Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

25 giugno 2026

Bologna
Royal Hotel Carlton

Linfoma di Hodgkin Paziente ricaduto-refrattario

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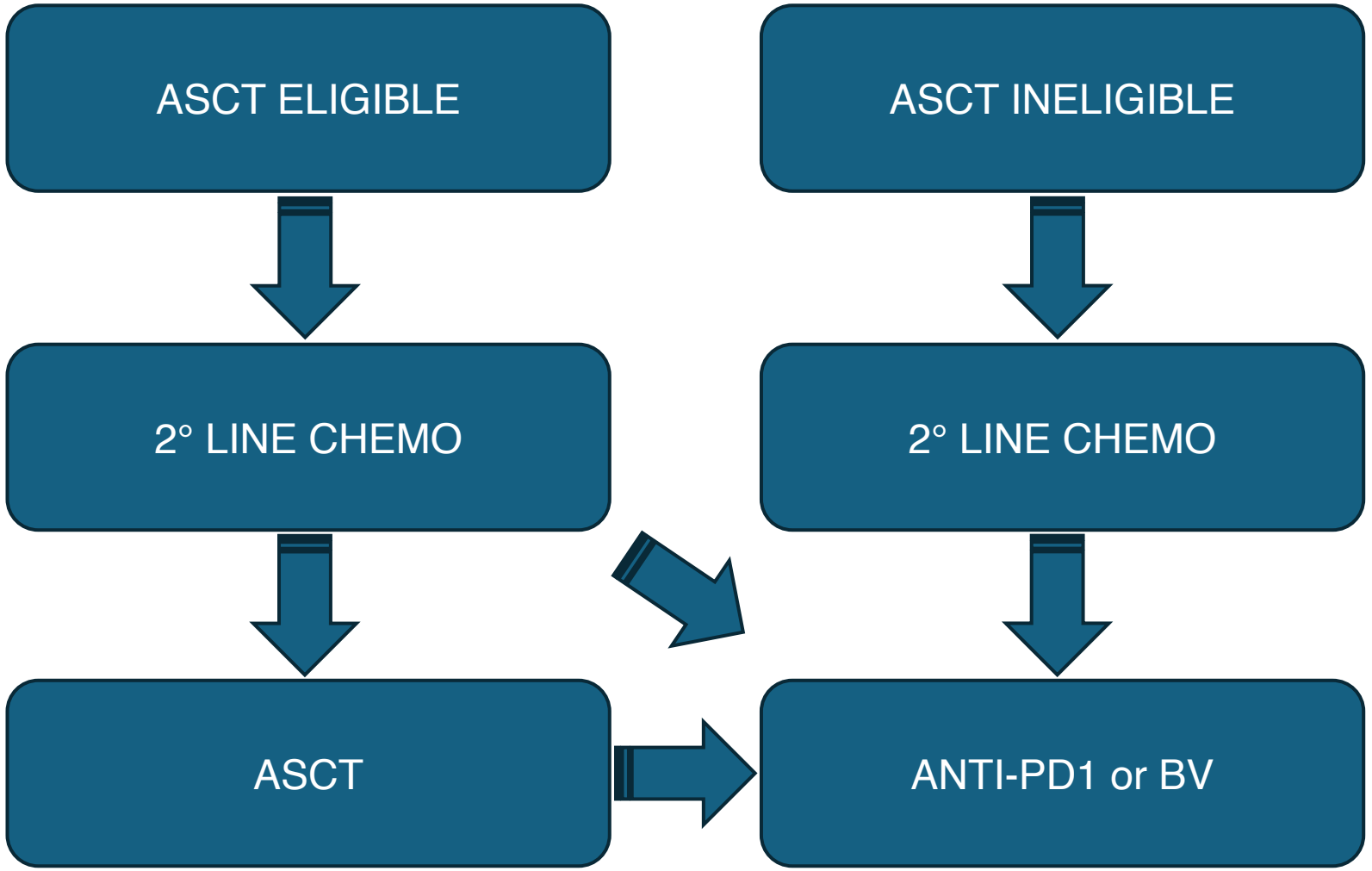
Disclosures of Enrico Derenzini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X					X	
Roche					X	X	
Incyte	X				X	X	
ADC-Therapeutics	X						
Beigene						X	X
AbbVie					X	X	
Astra Zeneca			X			X	
Lilly						X	
Sobi					X	X	
Gilead						X	
Regeneron			X				
J&J						X	
BMS						X	

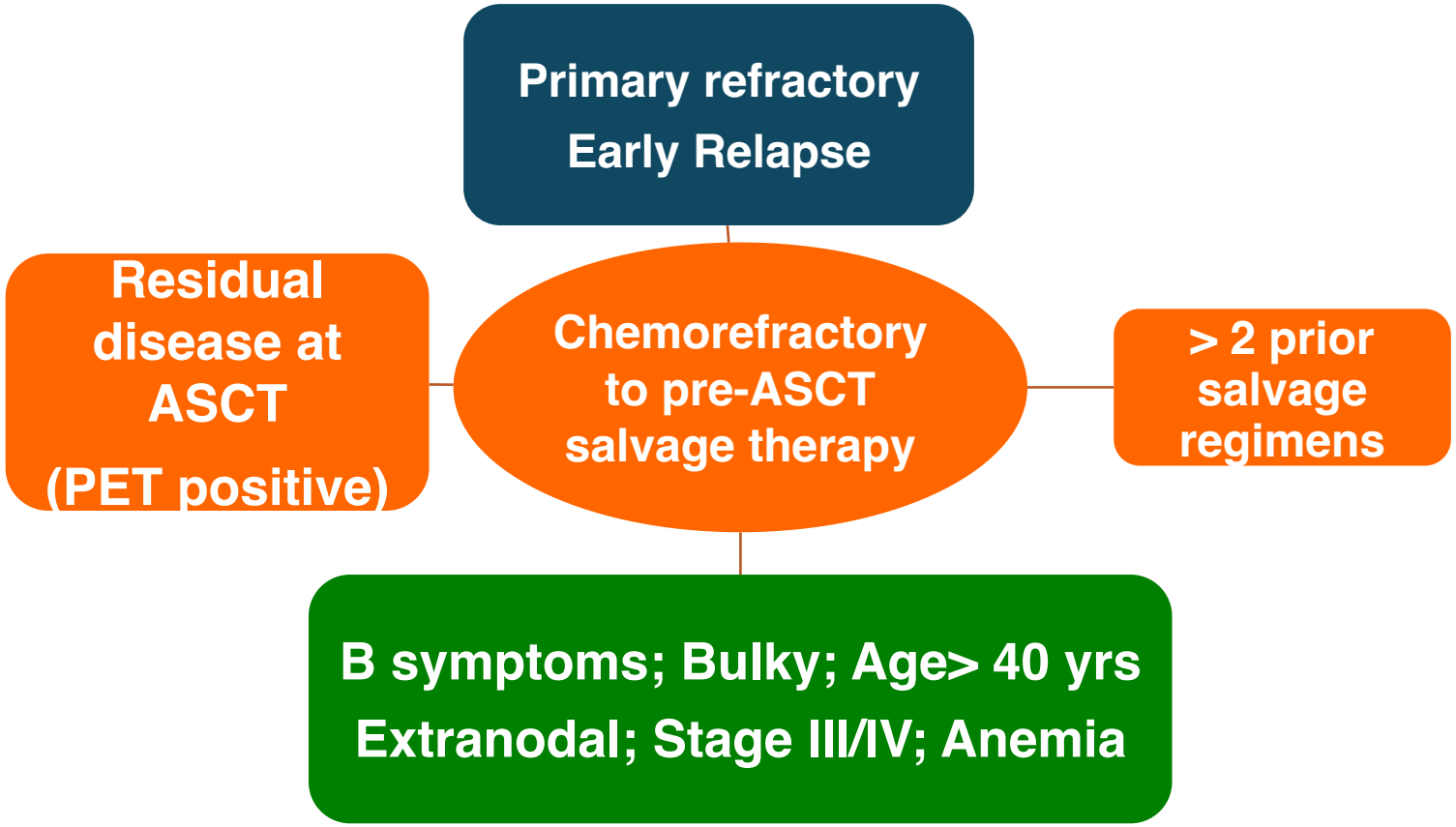
Relapsed/Refractory cHL

Current treatment landscape in Italy



DISCRASIA TRA ATTUALE SCENARIO TERAPEUTICO E POSSIBILITA' PRESCRITTIVA

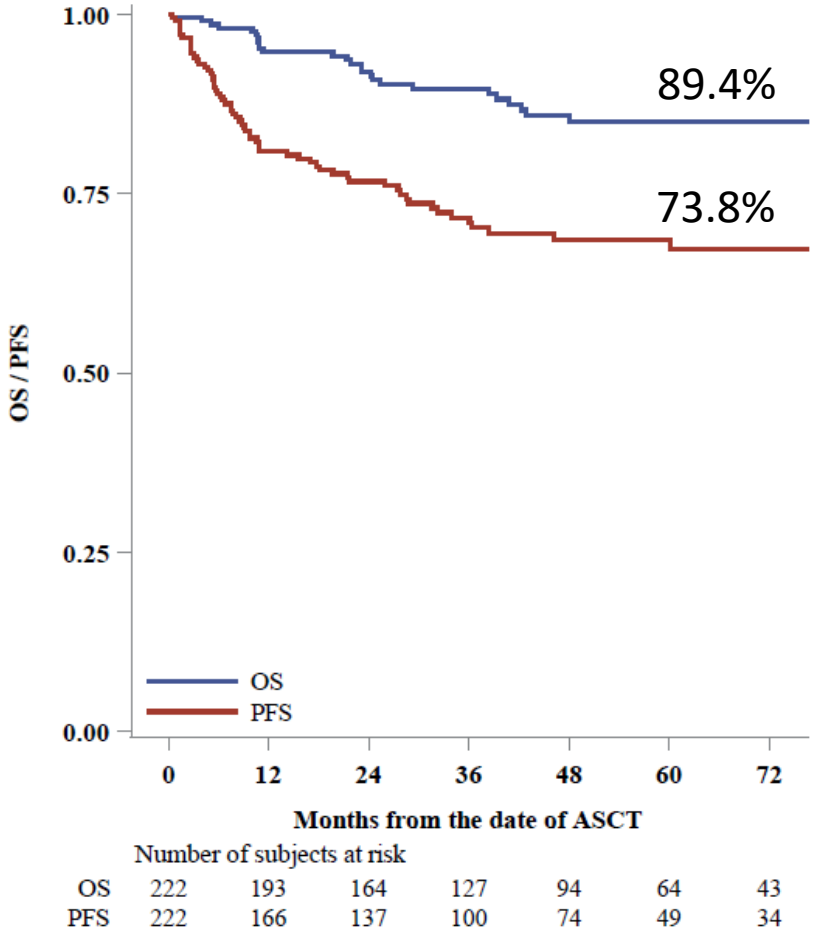
Risk factors for ASCT outcomes



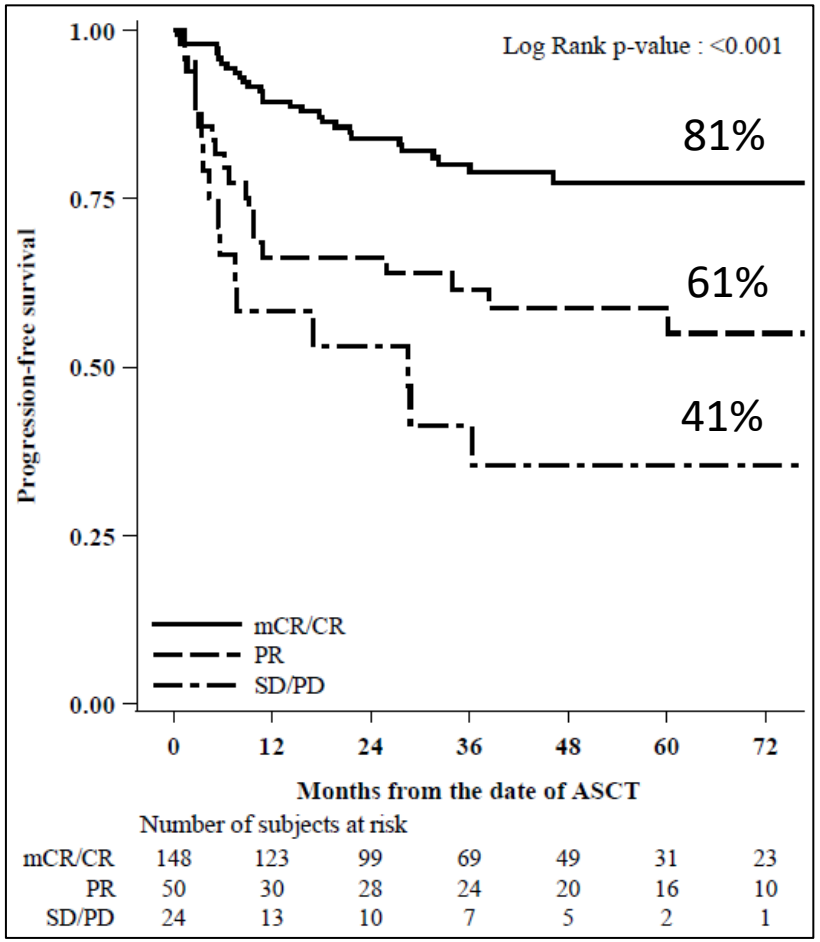
Primary refractory disease: PD during front-line CT or ≤ 3 mos after end of CT; PET positive (DS score 4 or 5) at the end of first-line CT

Early relapse: Relapse after > 3 months but < 12 months after enf of first-line CT

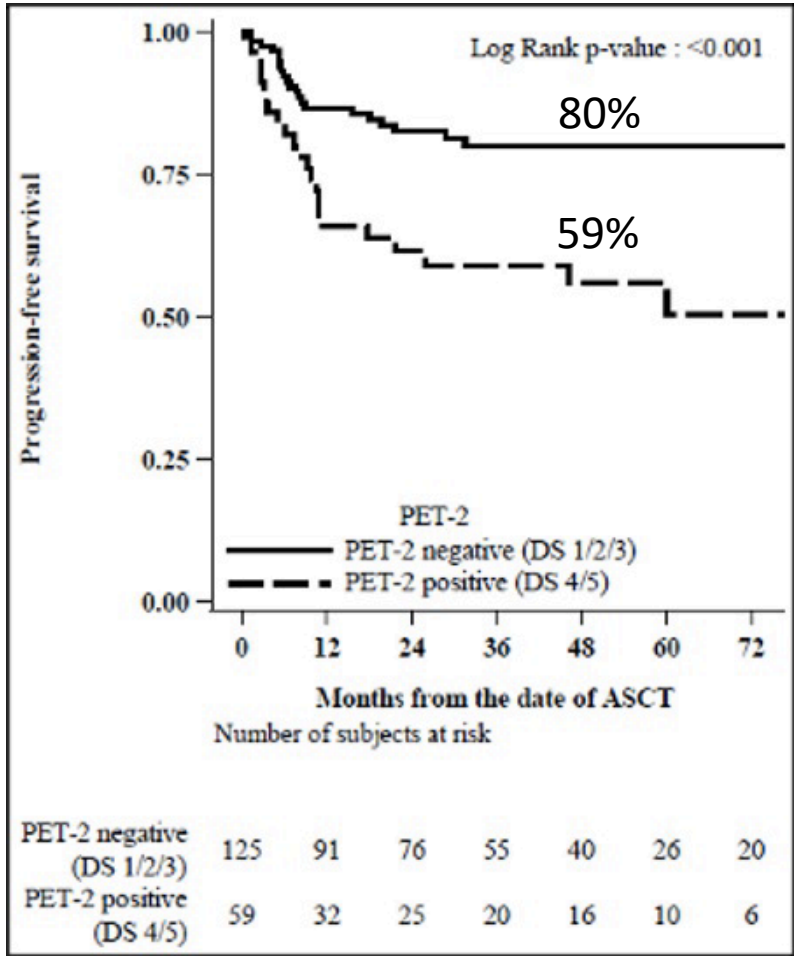
HD-CT and ASCT as first salvage treatment in 220 patients with R/R Hodgkin Lymphoma in the era of PET-adapted strategy



3-year PFS and OS after ASCT



3-year PFS according to status at ASCT



3-year PFS by PET-2 status at front-line treatment

Viviani S et al. Leuk Lymphoma 2024;65:460-471

How to Enhance First Salvage Strategies

- 20% to 30% of pts with Hodgkin lymphoma are refractory to or relapse after first-line treatment
- Standard salvage (second-line) regimens such as ICE/DHAP/GDP/IGEV/ BeGEV have high response rates but are associated with significant toxicities

Salvage Regimen	Pts, n	ORR, %	CR, %	Post-ASCT PFS, %	Post-ASCT OS, %
ICE[1]	65	88	26	68 (4-yr)	83 (4-yr)
DHAP[2]	102	88	21	69 (3-yr)	85 (3-yr)
ESHAP[3]	82	67	50	56 months	73 (5-yr)
GVD[4]	91	70	19	EFS: 52 (4-yr)	70 (4-yr)
GDP[5]	34	62	9	74 (1.5-yr)	91 (1.5 -yr)
IGEV[6]	91	81	54	53 (3-yr)	70 (3-yr)
BeGEV[7]	59	83	75	59 (5 yr)	78 (5 yr)

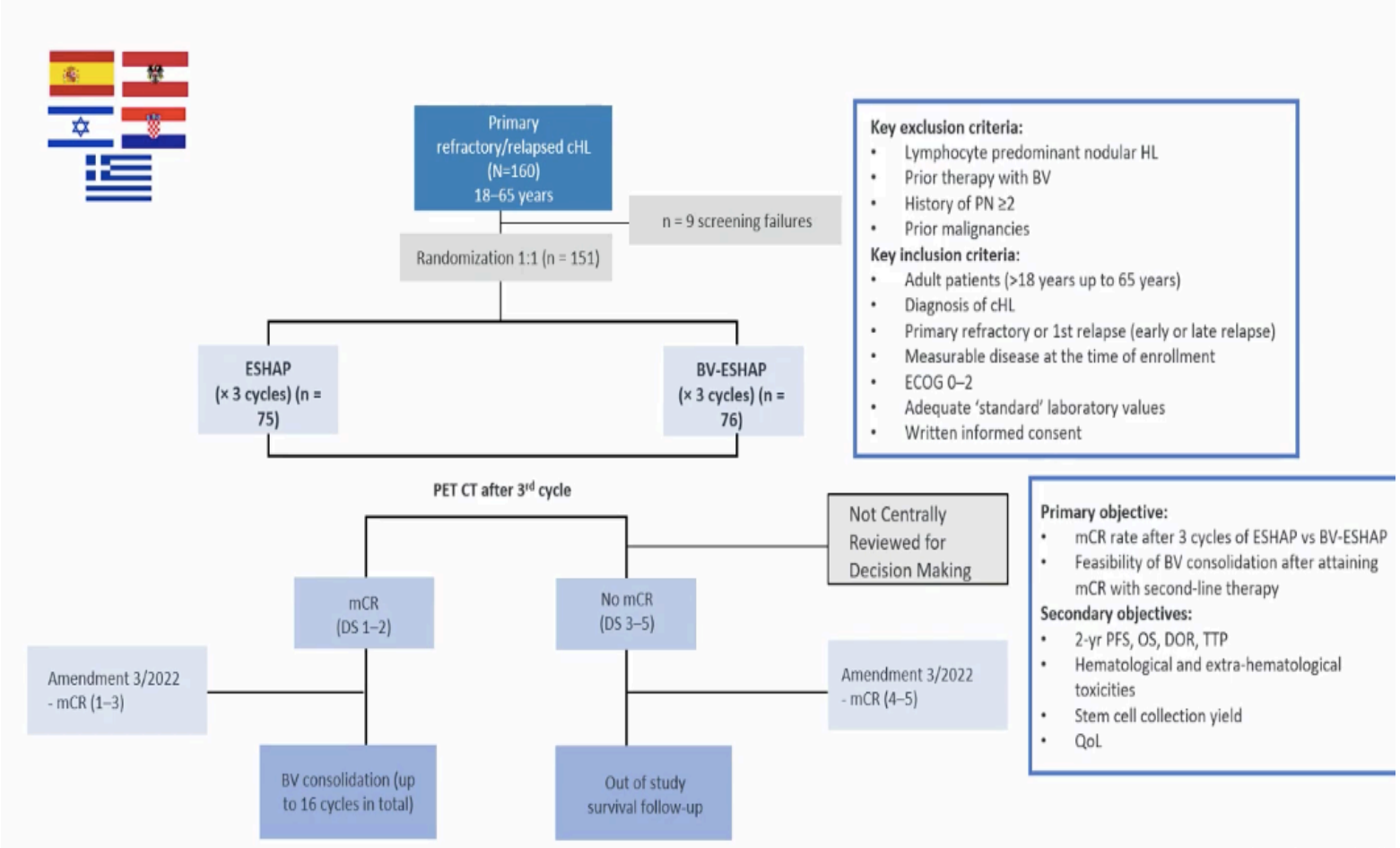
1.Moskowitz CH, Blood. 2001;97:616
2.Josting A, Ann Oncol. 2002;13:1628
3.Labrador J, Ann Hematol. 2014;93:1745
4.Bartlett NL, Ann Oncol. 2007;18:1071
5.Kuruvilla J, Cancer. 2006;106:353
6. Santoro A, Haematologica. 2007;92:35
7. Santoro A, Clin Oncol. 2016;34:3293

Brentuximab Vedotin ± Chemotherapy Regimens

Salvage Regimen	Pts, n	ORR, %	CR, %	PFS, %	OS,%
BV->ICE[1]	65	88	83	82 (2yr)	95 (2yr)
BV-Benda[2]	54	96	83	63	94
BV-ESHAP[3]	66	91	70	71	90
BV-DHAP[4]	52	90	82	78	96
BV->ICE/GVD[5]	57	70	65	67	93
BV-IGEV[6]	28	81	70	73	87

1.Moskowitz AJ, Blood. 2017;130:2196
2. LaCasce AS, Blood. 2018;132:40
3. Garcia-Sanz R, Ann Oncol. 2019;30:612
4.Kersten MJ, Haematologica. 2021;106:1129
5. Herrera AF, Ann Oncol. 2018;29:724
6. Abuelgasim KA, Bone Marrow Transplant. 2019;54:1168

BV-ESHAP significantly increases the CMR vs ESHAP in R/R cHL. Final Results of the BRESELIBET trial



BV-ESHAP x 3 vs ESHAP x 3, followed by BV consolidation in those who attained a CMR x 13-16 doses in both arms

Sureda A et al, T104, ISHL 2024

N=160 pts; 36% primary refractory, 52% stage III-IV

CMR 68.4% in BV-ESHAP vs 48% in ESHAP
(P=0.011)

2-y PFS 74.3%

80 pts consolidated with BV
(65% dose delay or modification, 38.5% delay and modification);
14 relapsed during BV, 2 during FU

BV consolidation might eventually substitute ASCT in pts who achieve CMR

Checkpoint inhibitors ± Brentuximab Vedotin ± Chemotherapy

Salvage Regimen	Pts, n	ORR, %	CR, %	PFS, %	OS,%
BV + Nivolumab[1]	91	85	67	77 (3-yr)	91 (3-yr)
Pembrolizumab+ GVD[2]	39	100	95	96 (30 mos)*	100 (1-yr)
N-ICE (Nivo alone or +ICE)[3]	43	93	91	72 (2-yr)	95 (2-yr)
Tislelizumab+ Gemox[4§]	30	100	97	96 (1-yr)	99 (1-yr)
Sintilimab + ICE[5]	34	--	62	Median PFS not reached	

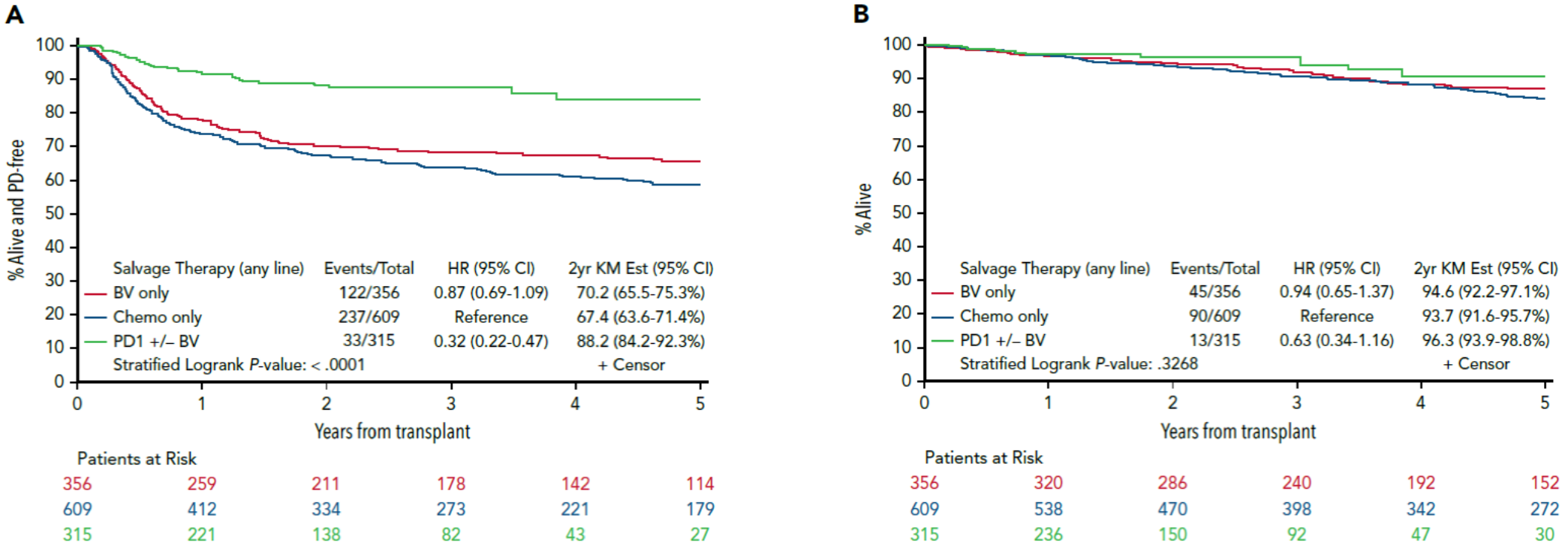
1.Advani R, Blood. 2021;138:427
2. Moskowitz AJ, J Clin Oncol. 2021;39:3109
3.Mei Mg, Blood 2022;139:3605
4.Ding K, Haematologica 2023;108:2146
5.LiuP, J Clin Oncol 2025;43 (16 S):7007

- Engraftment syndrome: 68%
- § no ASCT, Tislelizumab maintenance

Improved outcome with PD-1 blockade before ASCT

TRANSPLANTATION

PD-1–based combinations before autologous transplant are associated with improved outcomes in classical Hodgkin lymphoma

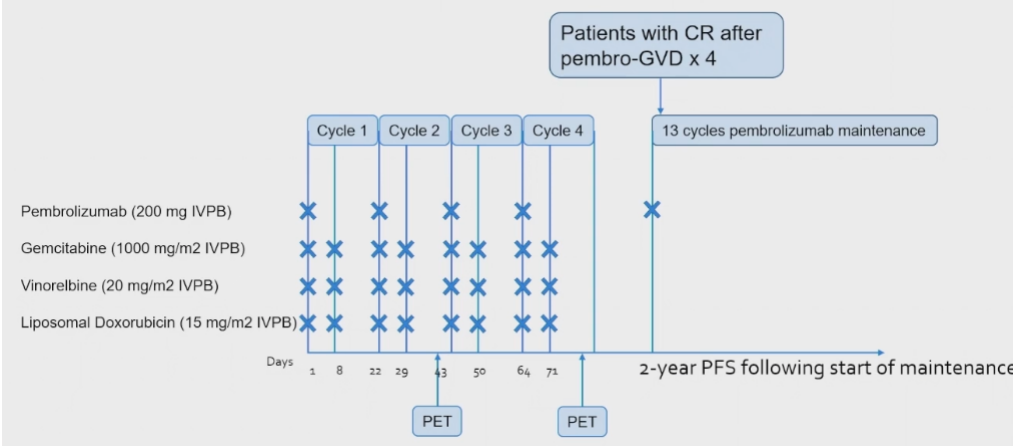


Desai SH, Blood 2026;147: 1125

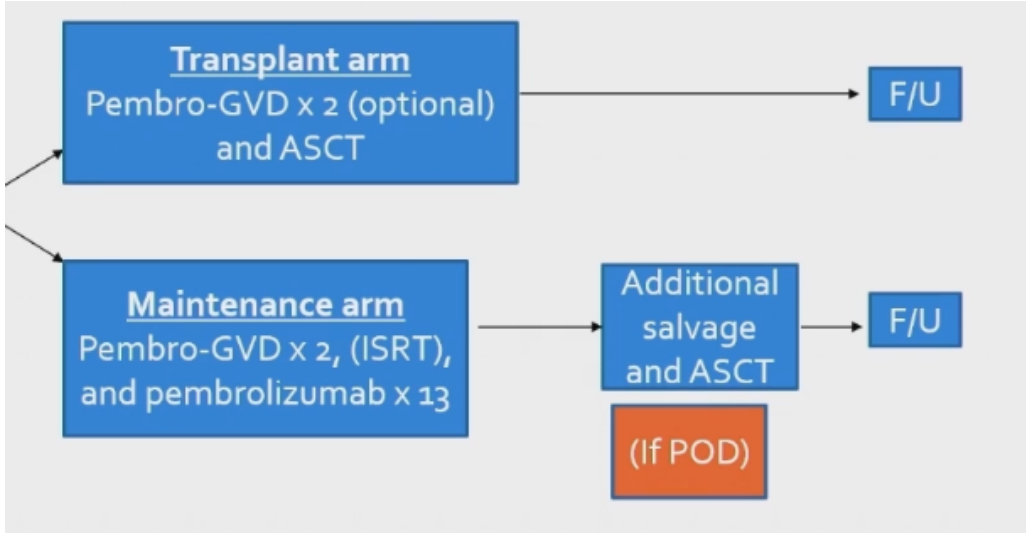
Have new drugs made Stem Cell Transplantation obsolete?

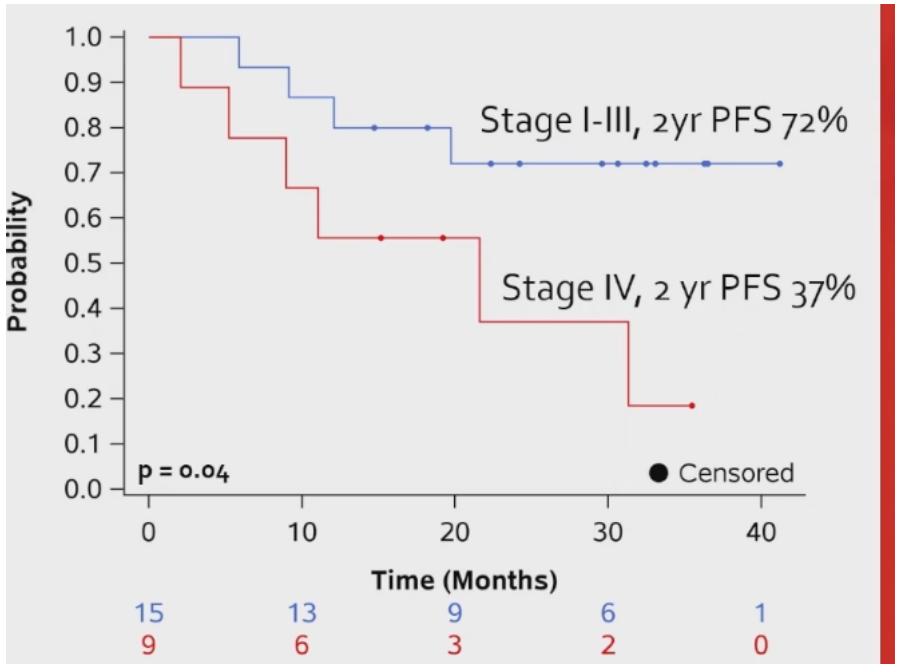
Pembrolizumab maintenance instead of ASCT in R/R cHL in CR after Pembro-GVD

- N= 40 (43% primary refractory; 40% stage IV)
- Post 4x P-GVD 90% CR
- 24 CRs proceeded to Pembro maintenance
- 2-y PFS 60%
- 9/10 relapses proceeded to ASCT
- Freedom from 3rd relapse >90%



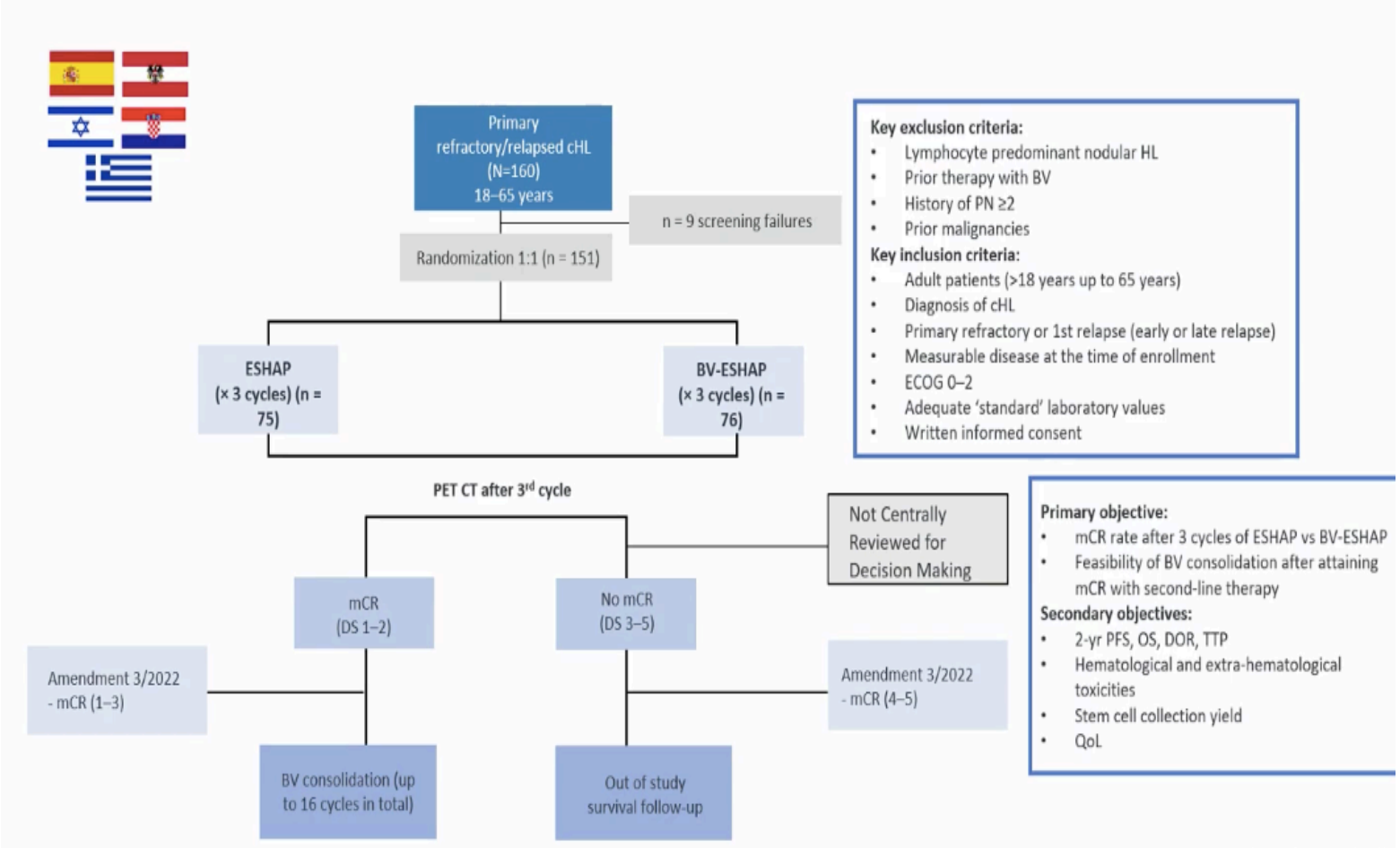
Ongoing trial for stage I-III R/R cHL with CR post 2 x PGVD





Moskowitz A et al, ISHL 2024

BV-ESHAP significantly increases the CMR vs ESHAP in R/R cHL. Final Results of the BRESELIBET trial



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Sureda A et al, T104, ISHL 2024

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(65% dose delay or modification, 38.5% delay and modification);
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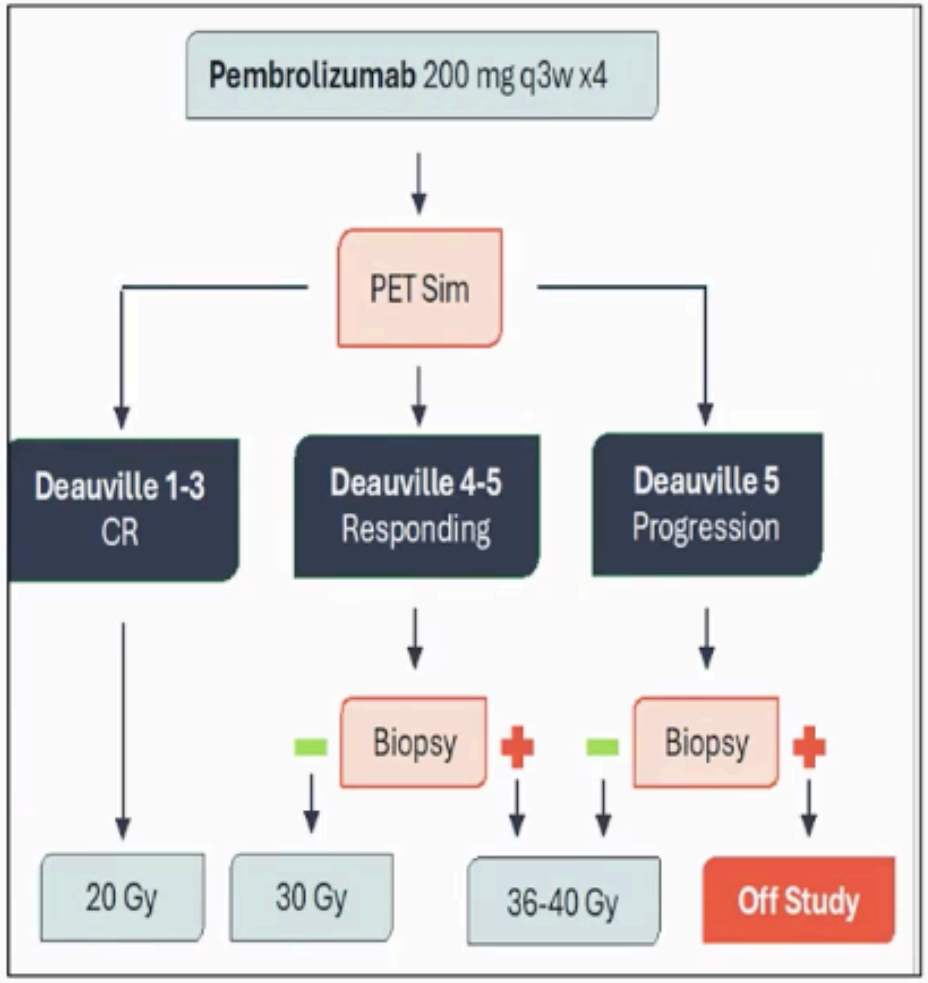
BV consolidation might eventually substitute ASCT in pts who achieve CMR

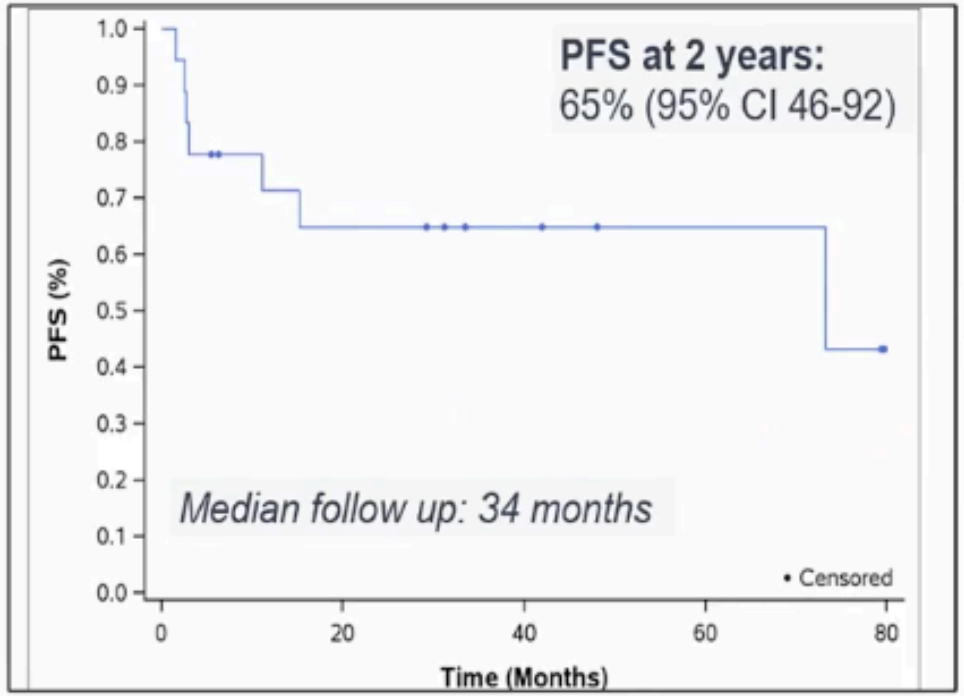
Pembrolizumab and ISRT alone as an alternative to transplant in patients with localized failure following chemotherapy for cHL



Initial stage I-IIA HL with non-bulky, local relapse after chemo only or combined modality therapy

N=15
33% CR post pembro
20% PR neg Bx
27% PR pos bx

Minimal toxicity



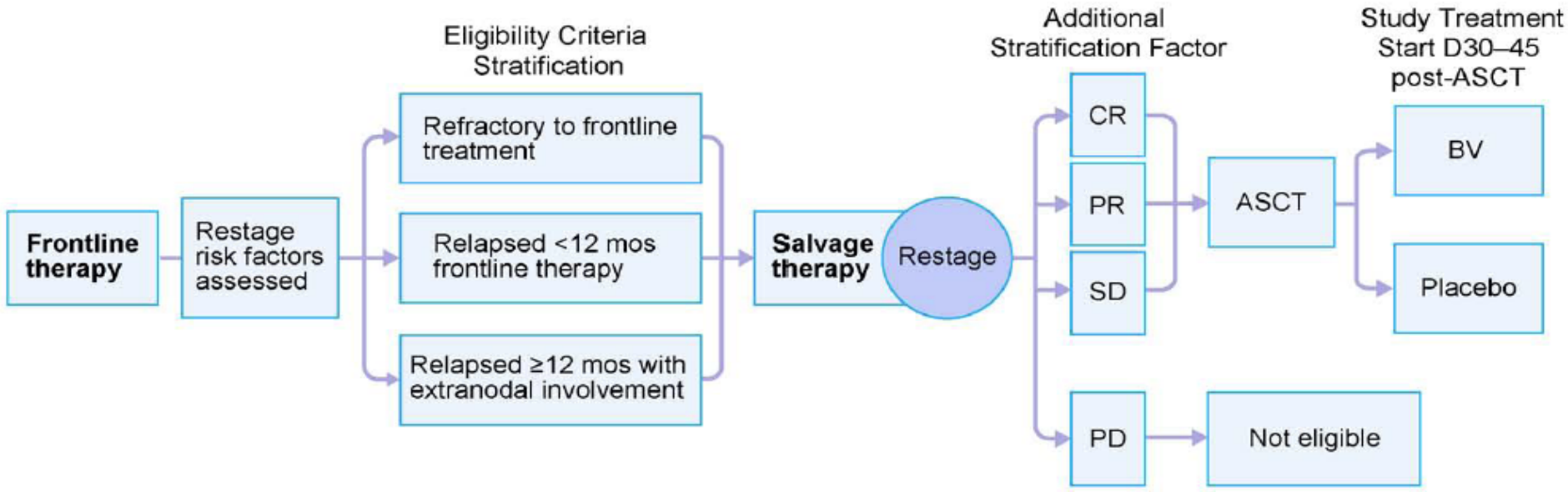
Dreyfuss et al, Abstract #P125

Post-ASCT Maintenance

AETHERA Trial: Placebo-controlled Phase 3 study
Brentuximab Vedotin for pts at risk of HL progression after ASCT

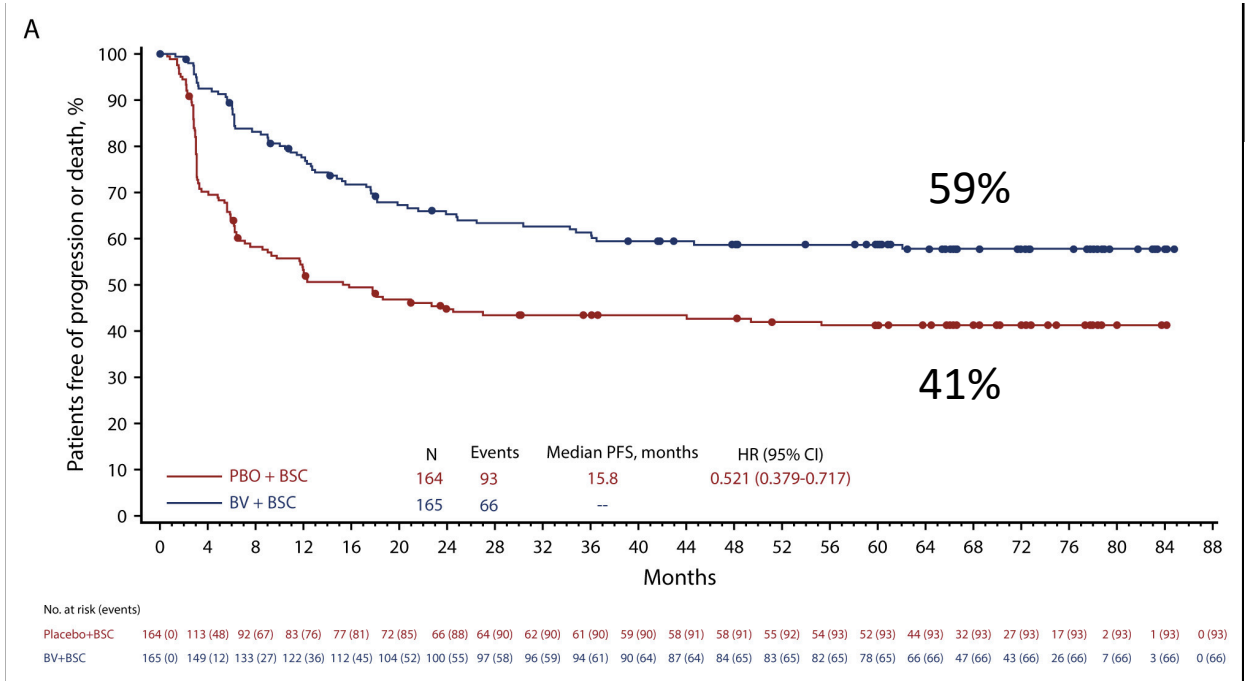
Study Design and Key Eligibility Criteria

- 329 patients were randomized at 78 sites in North America and Europe

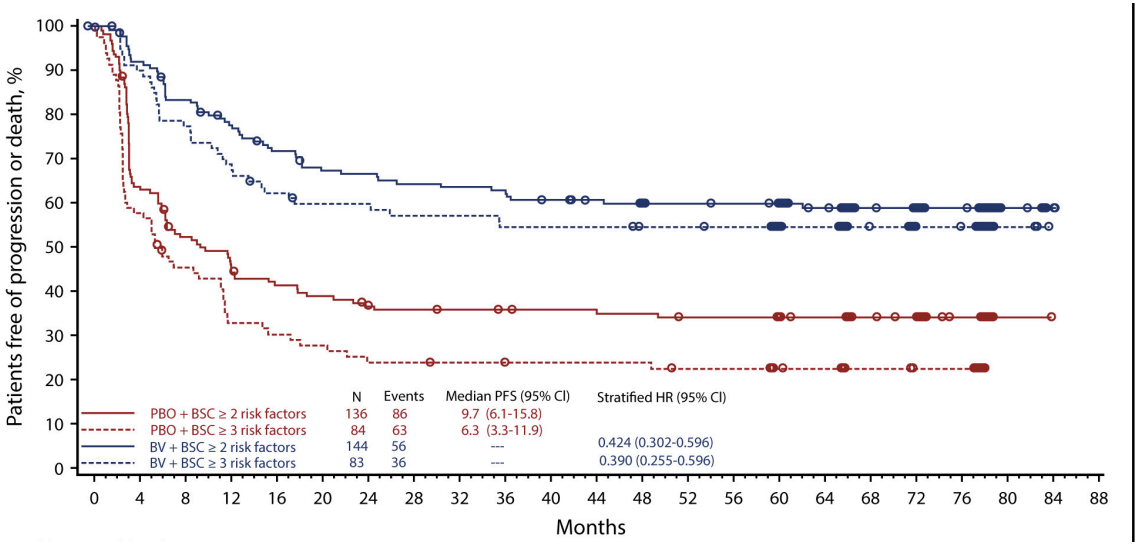


Moskowitz CH, Blood. 2018 Dec 20;132:2639

5-yr PFS rate with BV vs placebo



5-yr PFS in patients with ≥2 or ≥3 risk factors

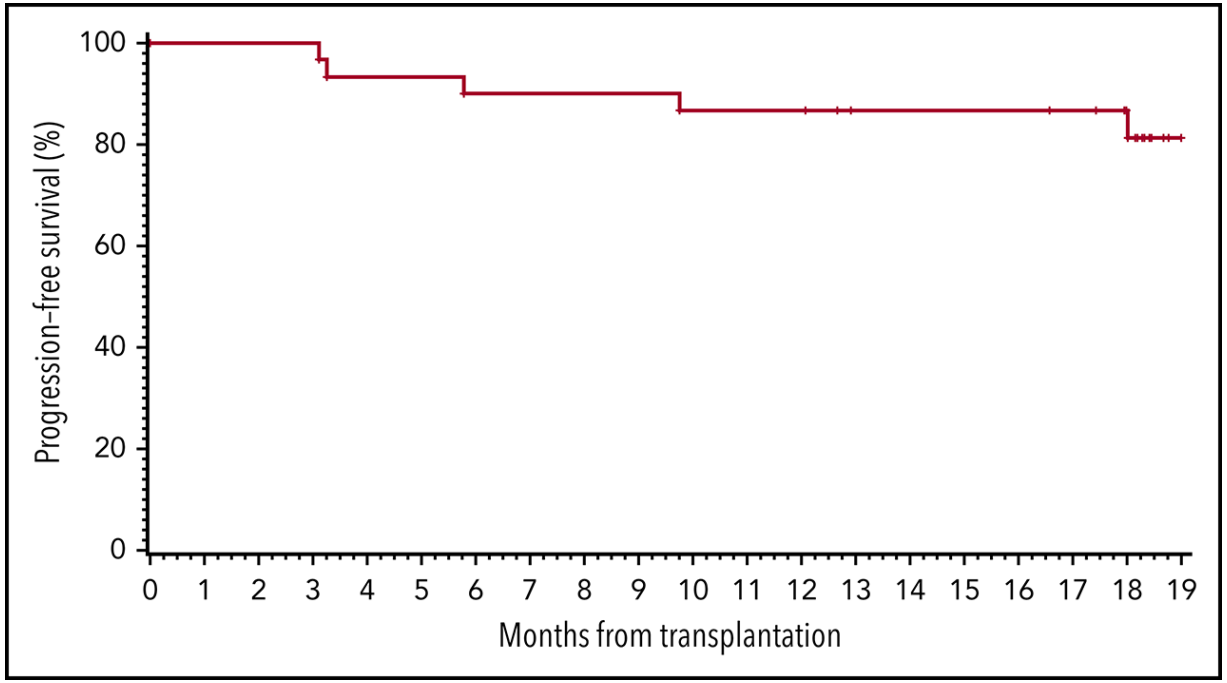


Risk factors:

- relapse < 12 months or refractoriness to frontline therapy;
- best response of partial response or stable disease to most recent salvage therapy;
- extranodal disease at pre–auto-HSCT relapse;
- B symptoms at pretransplantation relapse
- >2 prior salvage therapies

Moskowitz CH, Blood. 2018 Dec 20;132:2639

PD-1 blockade with Pembrolizumab after ASCT



- 28 evaluable patients
- 200 mg q 21 days up to 8 cycles
- 18-months PFS : 82%; OS 100%

1.Post-ACST pembrolizumab maintenance therapy does not impact recovery of T cells.

2.Pembrolizumab was associated with an elevation in circulating dendritic cells.

3.Features of post-ASCT immune reconstitution may be associated with PFS and irAEs.

Armand P, Blood 2019;134:22;
Merrymann W, Transplant Cell Ther. 2022;28:32.e1

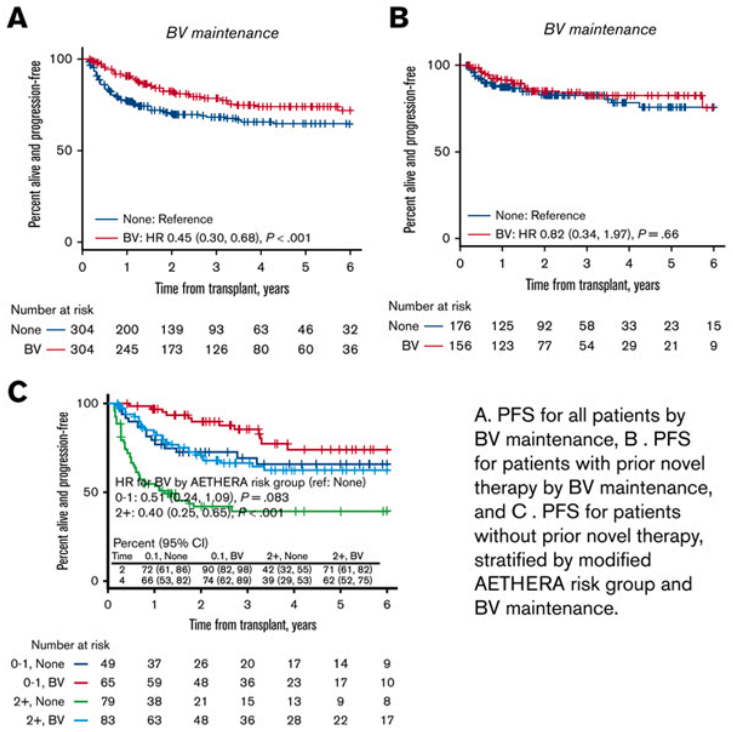
Impact of Novel Therapies on the Efficacy of Post-Transplantation Brentuximab Vedotin Maintenance in Hodgkin Lymphoma

Background: The AETHERA trial established brentuximab vedotin (BV) maintenance as standard of care after autologous stem cell transplant (ASCT) for relapsed/refractory classical Hodgkin lymphoma (r/r cHL). However, increasing frontline and salvage use of BV and PD-1 inhibitors has altered the treatment landscape.

We evaluated the real-world efficacy of BV maintenance, with emphasis on patients previously exposed to novel agents.

Patients and Methods: Retrospective review of adult r/r cHL patients who underwent ASCT between 2010 and 2022. A propensity-score matched analysis (to adjust for baseline differences and possible confounders) was conducted between patients who received BV maintenance and those who did not. Survival outcomes were estimated using Kaplan-Meier methods and compared using Cox proportional hazards models.

Outcomes: BV maintenance was associated with improved PFS in all patients. However, this association was most pronounced in high-risk patients without prior exposure to novel agents.



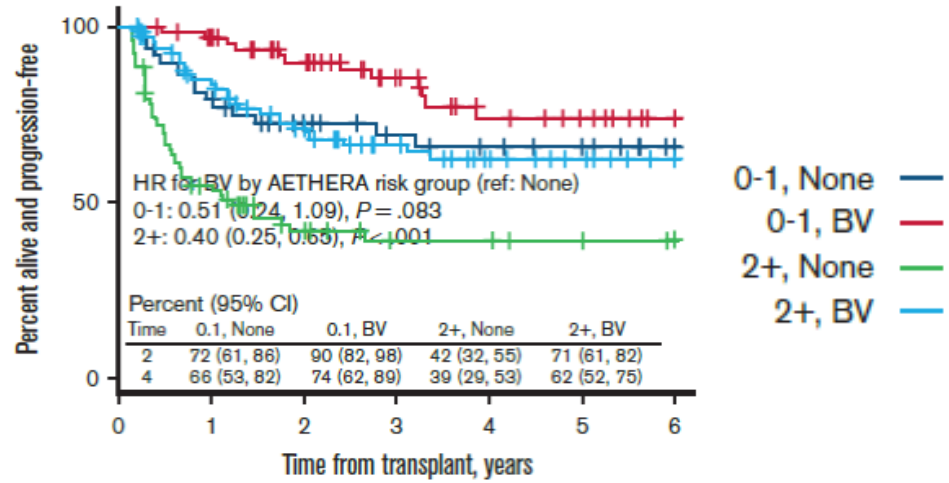
A. PFS for all patients by BV maintenance, B . PFS for patients with prior novel therapy by BV maintenance, and C . PFS for patients without prior novel therapy, stratified by modified AETHERA risk group and BV maintenance.

Conclusions: Benefit from BV maintenance was largely restricted to patients without prior exposure to novel therapies before ASCT (HR 0.32, *P* = .0019).

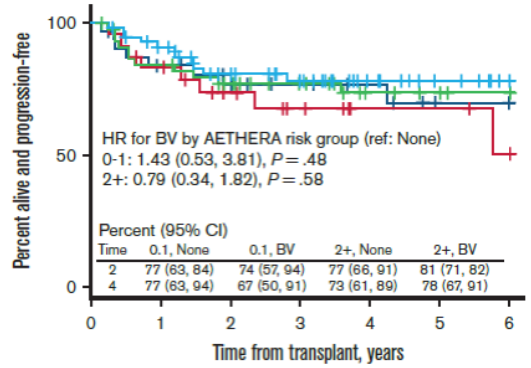
*Falade et al. DOI: 10.1182/**bloodadvances**.2025018683*

blood advances Visual Abstract

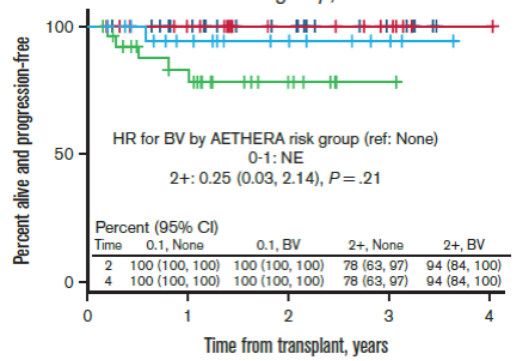
Patients that received no novel agents



Patients with prior BV exposure (no PD-1)
AETHERA risk group, Maintenance

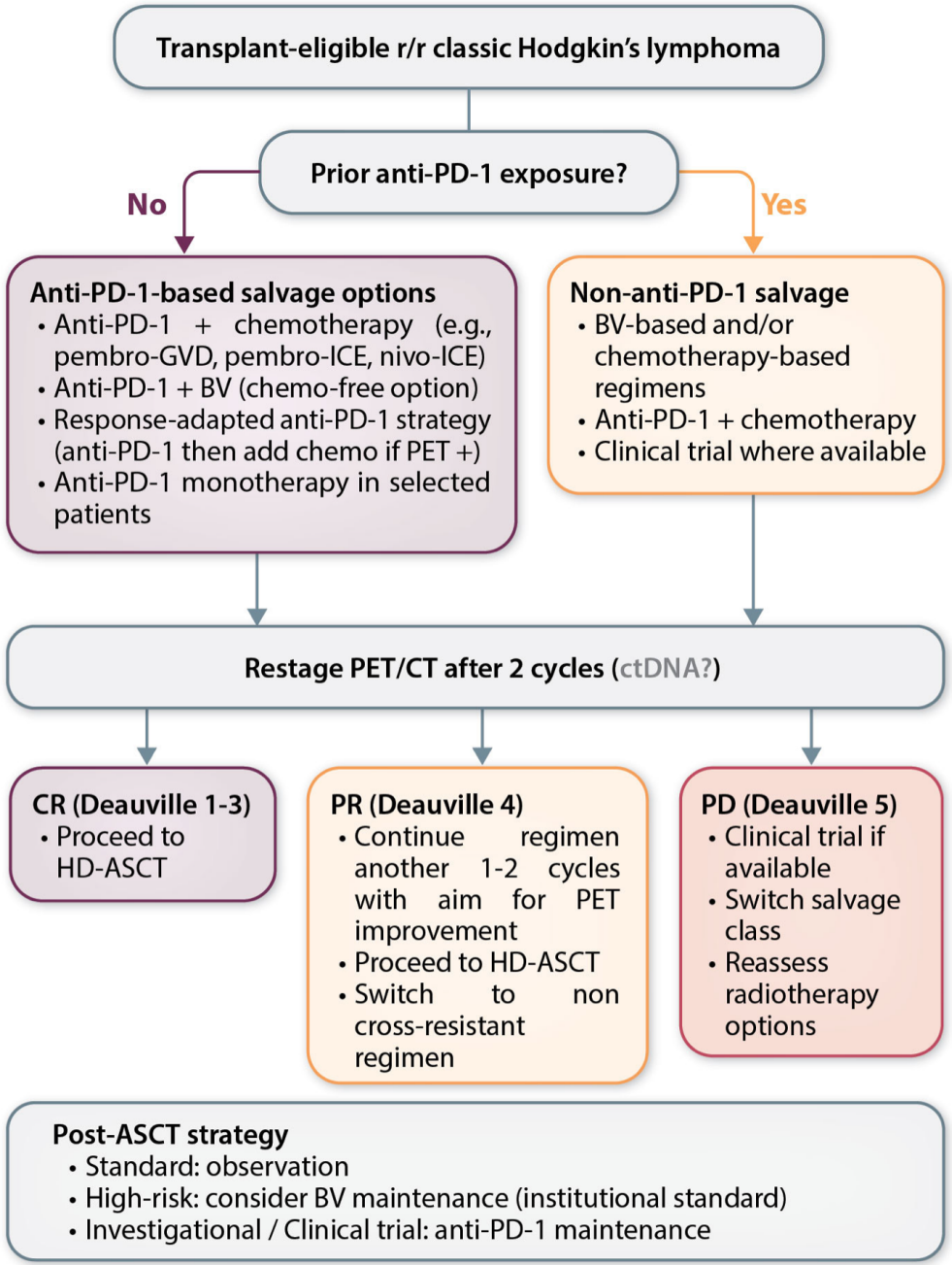


Patients with prior PD-1 exposure without BV
AETHERA risk group, Maintenance



Transplant-based Approach

Anti-PD-1-based Salvage in Relapsed or Refractory Classic Hodgkin's Lymphoma



Efficacy

Anti-PD-1 plus chemotherapy regimens have produced high PET-negative CR rates in phase II trials and retrospective series with efficient bridging to HD-ASCT.

Regulatory gap

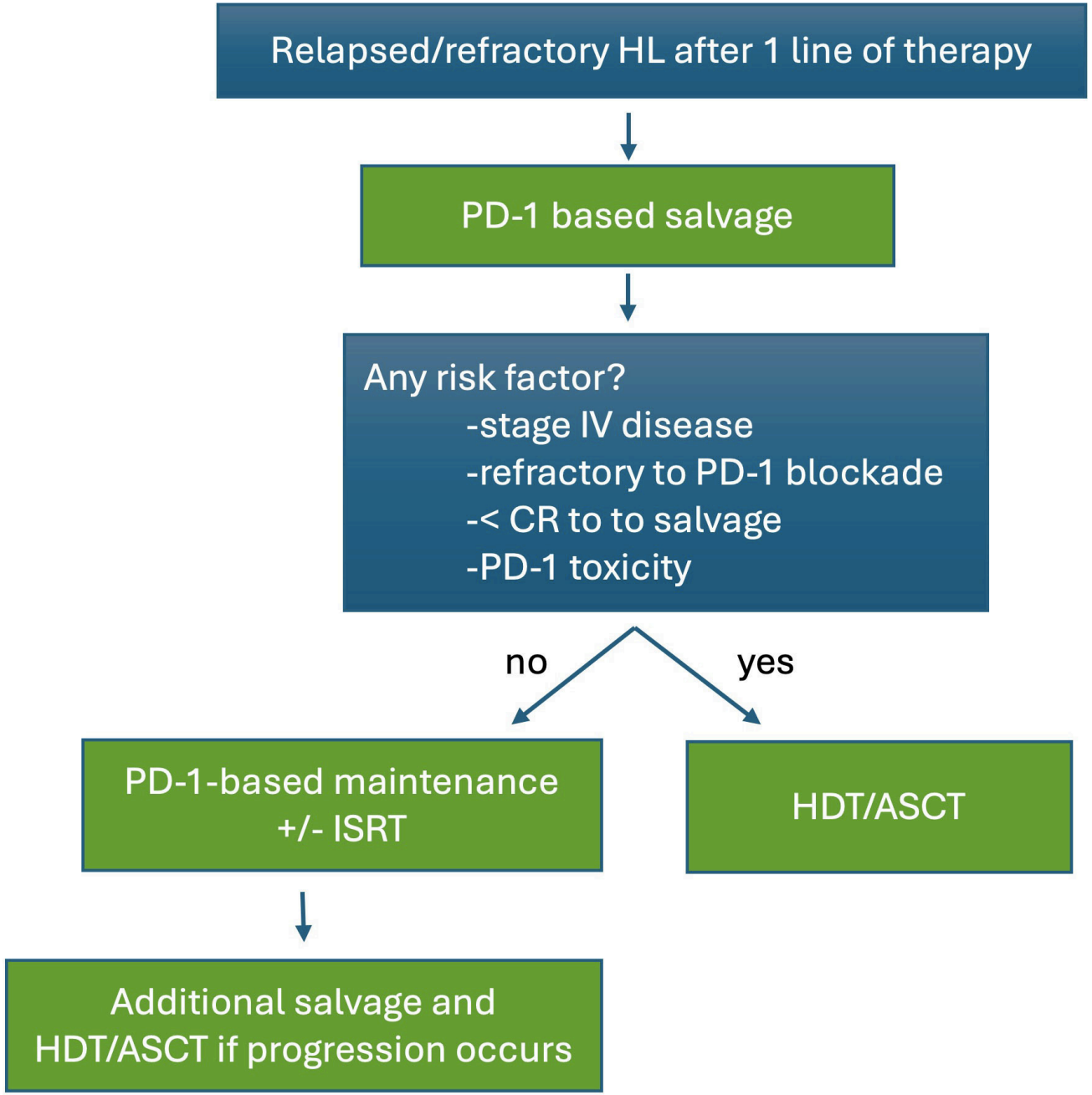
Checkpoint inhibitors are increasingly used as second-line bridge strategies, yet formal approval in transplant-eligible second-line settings remains inconsistent across regions.

Transplant-related inflammation

Alongside immune-related adverse events (irAE), anti-PD-1 exposure prior to transplant can increase the risk of engraftment syndrome, requiring careful timing and monitoring.

Non Transplant Approach

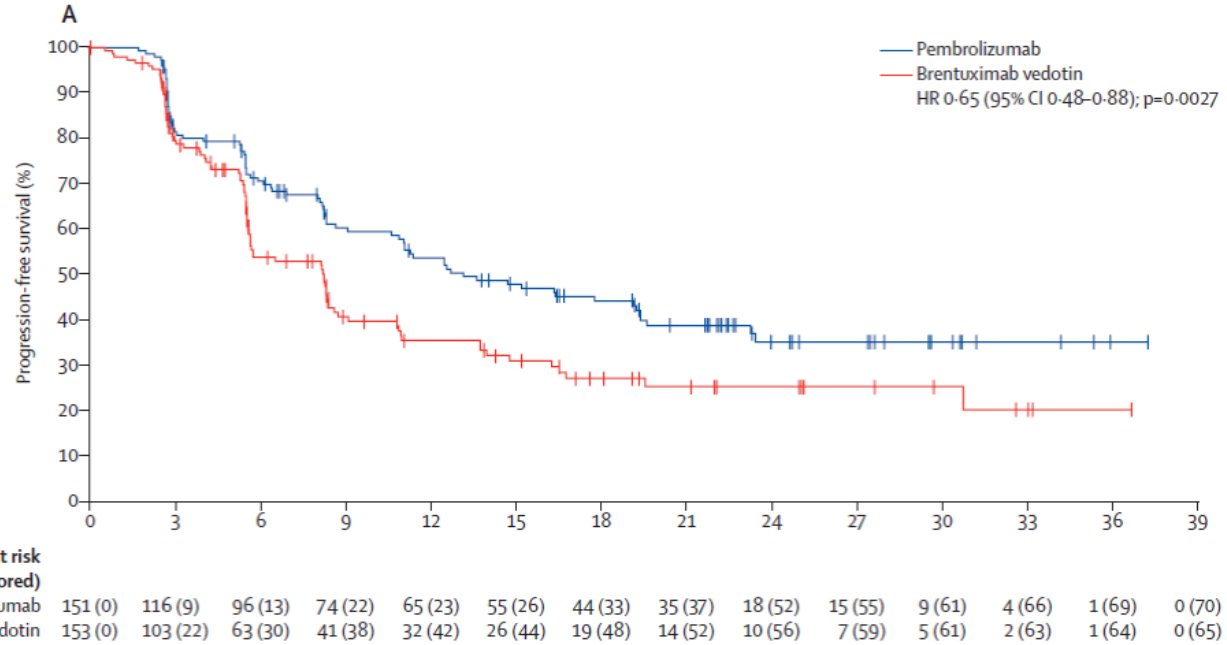
Selected Patients w/ comorbidities



Novel Treatment Strategies in r/r HL
BV/CPI exposed r/r HL

Starting point: Brentuximab Vedotin vs PD-1 blockade in r/r HL

Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study



	Pembrolizumab group (n=151)	Brentuximab group (n=153)
Proportion of patients with objective response	99 (65·6% [57·4–73·1])	83 (54·2% [46·0–62·3])
Best overall response		
Complete response	37 (25%)	37 (24%)
Partial response	62 (41%)	46 (30%)
Stable disease	21 (14%)	36 (24%)
Progressive disease	26 (17%)	28 (18%)
Not evaluable	1 (1%)	1 (1%)
No assessment	4 (3%)	5 (3%)

Kuruvilla et al, Lancet Oncol 2021

Alternative CPIs
Anti LAG3 mABs

Estimating Efficacy of Favezelimab Plus Pembrolizumab Relative to Pembrolizumab in Anti–PD-1–Refractory Hodgkin Lymphoma

Context of Research

Participants eligible from MK-4280-003 cohort 2 (NCT03598608)
- Received ≥2 doses of anti–PD-1 therapy
- Disease progression within 12 weeks of last dose of anti–PD-1
- Rx: pembrolizumab 200 mg + favezelimab 200 mg or 800 mg IV Q3W

Participants eligible from KEYNOTE-087 (NCT02453594)
- Received >2 doses of pembrolizumab beyond progression
- Disease progression within 12 weeks of last dose of pembrolizumab
- Rx: continued pembrolizumab 200 mg IV Q3W

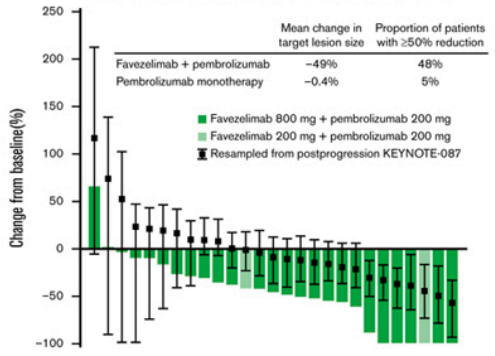
Relative contribution of favezelimab assessed
- Change in target lesion size
- Objective response rate (ORR)
- Bootstrapping method compared change in target lesion size

Main Outcomes

Best overall response per IWG 2007 criteria

	Favezelimab + pembrolizumab (MK-4280-003 cohort 2) n = 27	Pembrolizumab monotherapy (KEYNOTE-087) n = 81
ORR, % (95% CI)	37% (15%–51%)	2% (0%–6%)
Best response, n (%)		
Complete response	3 (11%)	0
Partial response	7 (26%)	2 (2%)
Stable disease	11 (41%)	23 (28%)
Progressive disease	6 (22%)	56 (69%)

Bootstrapping analysis of best percentage change from baseline in target lesion size



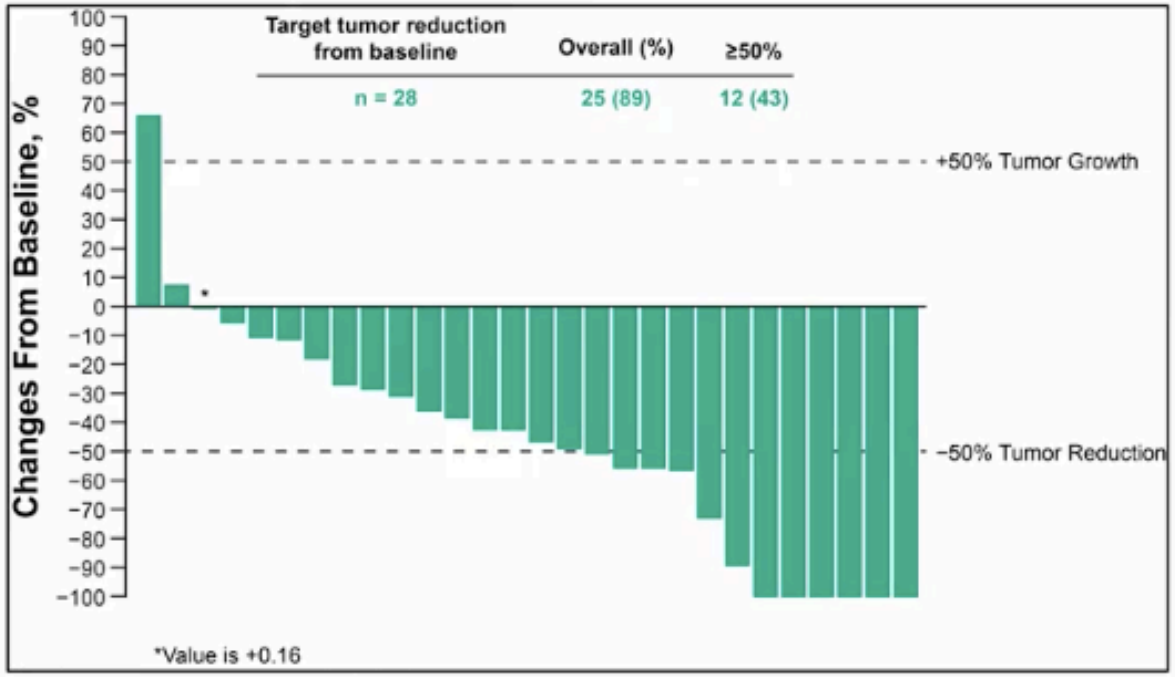
Conclusion: Favezelimab plus pembrolizumab had a higher response rate and greater reduction in tumor burden versus pembrolizumab alone in anti–PD-1–refractory classical Hodgkin lymphoma, suggesting favezelimab contributed substantially to efficacy in the MK-4280-003 study.

*Armand et al. DOI: 10.1182/**bloodadvances**.2024014654*

blood advances Visual Abstract

Updated Analysis of a Phase 1/2 Study Evaluating Pembrolizumab Plus the Anti–Lymphocyte-Activation Gene 3 (LAG-3) Antibody Favezelimab for Heavily Pretreated Anti–PD-1–Refractory cHL

LAG-3 is involved in T-cell regulation and is commonly co-expressed with PD-1 on anergic T cells
LAG-3 inhibitor, favezelimab (MK-4280),+ pembrolizumab (pembro) in pts relapsed after or ineligible for ASCT *and* PD after 2 doses of anti–PD-1 therapy within 12 weeks



Timmerman et al, Abstract #P138

34 patients

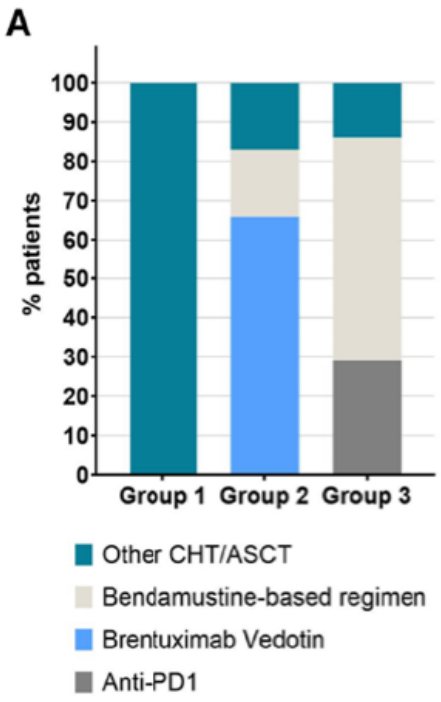
- **10 pts had objective response (ORR, 29%; CR 3 [9%]; PR 7 [21%])**
- **Median PFS 9.7 months. DOR 21.9 mo**

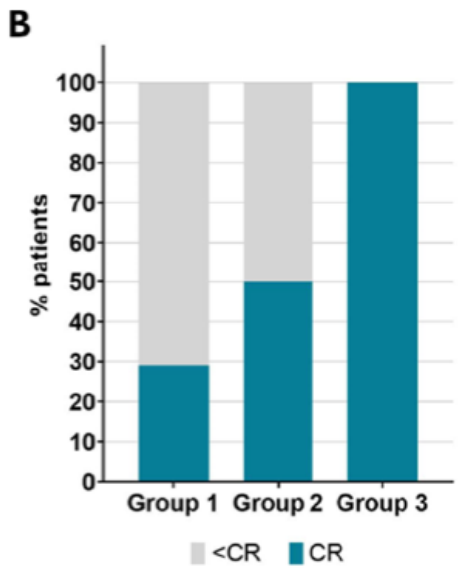
Trial in Progress: Lavie et al, Abstract #P112
The Phase 3 KEYFORM-008 Study Coformulated Favezelimab and Pembrolizumab Versus Chemotherapy in Patients With R/R cHL Refractory to Anti–PD-1 Therapy

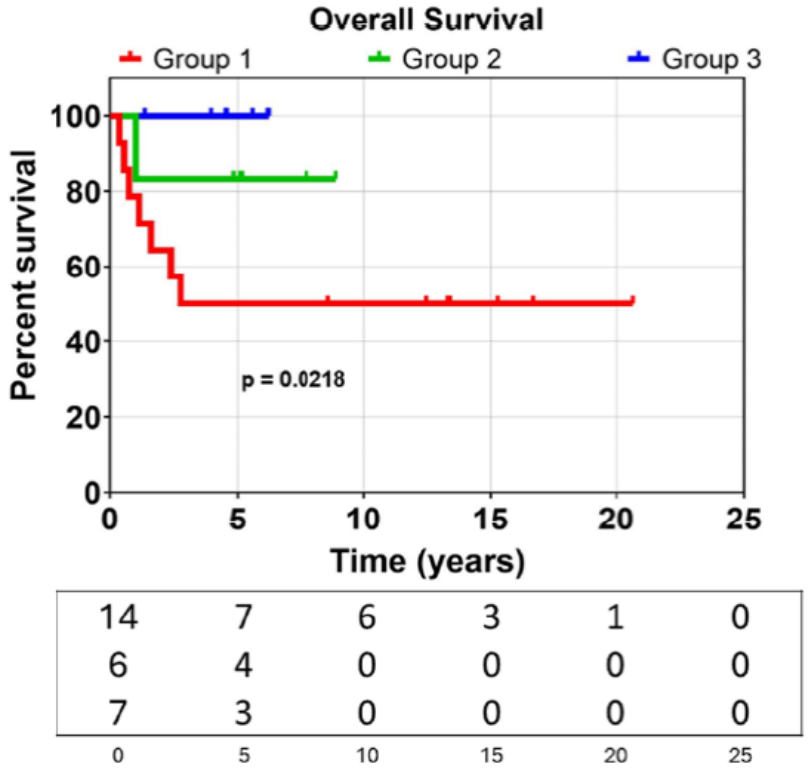
Cell Therapy
Allogeneic Transplant

Check for updates

Haploidentical allogeneic hematopoietic stem cell transplantation in relapsed/refractory Hodgkin lymphoma in the era of novel agents: a single-center experience







Maraglino et al, Leuk Lymph 2025

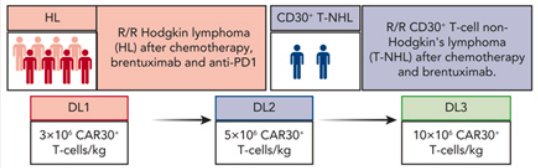
Academic CAR T Cells Against CD30 (HSP-CAR30) for the Treatment of Refractory or Relapsed CD30-Positive Lymphoma

Context of Research

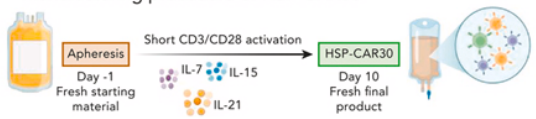
- Current CD30-directed CART therapy (CART30) has limited efficacy in patients with refractory or relapsed (R/R) CD30$^+$ lymphoma.
- Less-differentiated memory T cells have long-term persistence and enhanced antitumor efficacy.
- We have developed an autologous CART30 product (HSP-CAR30) with a significant increase in the proportion of less-differentiated CAR30$^+$ memory T cells.

Patients and Methods

- Phase 1 dose escalation clinical trial: 10 patients

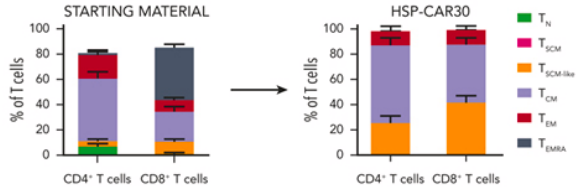


- Manufacturing procedure of HSP-CAR30

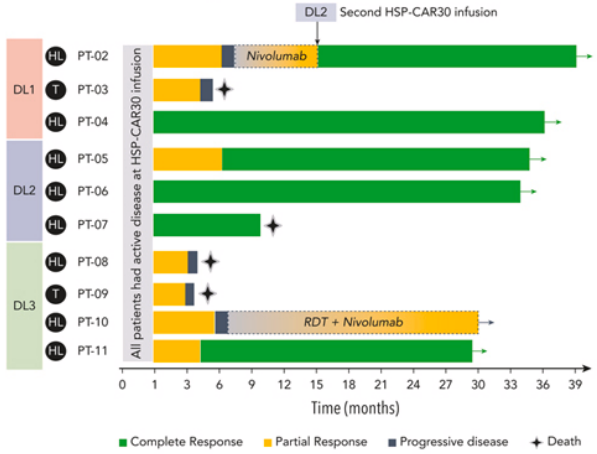


Findings

- HSP-CAR30: CART30 cell product with a high proportion of memory T cells



- HSP-CAR30 efficacy of treated patients

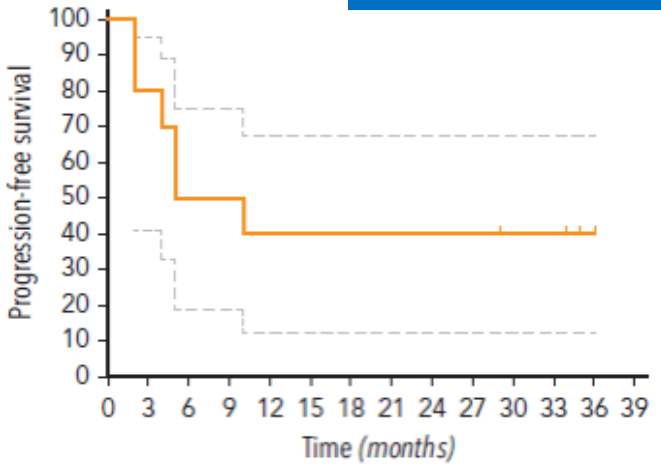


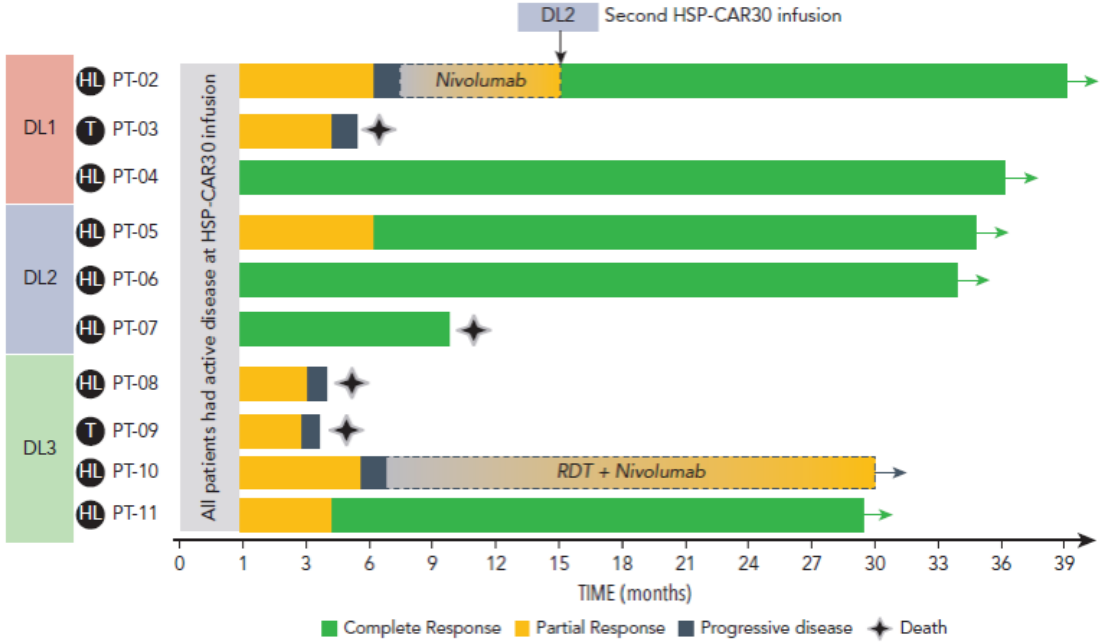
Conclusions: HSP-CAR30, an infused fresh CART30 with a high proportion of less-differentiated memory T cells, favors expansion and long-term persistence of memory CAR30$^+$ T cells. In a study of 10 patients with refractory CD30$^+$ lymphoma, 50% experienced durable complete responses to this treatment.

*Caballero et al. DOI: 10.1182/**blood**.2024026758*

blood Visual Abstract

Cell Therapy
CAR-T



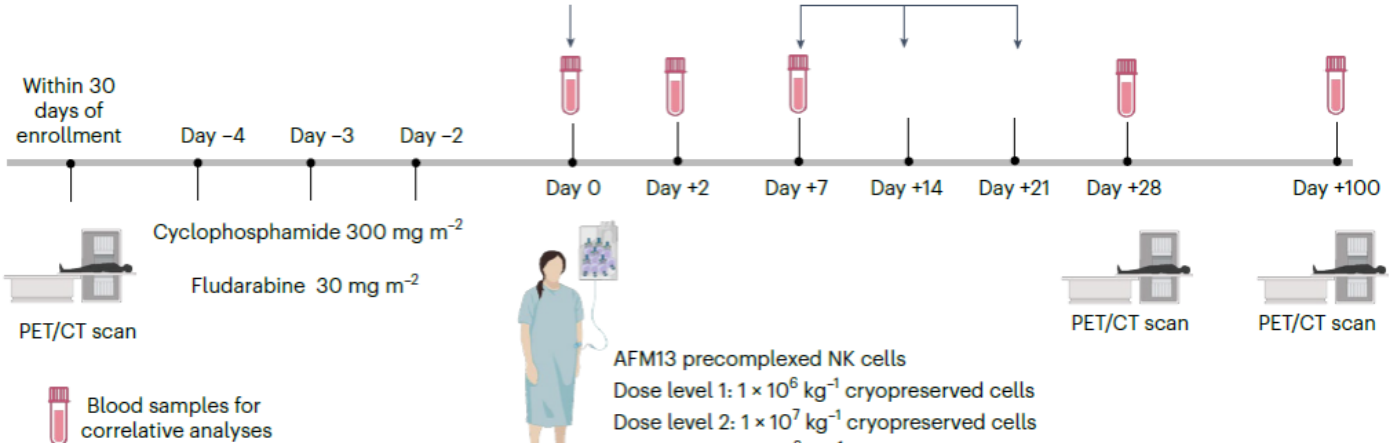


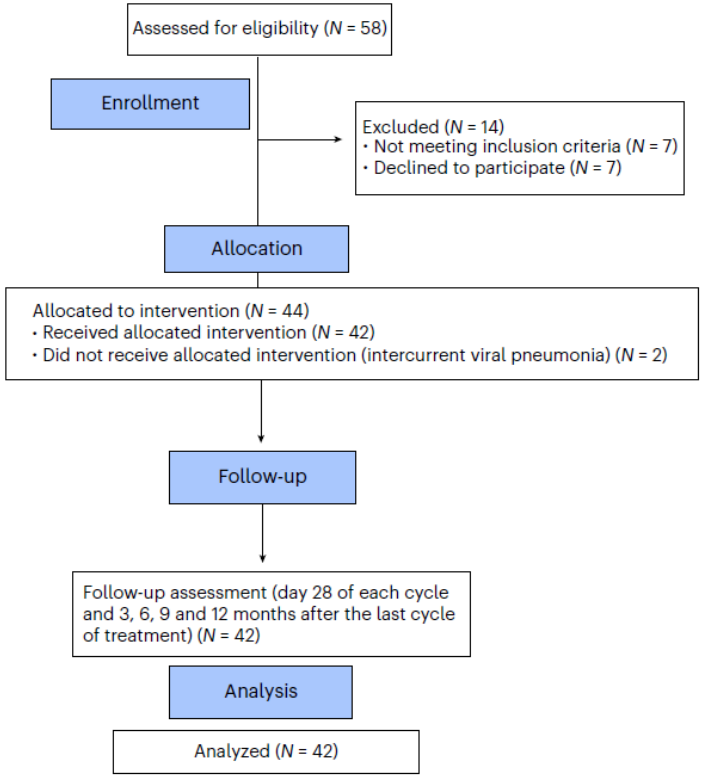
Caballero et al, Blood 2025

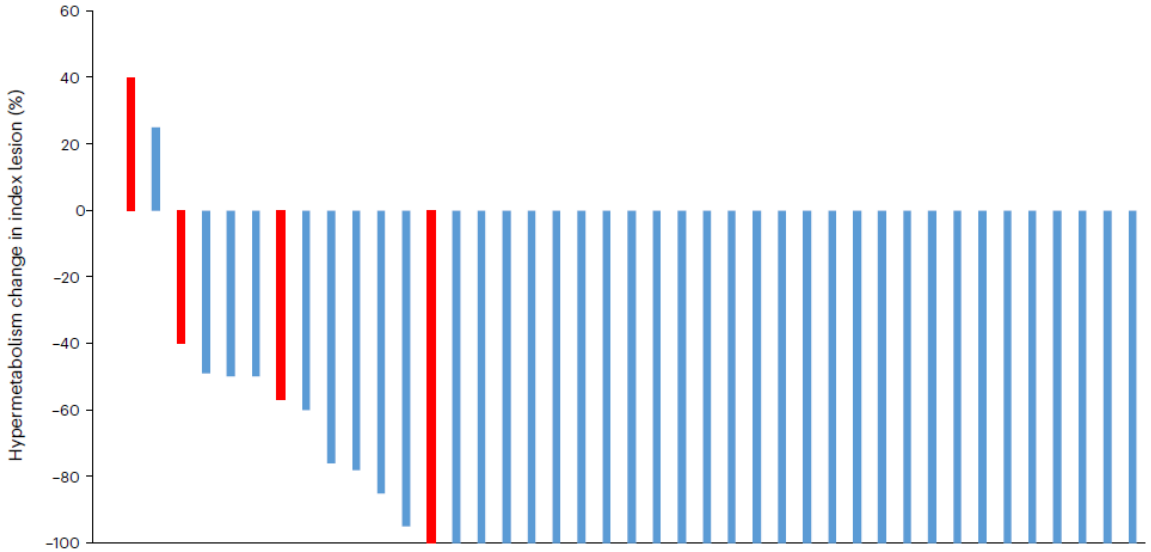
Article https://doi.org/10.1038/s41591-025-03640-8

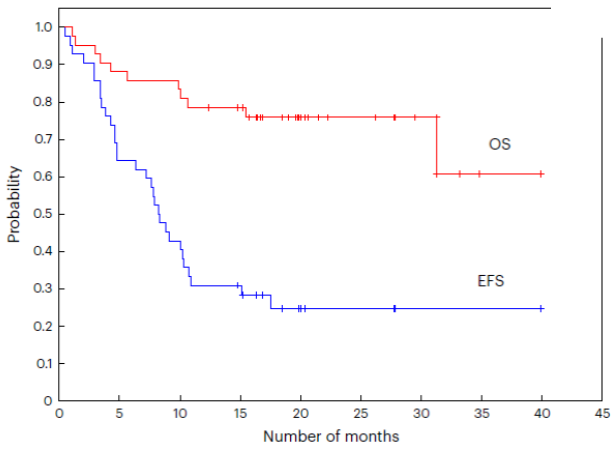
Allogeneic NK cells with a bispecific innate cell engager in refractory relapsed lymphoma: a phase 1 trial

Cell Therapy
Ex-vivo expanded alloNK cells









Nieto et al, Nat Med 2025

Small Molecules
PRMT5 inhibitors

2026 ASCO ANNUAL MEETING

A phase 1 study of the PRMT5 inhibitor AZD3470 in patients with relapsed/refractory classic Hodgkin lymphoma (PRIMAVERA)

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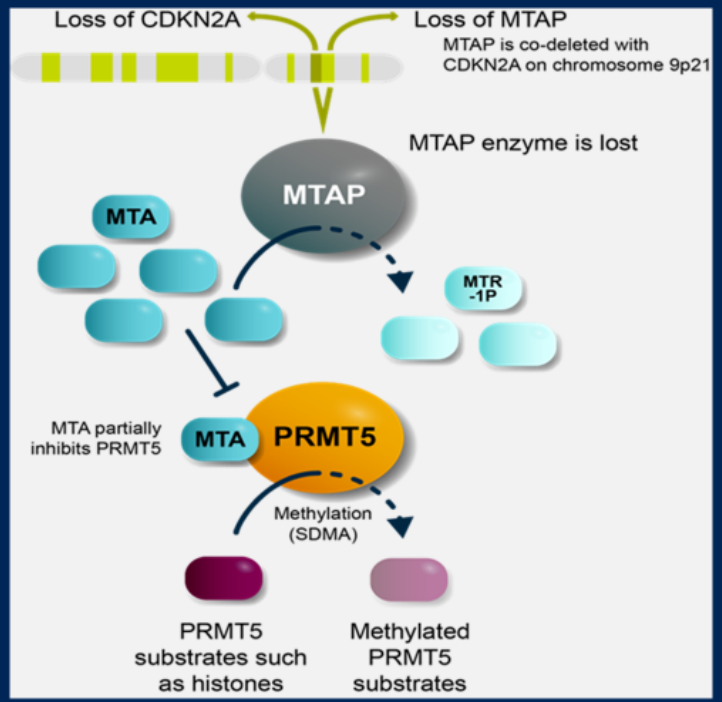
Speaker: Enrico Derenzini

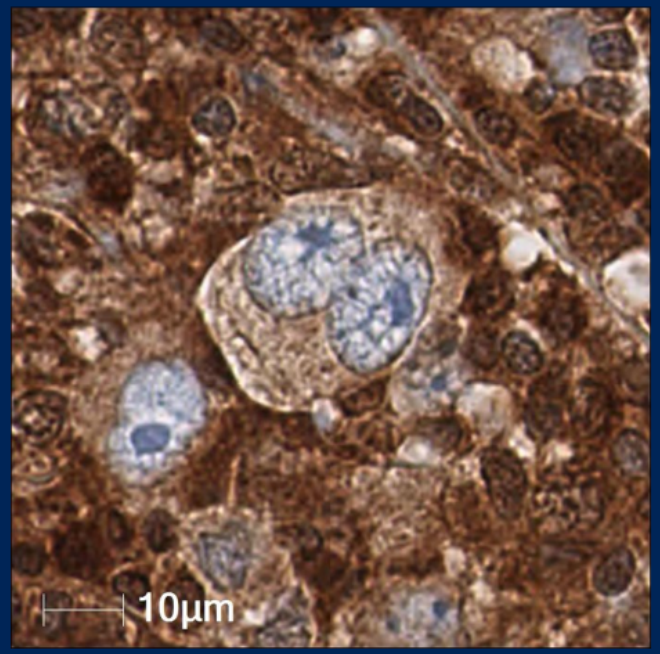
PRMT5 is a critical regulator of cancer biology[1,2]



- PRMT5 (protein arginine methyltransferase 5) symmetrically methylates arginine residues on histone and non-histone proteins to regulate cell growth and survival
- MTAP is a metabolic enzyme encoded by the *MTAP* gene on chromosome 9p21.3, near the tumor suppressor gene *CDKN2A*. It catalyzes MTA into MTR-1P, which plays a key role in the methionine salvage pathway
- Loss or deletion of the *MTAP* gene leads to accumulation of MTA , which acts as a competitive inhibitor of PRMT5, lowering its baseline activity and making it more sensitive to pharmacologic inhibition

1. Kim H, Ze'ev AR. Cell Stress 2020;4:199–215; 2. Hwang JW, et al. Exp Mol Med 2021;53:788–808
MTA, methylthioadenosine; MTAP, MTA phosphorylase; PRMT5, protein arginine methyltransferase 5; SDMA, symmetric dimethylarginine

PRMT5-MTAP synthetic lethality represents a novel opportunity to target *CDKN2A/MTAP*-deleted tumours[1]

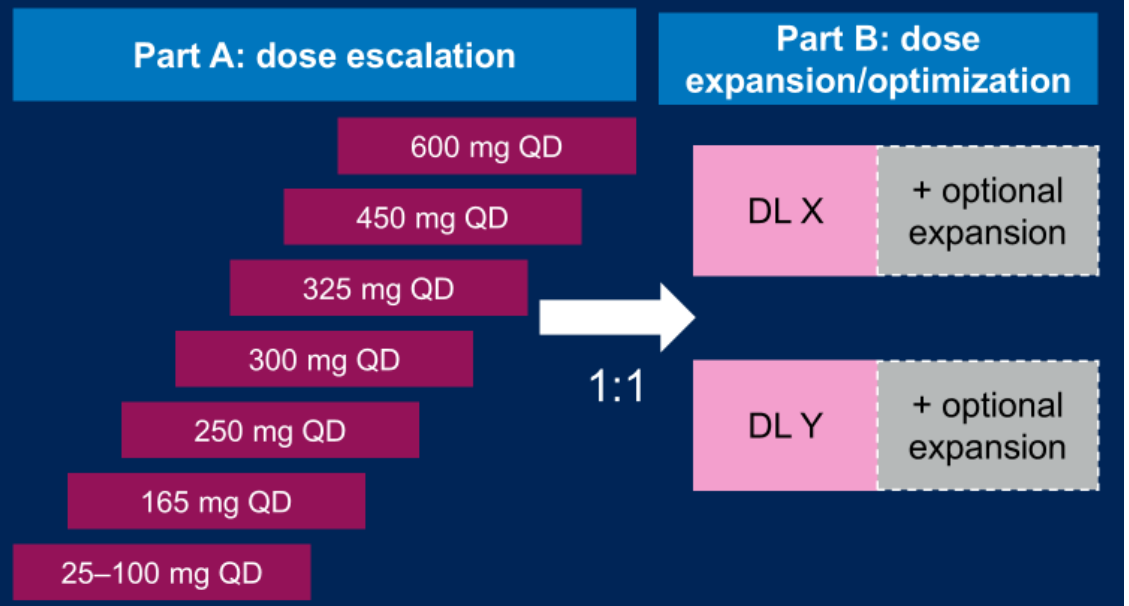


- *MTAP* deletion is observed in approximately 15% of all cancers
- In Hodgkin lymphoma, MTAP protein is lost in ~80% of patients via MTAP promoter hypermethylation, resulting in epigenetic silencing[2]
- AZD3470 is an MTA-cooperative second-generation PRMT5 inhibitor, with increased MTAP selectivity

1. Hwang JW, et al. Exp Mol Med 2021;53:788–808; 2. Urosevic J, et al. Blood 2023;142 (Supplement 1):4185
MTA, methylthioadenosine; MTAP, MTA phosphorylase; PRMT5, protein arginine methyltransferase 5; SDMA, symmetric dimethylarginine

PRIMAVERA (NCT06137144) study design

- Modular phase I/II dose escalation and expansion study evaluating oral AZD3470 monotherapy in patients with R/R cHL
  - Adults ≥18 years (≥15 years in Part B)
  - Histologically confirmed diagnosis of R/R cHL
  - ECOG performance status ≤1
  - **≥3 prior lines of therapy** for cHL including brentuximab vedotin and anti-PD1 therapy
- AZD3470 administered once daily



Endpoints

Primary: safety/tolerability, DLTs, RP2D

Secondary: ORR, CRR, PFS, OS

cHL, classic Hodgkin lymphoma; CRR, complete response rate; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PD1, programmed cell death protein 1; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase 2 dose; R/R, relapsed/refractory

PRIMAVERA TRIAL: SAFETY AND EFFICACY

	N=68	
	All	Possibly related
Any TEAE, n (%)	62 (91)	47 (69)
Grade ≥3 TEAE, n (%)	27 (40)	14 (21)
TEAE with outcome of death, n (%)	0	0
TEAE leading to AZD3470 dose reduction, n (%)	2 (3)	2 (3)
TEAE leading to AZD3470 discontinuation, n (%)	0	0
Serious AE, n (%)	13 (19)	3 (4)
Dose-limiting toxicity, n (%)	0	0

The most common AZD3470-related TEAEs (any grade) were anemia (27%), fatigue (21%), decreased appetite (15%) and dysgeusia (15%)

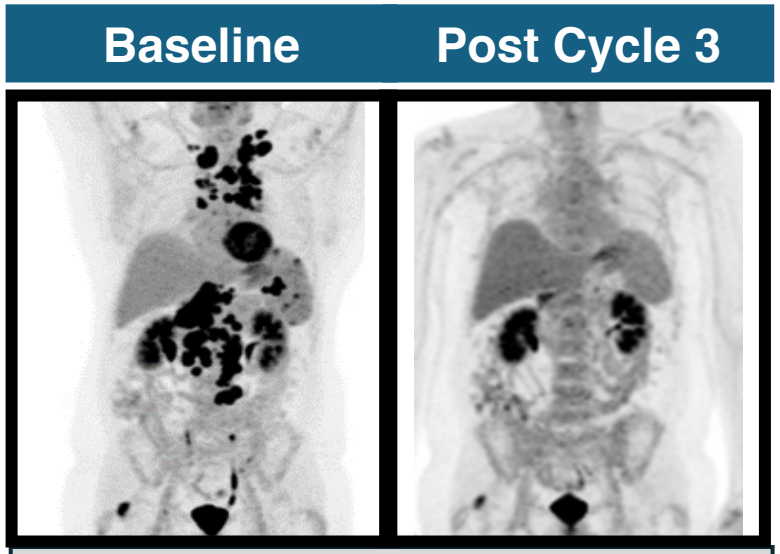
The most common AZD3470-related grade ≥3 TEAE was anemia (7%)

	25–100 mg QD (n=12)	165 mg QD (n=3)	250 mg QD (n=3)	300/325 mg QD (n=10)	450 mg QD (n=15)	600 mg QD (n=16)
ORR, n (%)	0	2 (67)	2 (67)	4 (40)	8 (53)	10 (63)
CR	0	0	0	0	4 (27)	7 (44)
PR	0	2 (67)	2 (67)	4 (40)	4 (27)	3 (19)
SD, n (%)	5 (42)	0	1 (33)	1 (10)	2 (13)	1 (6)
PD, n (%)	7 (58)	1 (33)	0	3 (30)	2 (13)	3 (19)
NE, n (%)†	0	0	0	2 (20)	3 (20)	2 (13)

ORR 58%

CR 35%

1. **AZD3470 shows clinical activity in patients with classic Hodgkin lymphoma previously treated with brentuximab vedotin and anti-PD1 therapy**
2. **Both the ORR and CR rate were highest at doses ≥450 mg: ORR 58%, CR rate 35%. Data for DoR/PFS are pending**
3. **No DLTs, discontinuations due to AZD3470-related TEAEs, or deaths; the most common AZD3470-related TEAE was anemia**
4. **Dose optimization is ongoing in this first dedicated study of a PRMT5 inhibitor in cHL**



- 66-year-old male
- Stage III
- 3 prior lines of anticancer therapy

Best overall response to AZD3470: complete response

75% reduction in target lesion

CONCLUSIONS

Gap between scientific evidence and regulatory rules in r/r HL

BV and CPIs improved outcome of r/r HL in the last decade

Exposure to CPIs has a profound impact
on the natural history of the disease

Novel CPIs and 2° gen PRMT5i showed prelimary efficacy
in double exposed r/r HL