range), months	1.9 (1.6-6.2)



RP2D: Recommended Phase 2 Dose ; TTR: Time to Response

Wang M et al, ASH 2025

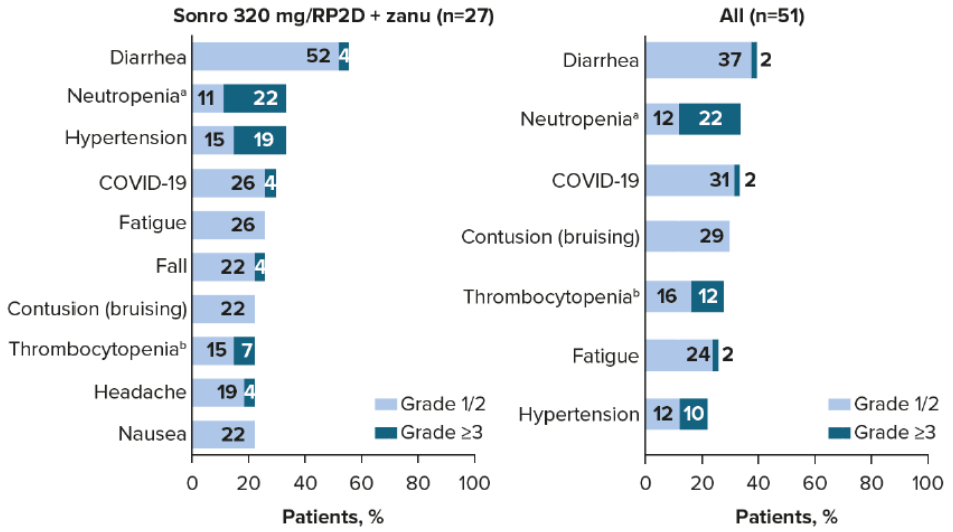
Combination treatment with novel BCL2 inhibitor sonrotoclax (BGB-11417) and zanubrutinib in patients with relapsed/refractory mantle cell lymphoma: Results f rom a phase 1/1b study



Zanubrutinib monotherapy (320 mg QD or 160 mg twice daily) was administered for 8-12 weeks, followed by sonrotoclax + zanubrutinib until disease progression, unacceptable toxicity, or protocol-defined elective discontinuation after week 96

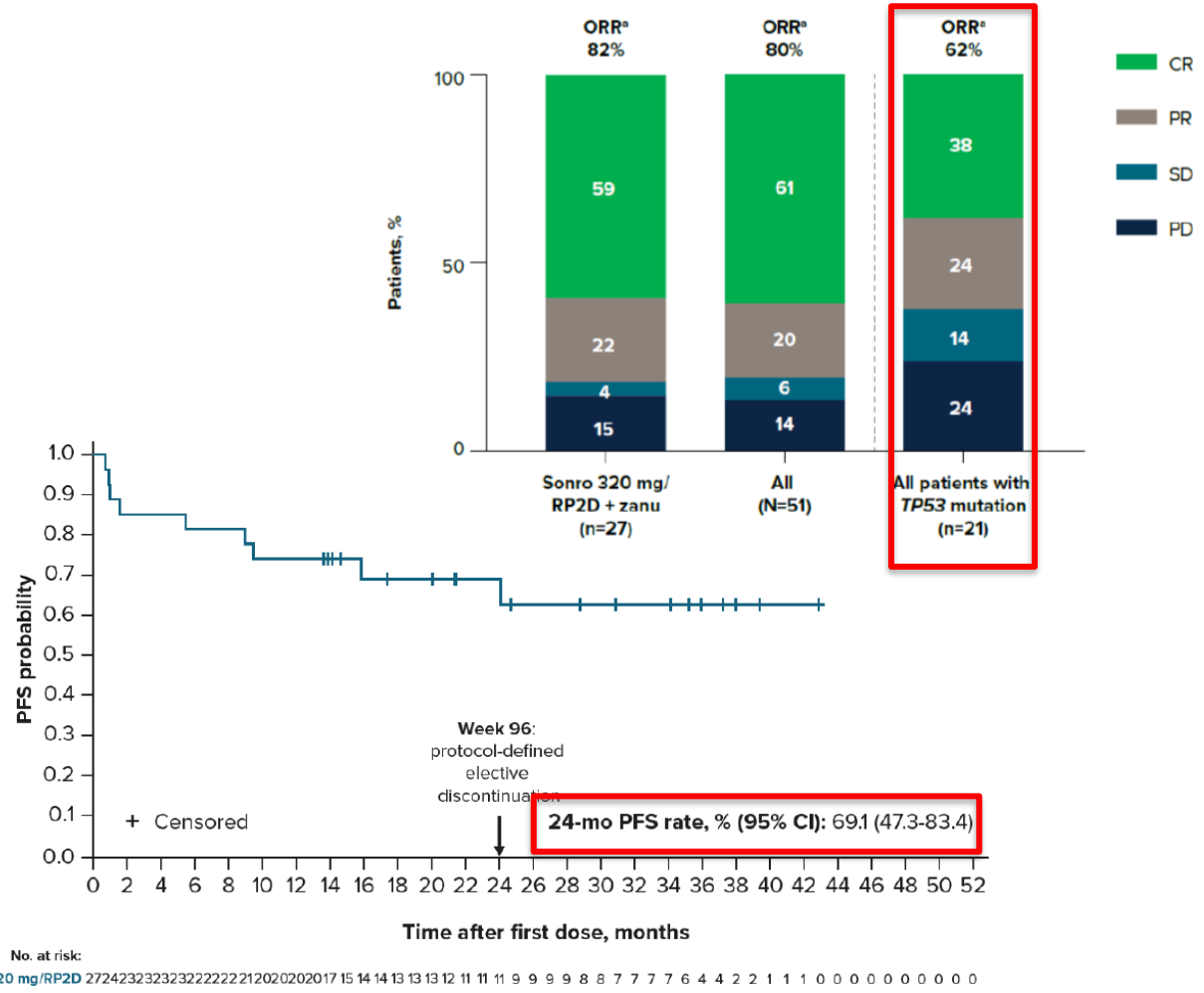
Sonrotoclax target doses (80, 160, 320, or 640 mg QD) were achieved through gradual dose ramp-up over approximately 4 weeks to mitigate the risk of TLS (tumor lysis syndrome)

Treatment - Emergent AEs in ≥20 % of Patients



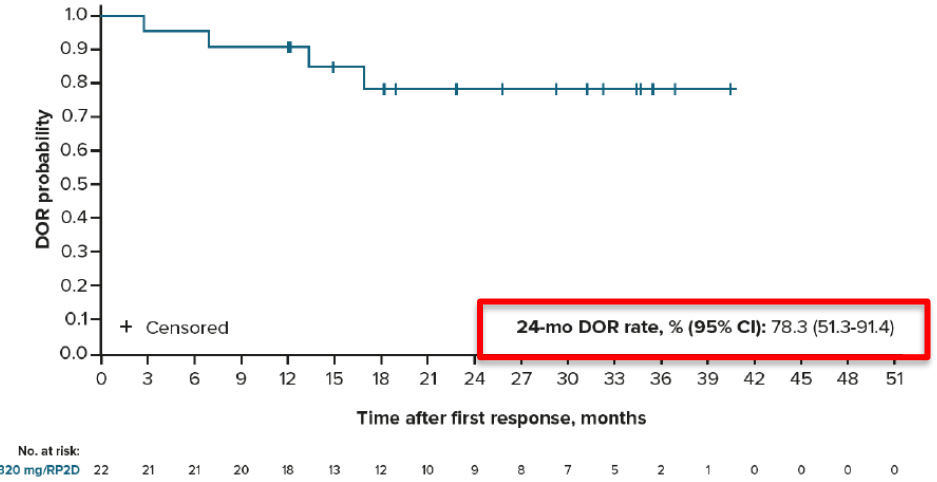
Soumerai J, et al. Poster Presentation at EHA 2026

Combination treatment with novel BCL2 inhibitor sonrotoclax (BGB-11417) and zanubrutinib in patients with relapsed/refractory mantle cell lymphoma: Results f rom a phase 1/1b study



RP2D=recommended phase 2 dose

Duration of Response: Sonrotoclax 320-mg/RP2D Cohort

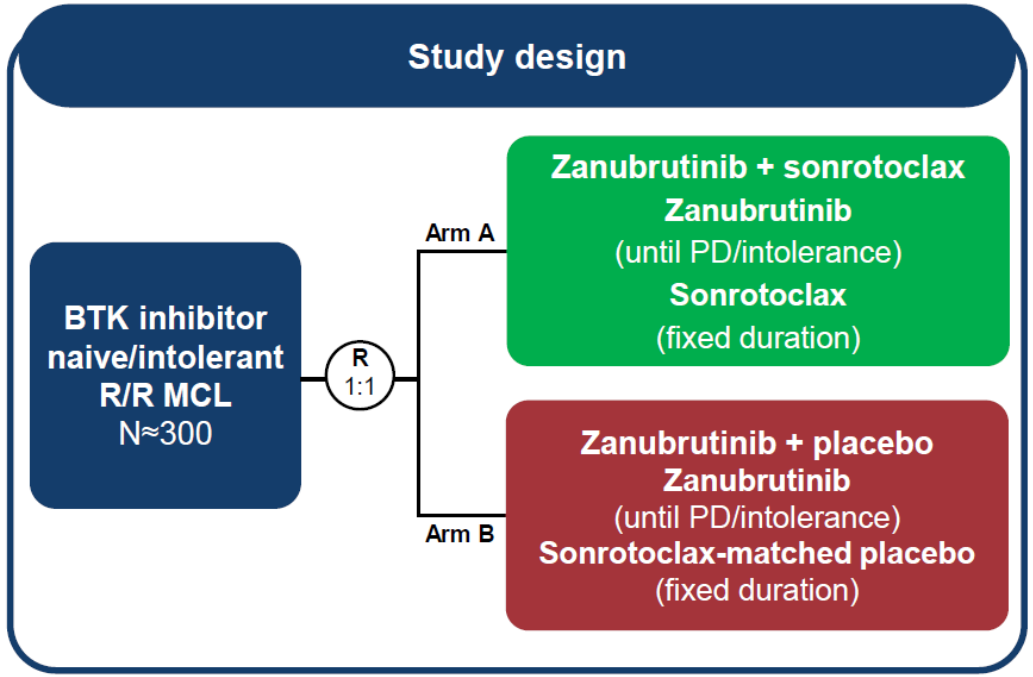


With a **median study follow-up of 28.3 mo** (range, 0.7-54.4 mo), the **median DOR was 50.9 mo** (95% CI, 34.8-NE) across all cohorts
In the sonrotoclax 320-mg/RP2D cohort, median DOR was not reached; the **24-mo DOR rate was 78.3%** (95% CI, 51.3%-91.4%; median DOR follow-up, 25.8 mo)

Soumerai J, et al. Poster Presentation at EHA 2026

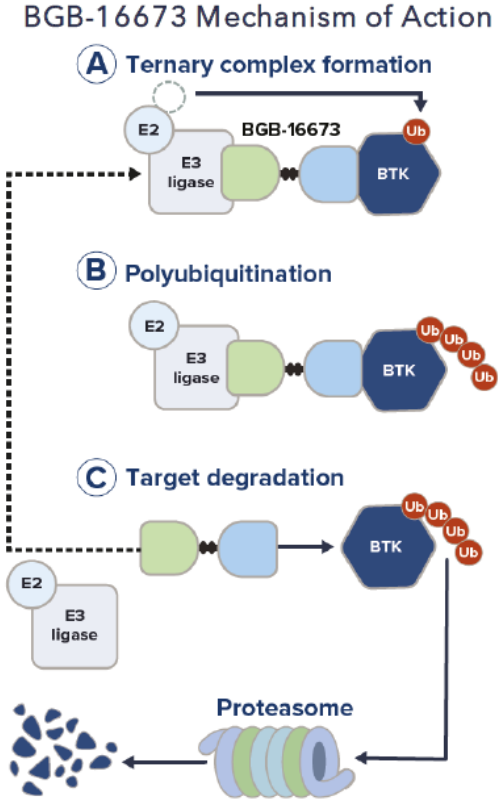
CELESTIAL-RRMCL (BGB-11417-302), a Phase3, Randomized, Double-Blind Study of Sonrotoclax (BGB-11417) + Zanubrutinib vs Placebo + Zanubrutinib in Patients With Relapsed or Refractory Mantle Cell Lymphoma





Martin Dreyling - Presented at the International Conference on Malignant Lymphoma (ICML); June 17-21, 2025; Lugano, Switzerland

CaDAnCe-101 study: Bruton tyrosine kinase (BTK) degrader BGB-16673 (TACABRUTIDEG) in BTK inhibitor–naive patients with CLL/SLL and other B-cell malignancies: results from the phase 1 study



Degrades both wild-type and mutant BTK

CaDAnCe-101 Study Design

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for cohort 1F

- Confirmed diagnosis of CLL/SLL, MCL, MZL, WM, or RT
- ECOG PS 0-2 (0-1 in EU)
- No prior BTK inhibitor treatment
- Adequate organ function

Key objectives for part 1

- **Primary:** safety[c] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, preliminary efficacy[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies (MZL, FL, MCL, CLL/SLL, WM, DLBCL, RT)
n≤72

Part 1b: Safety expansion
Selected R/R B-cell malignancies (MZL, MCL, CLL/SLL, WM)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies (MZL, WM, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion[b]
Selected BTK inhibitor–naive B-cell malignancies (MZL, MCL, CLL/SLL, WM, RT)
n≤75

Determination of BGB-16673 RDFE

Phase 2

Cohort 1:	Cohort 2:	Cohort 3:	Cohort 4:	Cohort 5:	Cohort 6:	Cohort 7:
Post-BTK inhibitor, R/R CLL/SLL	Post-BTK inhibitor, R/R MCL	Post-BTK inhibitor, R/R WM	Post-BTK inhibitor, R/R MZL	R/R FL	R/R non-GCB DLBCL	Post-BTK inhibitor, R/R RT

Mocanu I, et al. Poster Presentation at EHA 2026; PS1693.

CaDAnCe-101 study : Baseline Patient Characteristics

Characteristic	Total (N=54)
Age, median (range), years	68 (42-81)
Male, n (%)	38 (70.4)
ECOG PS, n (%)	
0	27 (50.0)
1	23 (42.6)
2	4 (7.4)
Disease status, n (%)	
Treatment naive	13 (24.1)
Treatment-naive CLL/SLL	11 (37.9)
Relapsed or refractory	41 (75.9)
Relapsed or refractory CLL/SLL	18 (62.1)

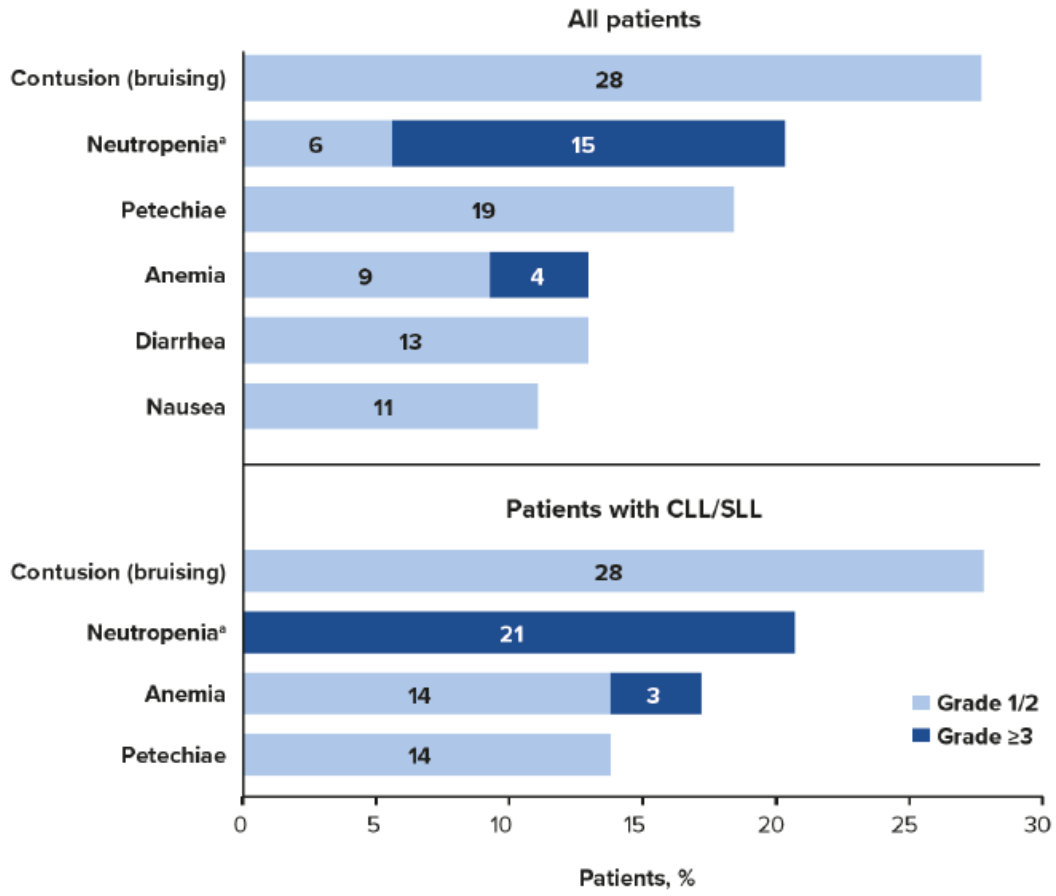
Characteristic	Total (N=54)
Disease type, n (%)	
CLL/SLL	29 (53.7)
MCL	8 (14.8)
MZL	10 (18.5)
WM	5 (9.3)
RT	2 (3.7)
Bulky disease LDi ≥5 cm, n (%)	16 (29.6)
No. of prior lines of therapy, median (range)	2 (1-9)
Prior therapy in previously treated patients, n/N (%)	
Anti-CD20 monoclonal antibodies	41/41 (100)
Chemotherapy	40/41 (97.6)
BCL2 inhibitors	4/41 (9.8)
CLL/SLL risk features, n/N (%)[a,b]	
Binet stage C (CLL)	6/26 (23.1)
Unmutated IGHV	6/6 (100)
del(17p) and/or TP53 mutation	8/25 (32.0)
Complex karyotype (≥3 abnormalities)	1/4 (25.0)

Mocanu I, et al. Poster Presentation at EHA 2026; PS1693.

CaDAnCe-101 study : TEAES (treatment-emergent adverse events) in ≥10% of Patients

- The most common any-grade TEAEs in all patients were contusion (bruising; 27.8%), neutropenia/neutrophil count decreased (20.4%), and petechiae (18.5%); **the most common grade ≥3 TEAE was neutropenia/neutrophil count decreased (14.8%).**
- In patients with CLL/SLL, the most common grade ≥3 TEAE was neutropenia/neutrophil count decreased (20.7%)
- **One patient with MCL developed grade 3 paroxysmal atrial fibrillation, which resolved to sinus rhythm**
- No cases of major hemorrhage, opportunistic infections (including invasive fungal infections), or febrile neutropenia occurred
- Grade 3 infections were reported in 3 patients (5.6%), and no grade 4 or 5 infections occurred

- One TEAE led to treatment discontinuation and death due to metastatic neoplasm; one additional TEAE led to treatment discontinuation due to exacerbation of chronic back pain



Mocanu I, et al. Poster Presentation at EHA 2026; PS1693.

CaDAnCe-101 study : Best Overall Response in Patient s With CLL/SLL

	CLL/SLL (n=22)
Best overall response, n (%)	
CR	0
PR	15 (68.2)
PR-L	4 (18.2)
SD	3 (13.6)
PD	0
Overall response rate, n (%)[a]	19 (86.4)

- BGB-16673 shows promising antitumor activity in BTK inhibitor–naive patients with CLL/SLL. A high response rate was observed and all responses were ongoing at data cutoff
- Response rates were ***consistent in patients with high-risk disease features***, including del(17p) and/or TP53 mutation and unmutated IGHV.
- These encouraging safety and efficacy results could inform future clinical trials

Mocanu I, et al. Poster Presentation at EHA 2026; PS1693.

AlloSCT in R/R-MCL?

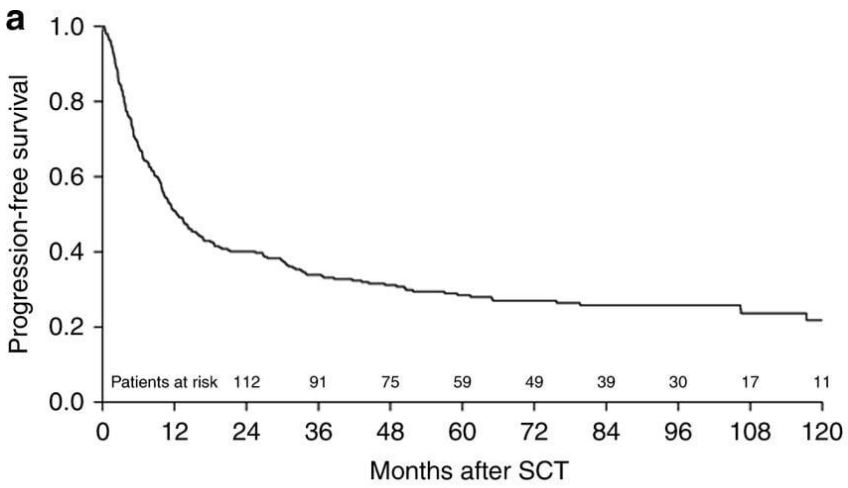
Study	Timing	N° Patients	ORR/CR	Median FU	2-yr NRM	5-yr PFS	5-yr OS	Main Toxicities
Le Gouill et al.	Salvage	70	95%/89%	24mo	32%	≈25%	≈25%	GVHD
Krüger et al.	First line	24	86%/76%	2.8yr		≈67%	≈73%	Stomatitis, infection, GVHD
	Salvage	15	91%/83%	2.8yr		≈67%	≈73%	
Rule et al.	First line	25	92%/60%	60.5mo	13%	56%	76%	Infection, mucositis, GVHD
Fenske et al.	First response	50		48mo	≈30%	55%	62%	
	Salvage	88		37mo	≈25%	24%	31%	
Tessoulin et al.	Salvage	106	97%/86%	45mo	≈30%	≈35%	≈55%	GVHD, infection

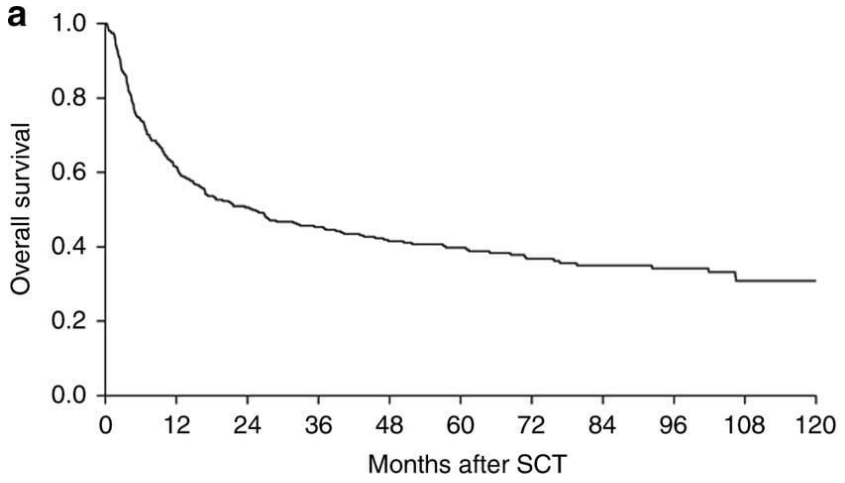


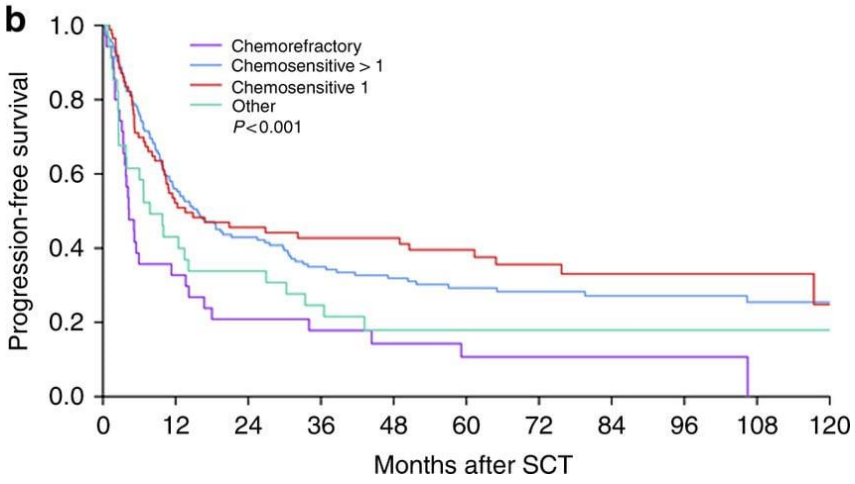


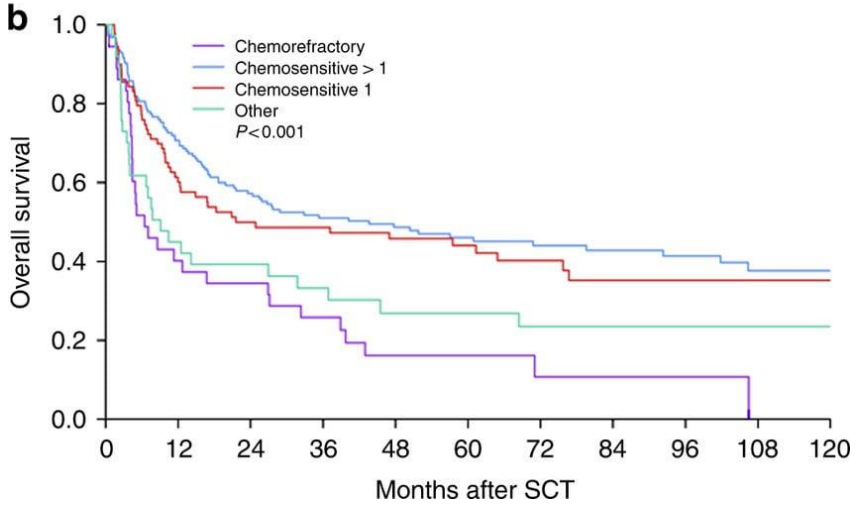
Marangon M. et al. Cancers 2021, 13, 291.

Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation (RIST) in patients with mantle cell lymphoma









	PFS	OS
1-YR	51%	62%
4-5 YR	**31%**	**40%**

NRM 100 days 10%

NRM 1 year 24%

Robinson SP et al, BMT 2018

MCL: Current treatment algorithm

UPFRONT

Standard first line

young (<65y) & fit → R-CHOP + Ibrutinib / R-DHAP (TRIANGLE) → No Auto-SCT*

older (>70y) & unfit → BR + R + Acalabrutinib (ECHO)

Grayzone (65-70y)  ?

** Consider autoSCT consolidation if young (age < 60) and very high risk (Ki67≥50%, blastoid morphology); No in TP53 mutations.*

FIRST RELAPSE

Non-covalent BTKi (Pirtobrutinib)

bridge?

very high risk early POD

Consolidation?

SECOND RELAPSE or FURTHER

CAR-T candidate?

NO → Pirtobrutinib
Bispecifics (Glofitamab)
BCL2i (Venetoclax, Sonrotoclax)
Clinical trial
R-BAC, VR-CAP, Lenalidomide (R2)
Allo-SCT

YES → CAR-T (Brexu-Cel)**

Relapse → Pirtobrutinib / Bispecifics (Glofitamab) / BCL2i (Venetoclax, Sonrotoclax) / Clinical trial / R-BAC, VR-CAP, Lenalidomide (R2) / Allo-SCT

*** Consider allo-SCT consolidation if young and very high risk (Ki67≥50%, blastoid/pleomorphic morphology, TP53 mutations).*

Personal opinion; ESMO guidelines; Silkenstedt E, Dreyling M.- Blood. 2025; Dreyling M – Hematology 2024; EHA-EU MCL GUIDELINES

CONCLUSIONS

- **Standard of care 1L young fit patients: Cytarabine Ibrutinib and rituximab containing chemotherapy followed by Ibrutinib ASCT (?) and Rituximab (?) maintenance TRIANGLE data**
- **Elderly or unfit pts: BR- Acalabrutinib (ECHO)**
- **Relapse/Refractory (R/R) MCL is still an unmet clinical need, particularly if already exposed to BTK inhibitors.**
- **Therapeutic landscape in R/R MCL is rapidly changing**
- **As BTKi are moving to first line, R/R patient's management will be a critical issue.**
- **CAR-T cells are the most effective approach, after BTKi failure.**
- **Both chemo-immunotherapy and Allo-SCT could maintain a role in specific selected settings**
- **Many novel products are entering the clinical arena holding unprecedented promise for these patients**