GIORNATE EMATOLOGICHE VICENTINE

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L’uso dei nuovi agenti anticorpali nel trattamento del linfoma di Hodgkin

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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BeOne					X	x	
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bering					x	x	
Incyte					X		
Kite Gilead					X		
Astrazeneca						x	
Janssen					X		
Roche					X		x
SOBI					X		
Takeda			X		x	X	

Brentuximab Vedotin
R/R cHL
Post autoSCT
Second line
First line

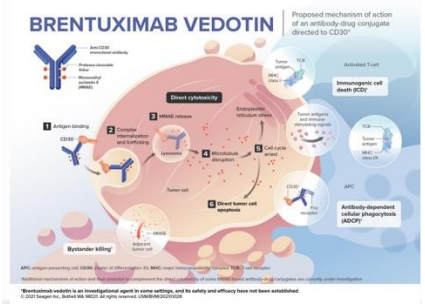
Anti-PD1
R/R cHL
Post autoSCT
Second line
First line

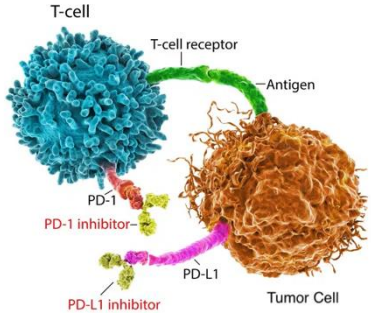
New options
Camidanlumab teserine
Anti-PD1 + epigenetic modifiers
Anti-PD1 + AntiLAG3
AntiPD1 + bispecific Ab
AntiCD30+ CART

Diagnosis **First-line** **Second-line** **Consolidation** **Salvage therapy**

Brentuximab Vedotin

Anti-PD1

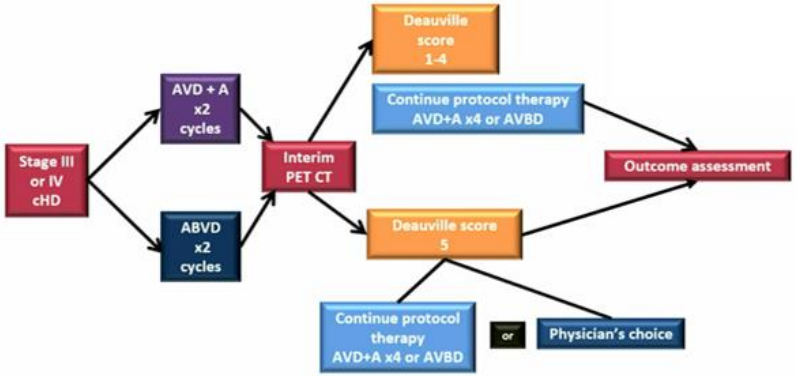


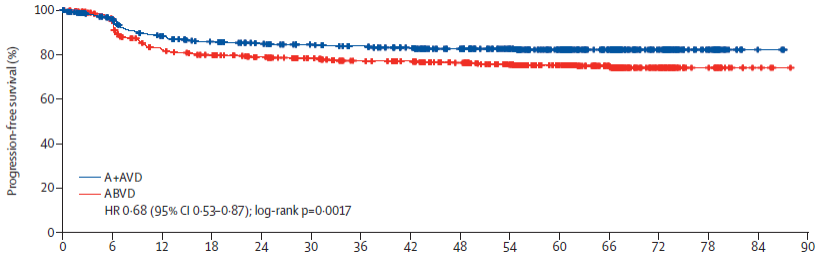


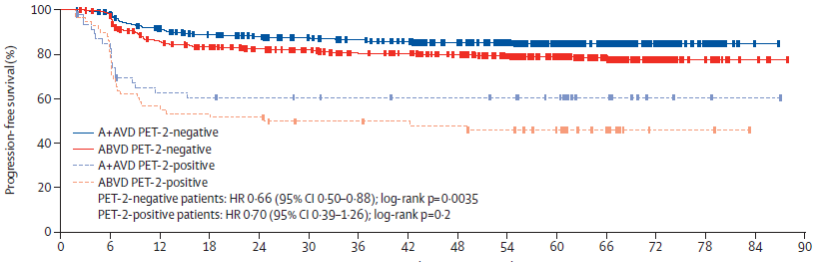
Diagnosis **First-line** **Second-line** **Consolidation** **Salvage therapy**

Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial

David J Straus, Monika Długosz-Danecka, Joseph M Connors, Sergey Alekseev, Árpád Illés, Marco Picardi, Ewa Lech-Maranda, Tatyana Feldman, Piotr Smolewski, Kerry J Savage, Nancy L Bartlett, Jan Walewski, Radhakrishnan Ramchandren, Pier Luigi Zinzani, Martin Hutchings, Javier Munoz, Hun Ju Lee, Won Seog Kim, Ranjana Advani, Stephen M Ansell, Anas Younes, Andrea Gallamini, Rachael Liu, Meredith Little, Keenan Fenton, Michelle Fanale, John Radford

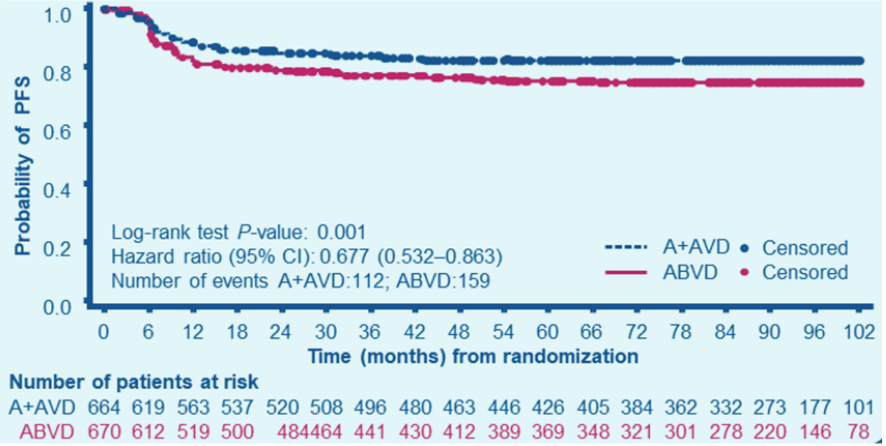




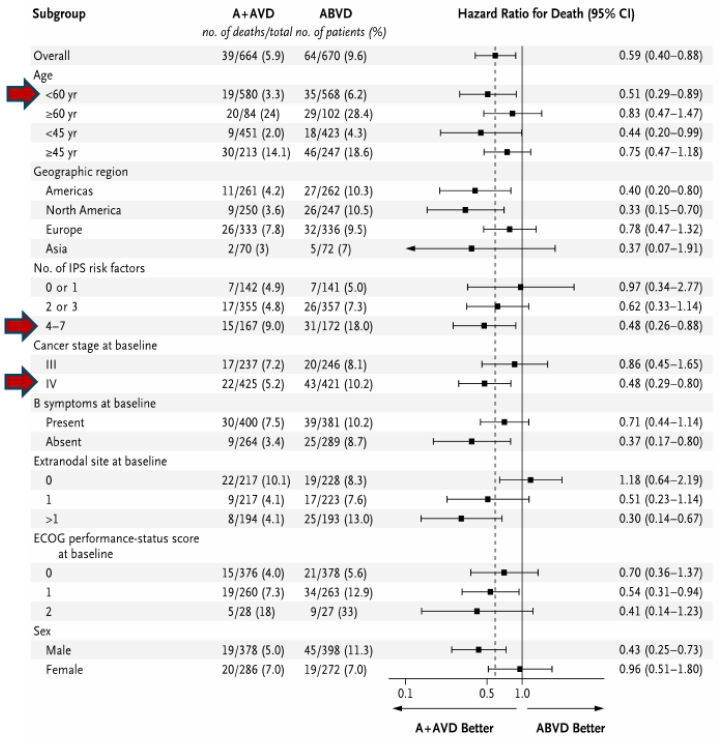


ADVANCED ECHELON-1

7-years probability of PFS



OS rate: BV+AVD 93.5% vs ABVD 88.8%;
HR 0.617 (95% CI: 0.423–0.899); *P*=0.011



Ansell S, ASCO 2024, poster presentation

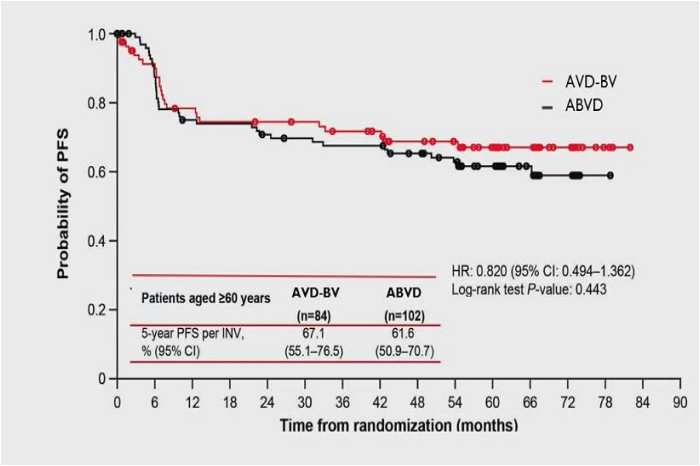
Ansell S, NEJM 2022

AVD plus concurrent BV

186 (14%) pts ≥ 60y, median 67; ECOG 2 11% (vs 3%)
80% BV dose mod, 71% bleo dose mod (28% discon)
TRM 3.6% (vs 5.1% ABVD) / 37% FN (vs 17%)
18% Grade 3-4 PN (vs 3% in <60y)
2% lung toxicity (vs 13%)

Bleomycin-free regimen as good as ABVD

Evens AM et al, Haematologica 2022

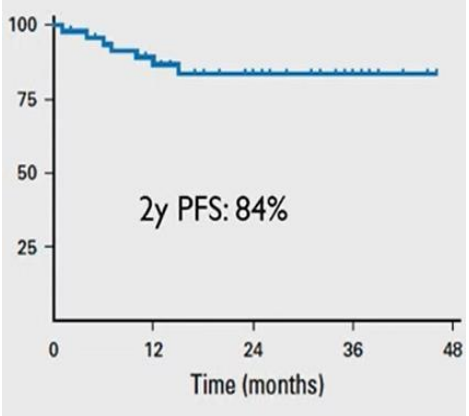


AVD plus sequential BV

48 pts, median age 69 (60-88)
77% completed 6 cycles AVD
33% Grade 2 PN (4% G3)
8% febrile neutropenia

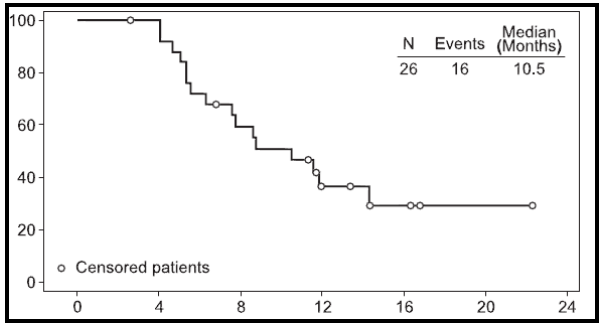
Tolerable, apparently high efficacy

Evens AM et al, J Clin Oncol 2018

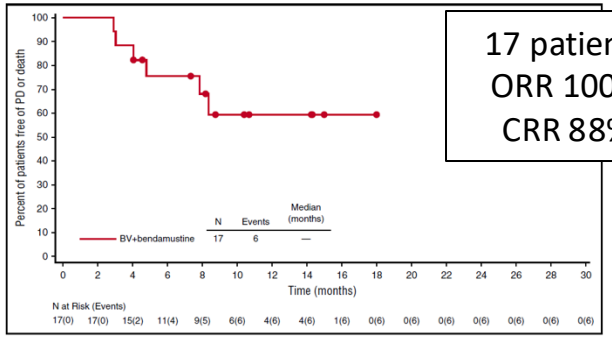


BV mono & BV-plus therapies

BV monotherapy

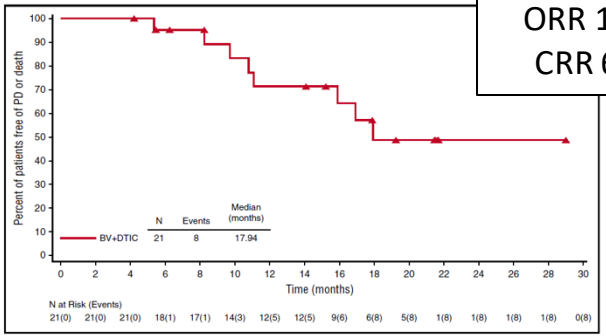


BV + BENDA

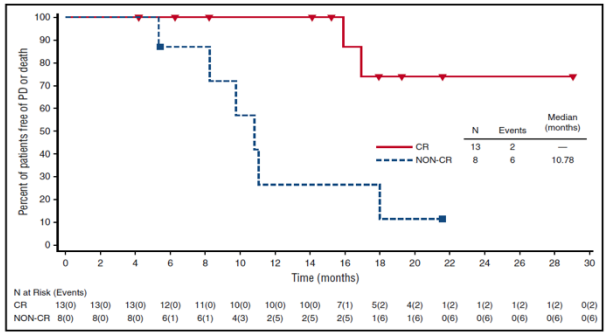


17 patients
ORR 100%
CRR 88%

BV + DACARBAZINE



19 patients
ORR 100%
CRR 68%



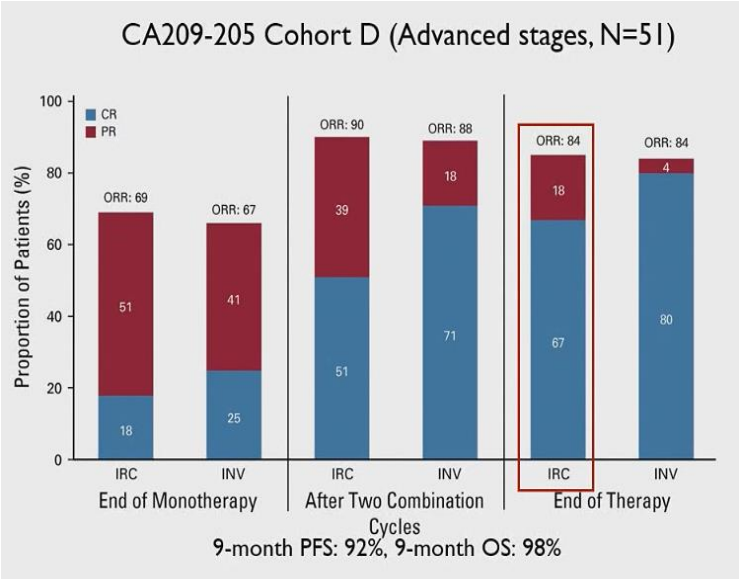
BV monotherapy not effective
BV plus benda toxic
BV plus dacarbazine good option!

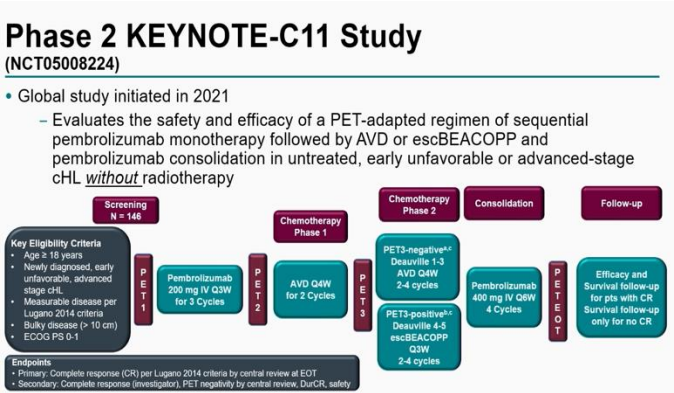
Around 30%
Grade 3 PN

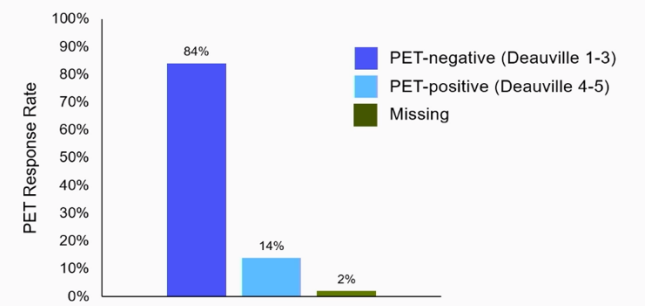
Forero-Torres A et al, 2015
Friedberg JW et al, 2017

Improving first line treatment efficacy

4 x NIVO → 6 x NIVO+AVD

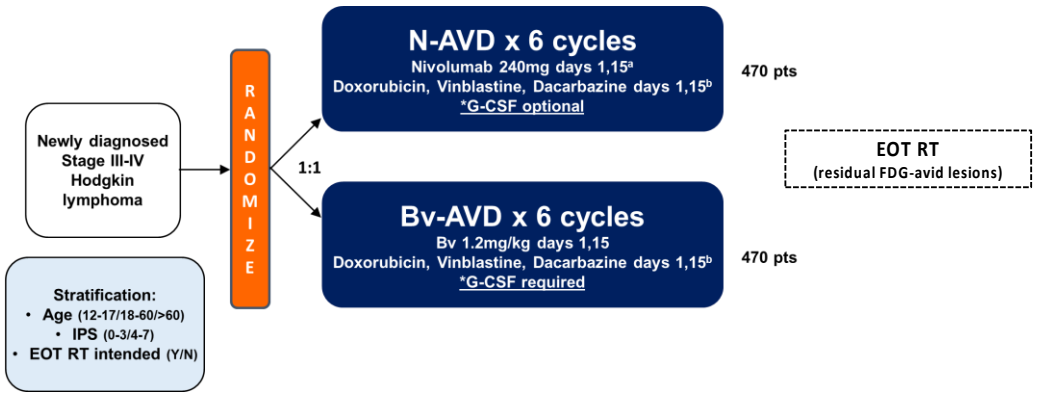






Advani RH et al, ASH 2022
Ramchandren R et al, 2019

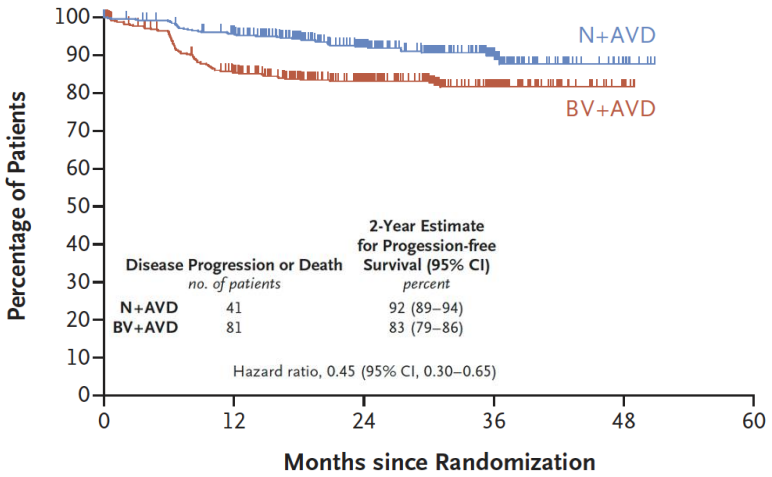
ADVANCED SWOG S1826



Characteristic	N+AVD (N=487)	BV+AVD (N=483)
Age		
Median (range) — yr	27.6 (12.0–83.7)	26.8 (12.0–81.7)
Distribution — no. (%)		
12–17 yr	118 (24)	118 (24)
18–60 yr	321 (66)	318 (66)
>60 yr	48 (10)	47 (10)
Female sex — no. (%)	216 (44)	210 (43)
Race or ethnic group — no. (%)†		
White	372 (76)	361 (75)
Black	58 (12)	56 (12)
Asian	11 (2)	17 (4)
Other or unknown	46 (9)	49 (10)
Hispanic	66 (14)	58 (12)
Disease stage — no. (%)		
III	185 (38)	168 (35)
IV	302 (62)	315 (65)
B symptoms present — no. (%)‡	288 (59)	273 (57)
IPS — no. (%)§		
0–3	332 (68)	328 (68)
4–7	155 (32)	155 (32)
Bulky disease — no. (%)¶	156 (32)	127 (26)
HIV-positive status — no. (%)	11 (2)	5 (1)

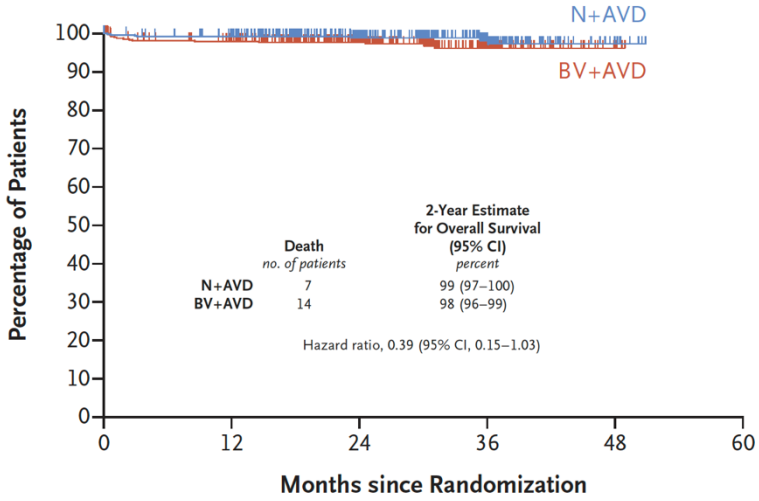
Herrera A, NEJM 2024

Progression-free survival



No. at Risk						
N+AVD	487	450	281	101	9	0
BV+AVD	483	392	244	97	7	0

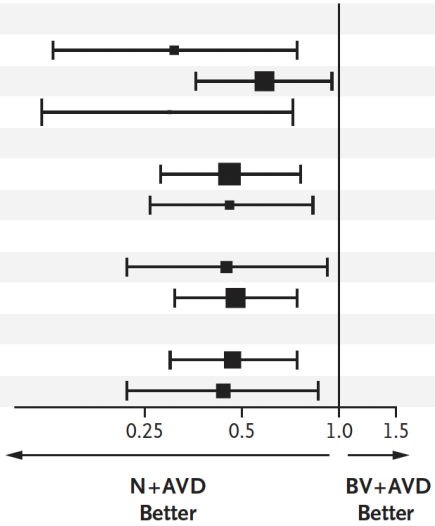
Overall survival



No. at Risk						
N+AVD	487	467	300	110	9	0
BV+AVD	483	447	274	107	7	0

Herrera A, NEJM 2024

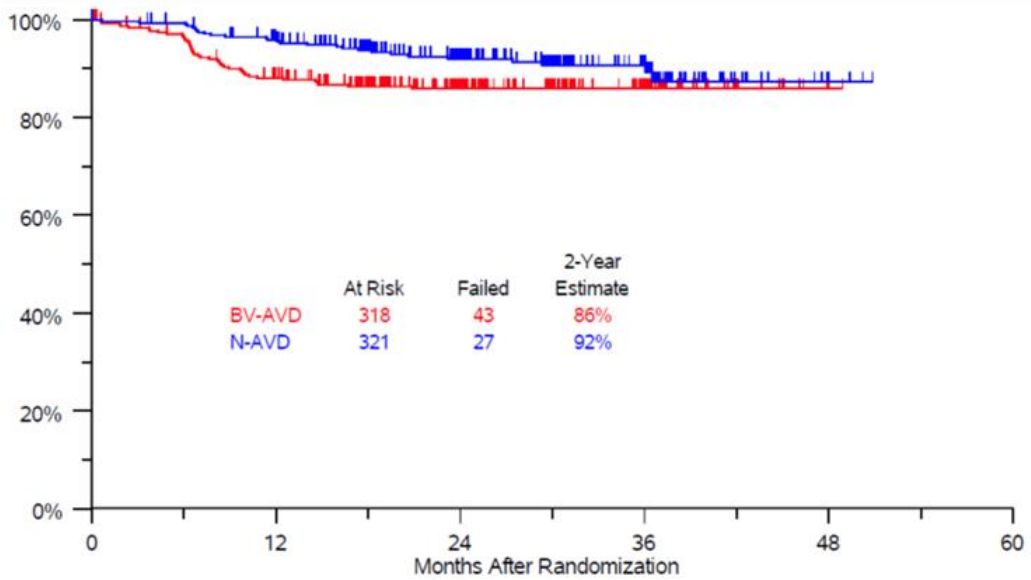
Subgroup	N+AVD	BV+AVD	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. (%)		
Age			
12–17 yr	7/118 (5.9)	21/118 (17.8)	0.31 (0.13–0.74)
18–60 yr	27/321 (8.4)	43/318 (13.5)	0.59 (0.36–0.95)
>60 yr	7/48 (14.6)	17/47 (36.2)	0.30 (0.12–0.72)
IPS risk group			
0–3	24/332 (7.2)	48/328 (14.6)	0.46 (0.28–0.76)
4–7	17/155 (11.0)	33/155 (21.3)	0.46 (0.26–0.83)
Stage			
III	12/185 (6.5)	22/168 (13.1)	0.45 (0.22–0.92)
IV	29/302 (9.6)	59/315 (18.7)	0.48 (0.31–0.74)
Symptoms			
B	29/288 (10.1)	54/273 (19.8)	0.47 (0.30–0.74)
A	12/199 (6.0)	27/210 (12.9)	0.44 (0.22–0.86)



Herrera A, NEJM 2024

ADVANCED SWOG S1826

PFS in patients aged 18-60 yrs



Early Discontinuation: 8% vs 12%

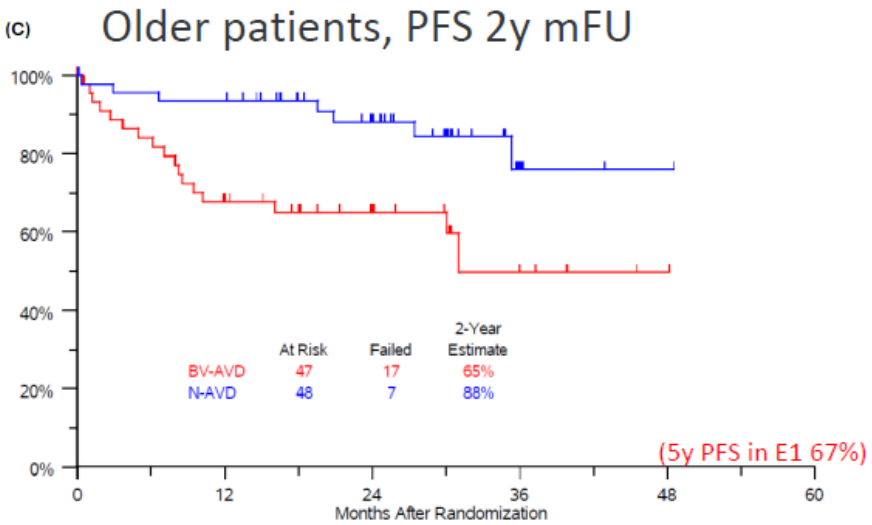
Neutropenia ≥G3
- 56% vs 34% (but: 56% vs 97% G-CSF)

Anemia & Thrombocytopenia
- 39% vs 46% and 11% vs 18%

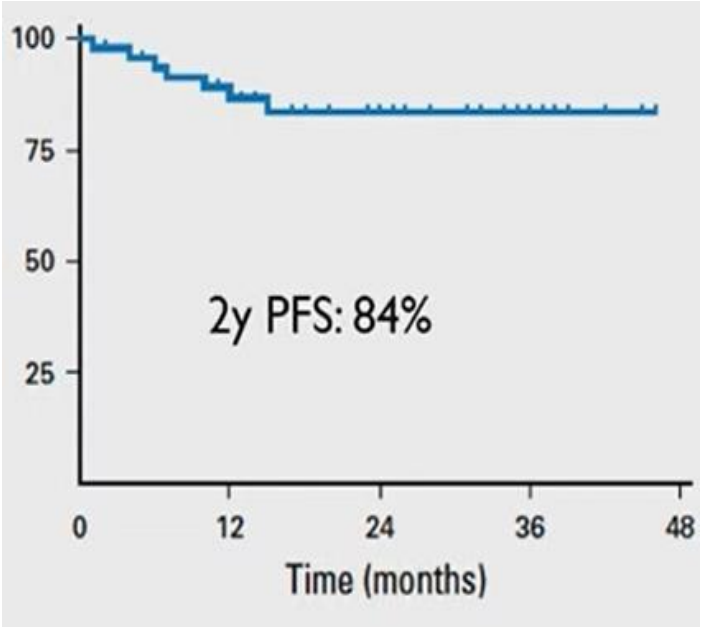
PNP (sensory), of any degree
- 29% vs 56% (G≥2: 3% vs 32%)

Immune-related AE (irAE)
- 10% Thyroiditis with N-AVD
- Otherwise, no differences and rarely reported overall, compared to phase 2 trials

Herrera A, NEJM 2024



Herrera A, NEJM 2024

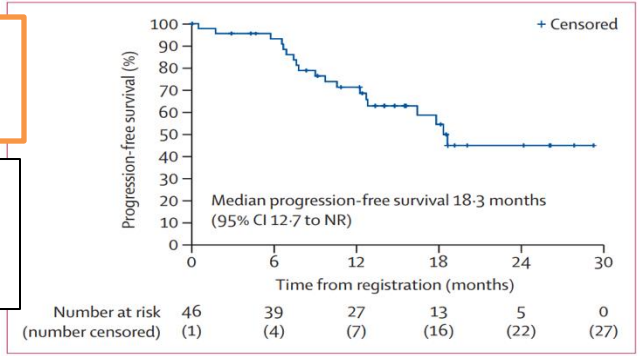


Evens AM et al, J Clin Oncol 2018

Enabling non-fit patients to receive effective therapy

BV plus Nivo
ACCRU

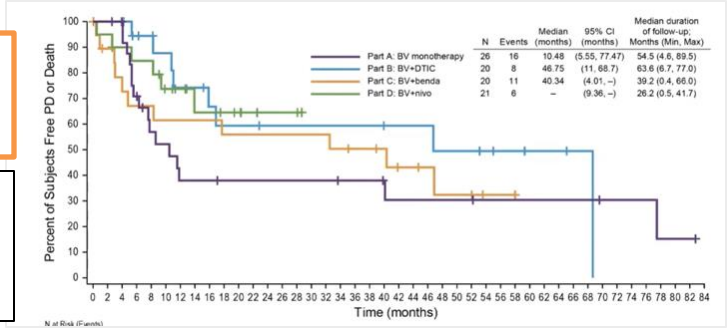
46 patients
ORR 64%
CRR 52%



Cheson BD et al, 2020

BV plus Nivo
SGN35-015

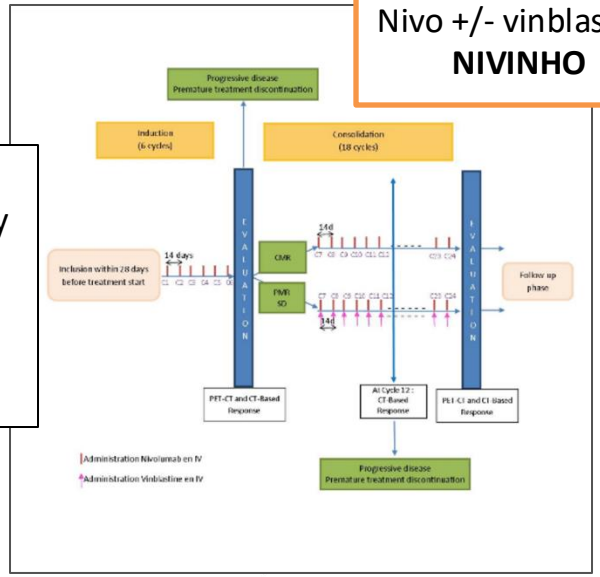
18 patients
ORR 95%
CRR 79%

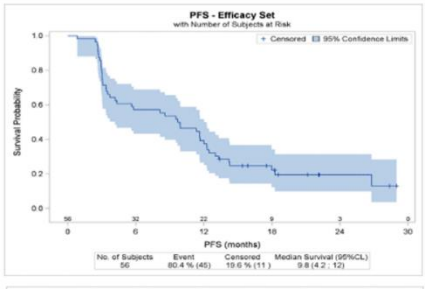


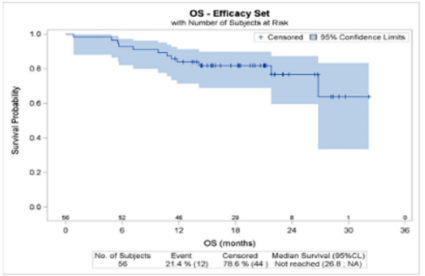
Yasenchak C, ASH 2020

Nivo +/- vinblastine
NIVINHO

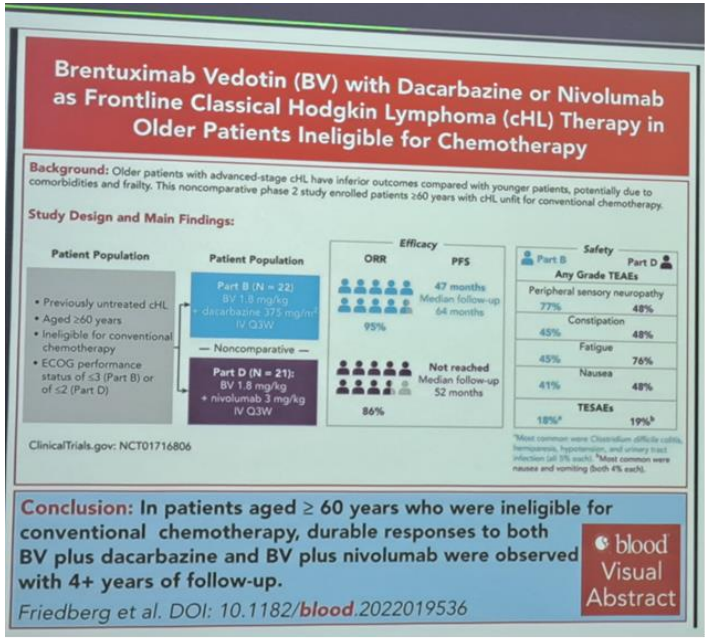
56 pts
median 75y
CIRS-G 10
ORR 47%
CR
29%(16%)

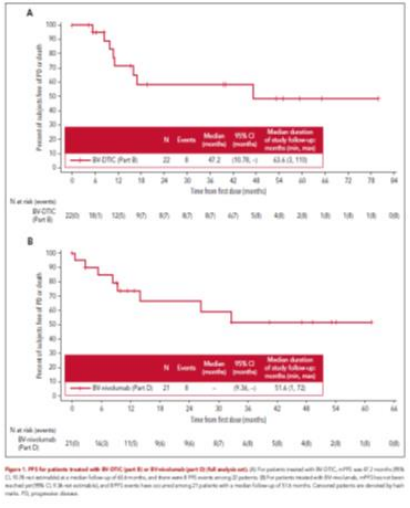


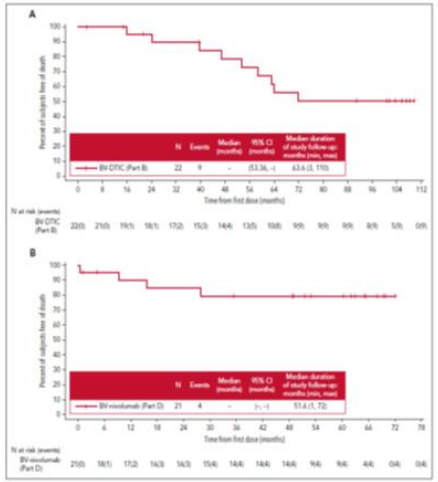




Lazarovici J et al, ASH 2021







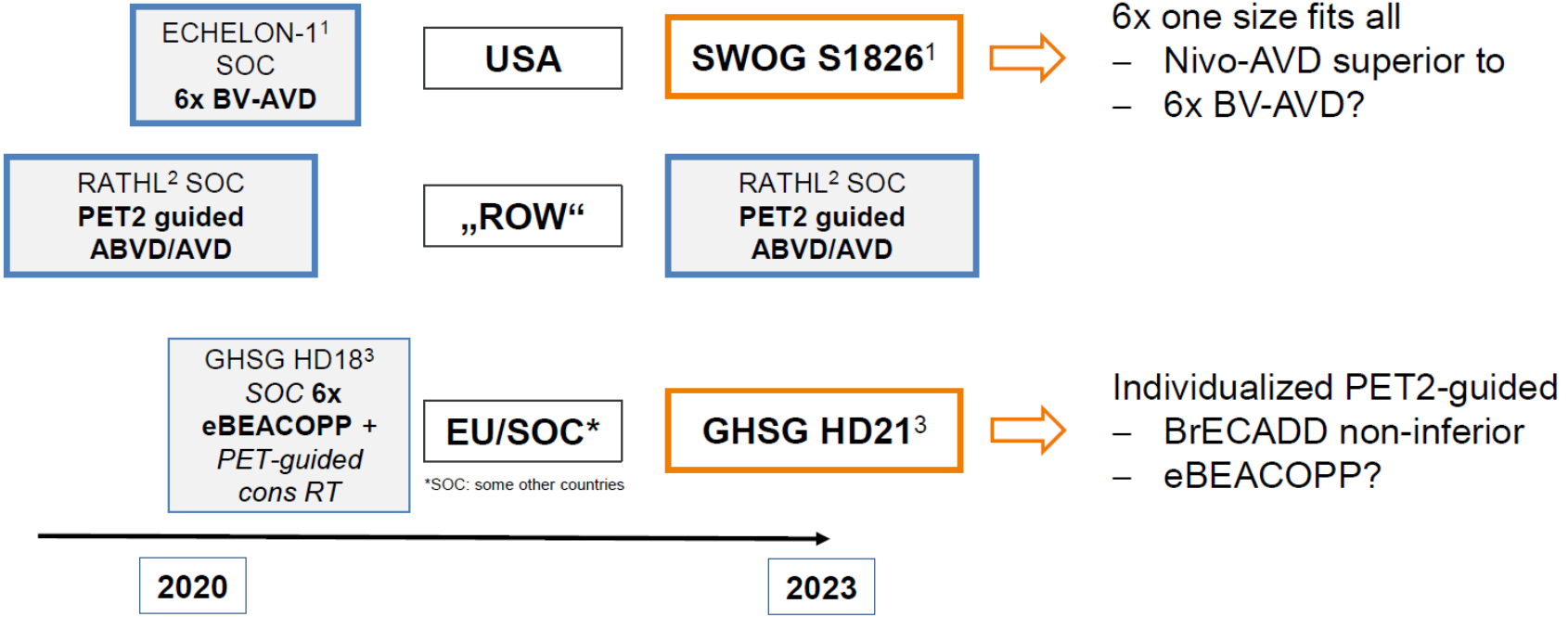
KEY POINTS

- With a median follow-up of 63.6 months, mPFS of patients aged ≥60 years with cHL treated with upfront BV-DTIC was 47.2 months.
- Noncomparatively, mPFS of patients aged ≥60 years with cHL treated with BV-nivolumab was not reached with a median follow-up of 51.6 months.

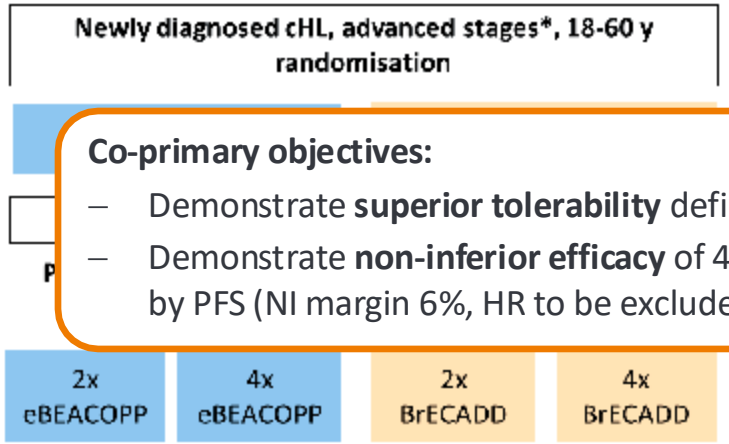
Ten patients (45%) with BV-DTIC and 16 patients (76%) with BV-nivolumab experienced grade ≥3 treatment-emergent adverse events; sensory peripheral neuropathy (PN; 27%) and neutropenia (9%) were most common with BV-DTIC, and increased lipase (24%), motor PN (19%), and sensory PN (19%) were most common with BV-nivolumab.

Despite high median age, inclusion of patients aged ≤88 years, and frailty, these results demonstrate safety and promising durable efficacy of BV-DTIC and Bvnivolumab combinations as frontline treatment, suggesting potential alternatives for older patients with cHL unfit for initial conventional chemotherapy.

What is „state of the art“ for advanced stage HL?



ADVANCED HD21



* Includes stage III with B, LMM or LD, and stage II and IV

Drug	Day	BEACOPP[1] Dose (mg/m²)	BrECADD Dose (mg/m²)
Bleomycin	8	10	-
Etoposide	1–3	200	150
Dacarbazine	2–3	-	250
Dexamethasone	1–4	-	40

Co-primary objectives:

- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

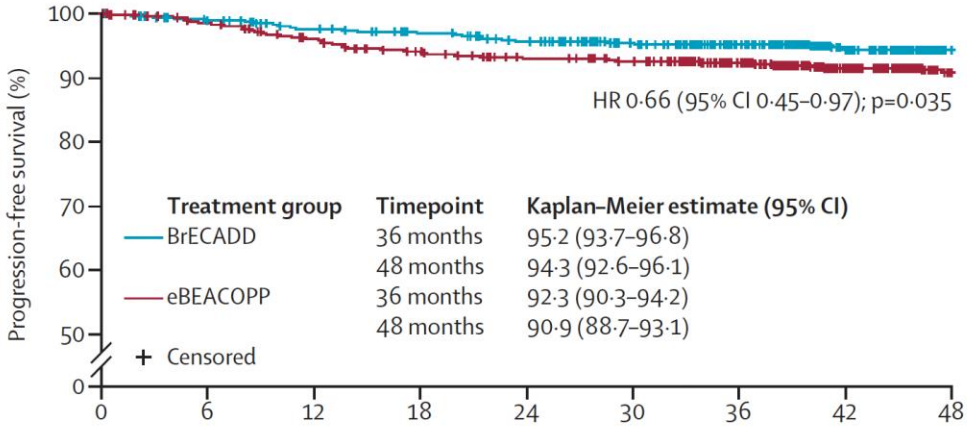
- Introducing **Brentuximab vedotin** (BV), **omitting Bleomycin** (Bl, **pulmonary toxicity**) and **Vincristin** (Vi, **neuropathy**)
- Replacing **Procarbazine** (Pr) with **less geno-/gonadotoxic Dacarbazine** (DTIC)
- Replacing 14 days of **Prednisone** (P) to 4 days of **Dexamethasone** (D)

Borchmann P, Lancet 2024

	eBEACOPP (n=740)	BrECADD (n=742)
Median age, years	31 (24–42)	31 (24–42)
Age group, years		
18–19	31 (4%)	27 (4%)
20–29	287 (39%)	292 (39%)
30–39	199 (27%)	212 (29%)
40–49	112 (15%)	92 (12%)
50–60	111 (15%)	119 (16%)
Sex		
Male	419 (56%)	419 (56%)
Female	321 (44%)	323 (44%)
Race		
White	672 (91%)	680 (92%)
Asian	13 (2%)	11 (1%)
Black	2 (<1%)	0
Other or unknown	53 (7%)	51 (7%)
Ann Arbor stage		
IIa	0	2 (<1%)
IIb	117/739 (16%)	115 (16%)
IIIa	132/739 (18%)	129 (17%)
IIIb	156/739 (21%)	164 (22%)
IVa	112/739 (15%)	104 (14%)
IVb	222/739 (30%)	228 (31%)
International Prognostic Score		
0–1	175 (24%)	195 (26%)
2–3	395 (53%)	390 (53%)
4–7	170 (23%)	157 (21%)

PFS 4-year-estimated

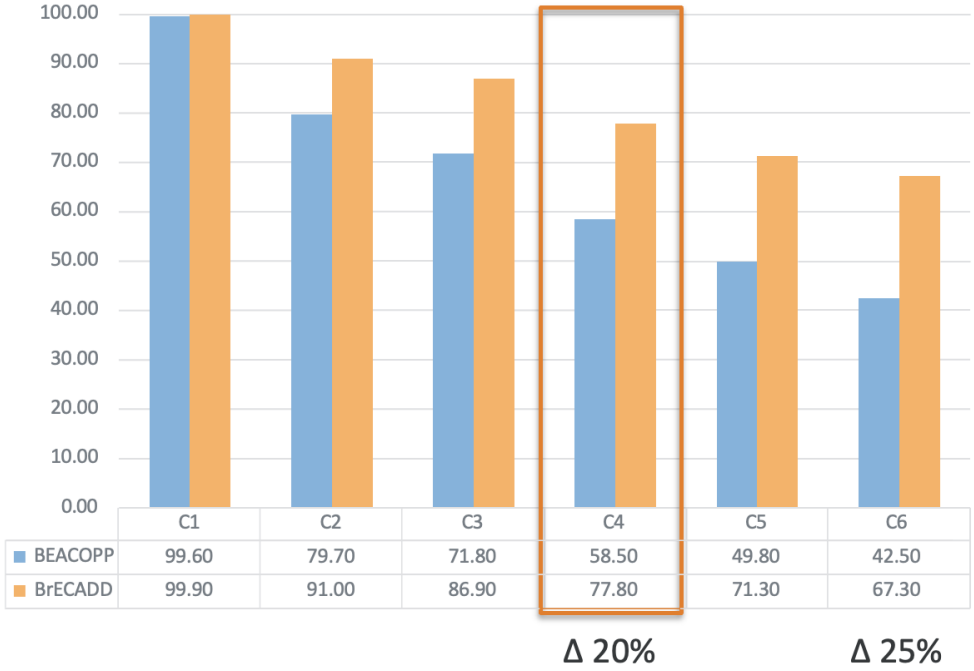
- **BrECADD 94.3% (92.6-96.1)**
- **eBEACOPP 90.9% (88.7-93.1)**



Number at risk (number censored)									
BrECADD	742 (0)	721 (14)	701 (23)	688 (32)	670 (41)	639 (70)	588 (120)	488 (217)	374 (329)
eBEACOPP	740 (0)	711 (18)	685 (26)	663 (35)	643 (47)	628 (59)	578 (107)	471 (209)	372 (306)

Borchmann P, Lancet 2024

Meaningful reduction of TRMB with BrECADD



While also BrECADD comes with relevant acute toxicity, it is better tolerable compared to eBEACOPP:

↓ Treatment-related morbidity (TRMB): 42% vs 59% (RR 0.72; 95%CI: 0.65-0.80, p<0.0001)

↓ Erythrocyte transfusions (24% vs 52%)
↓ Thrombocyte transfusions (17% vs 34%)

↓ Polyneuropathy (39% vs 49%, ≥°2 7% vs 16%)

↓ Treatment-related mortality: 0% vs <1%

Resolution of TRMB events after EOT: 675/677 (>99%)
Myeloid SPM (sAML/MDS): 2/742 (<1%)

Higher relative dose intensity and patients able to receive full dose level

Borchmann P, Lancet 2024

2025 Guidelines

US

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Hodgkin Lymphoma (Age 18–60 years)

CLINICAL PRESENTATION:
Classic Hodgkin Lymphoma: Stage III–IV
PRIMARY TREATMENT[q]

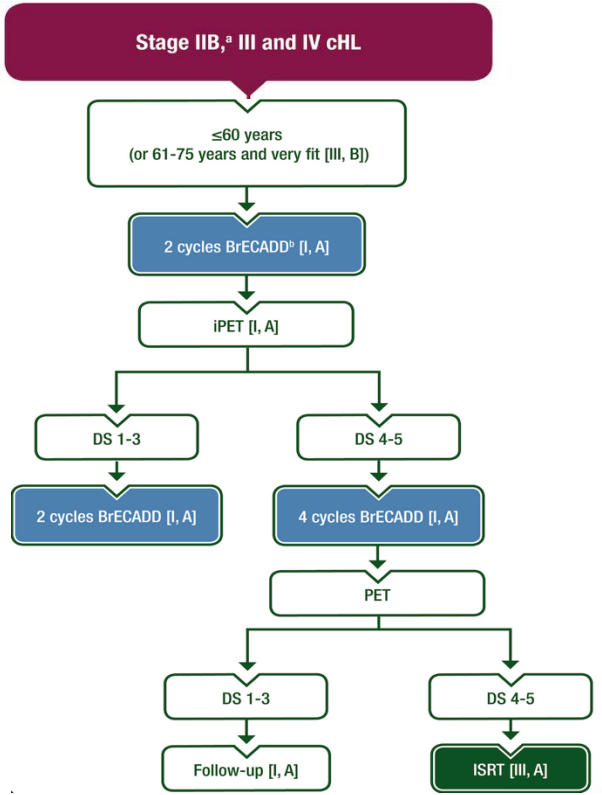
Preferred regimens:

Stage III–IV:
- Nivolumab-AVD[r,y,z] (category 1)
- or
- BrECADD + G-CSF[r] (category 1) (for ages 18-61 y)

Useful in Certain Circumstances

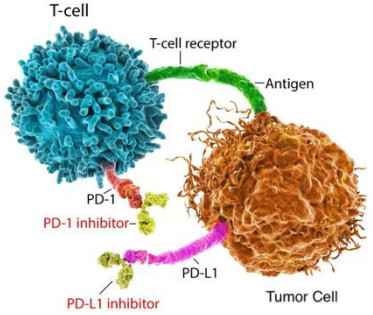
- BV-AVD + G-CSF[r] (category 1) (if not a candidate for CPI; contraindicated in those with neuropathy)
- or
- ABVD[h,y] x 2 cycles[r] (category 1) (if BV and CPI not available or contraindicated) → Restage with FDG-PET/CT[c,aa]
  - Deauville 1–3[s] → AVD x 4 cycles[bb] (adapted from RATHL)[5]
  - Deauville 4–5[s,v] → BrECADD + G-CSF[r,x] x 3 cycles → Restage with FDG-PET/CT[c]

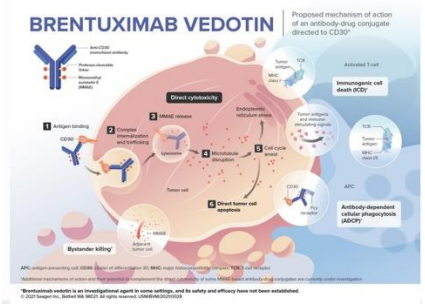
EU



Brentuximab Vedotin

Anti-PD1



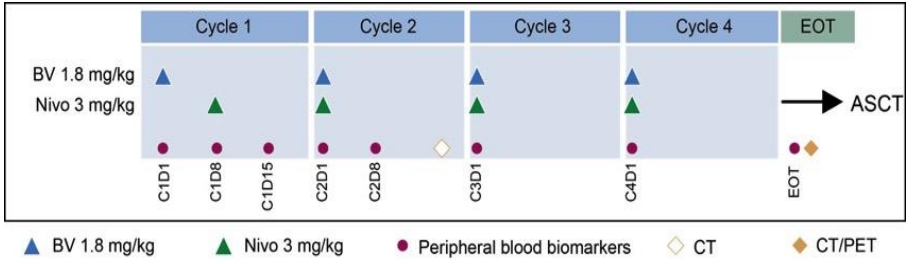


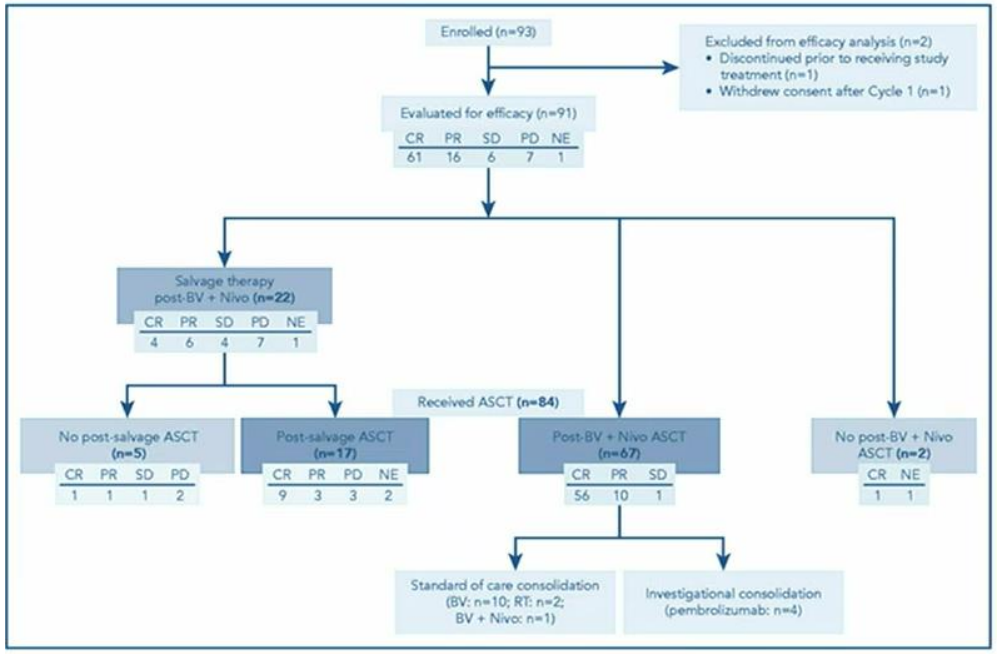
Diagnosis **First-line** **Second-line** **Consolidation** **Salvage therapy**

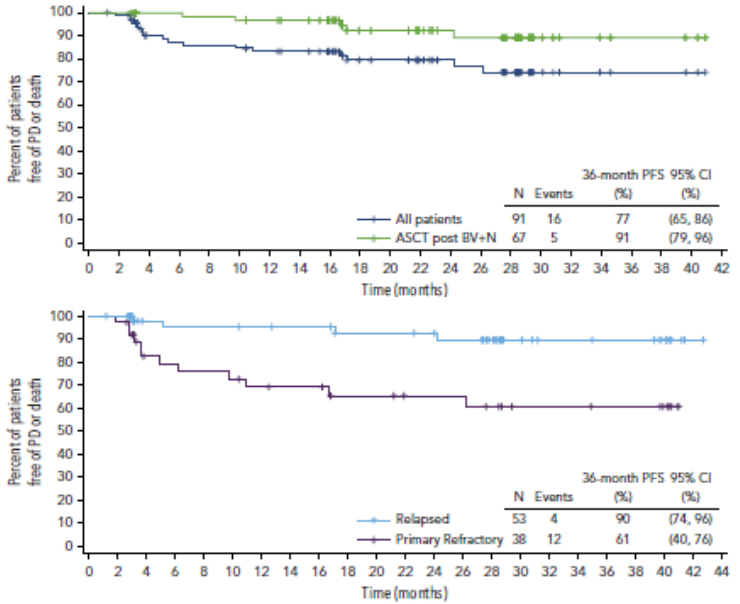
CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results

Ranjana H. Advani,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Beth A. Christian,[8] Stephen M. Ansell,[9] Craig H. Moskowitz,[10] Lisa Brown,[11] Chiyu Zhang,[11] David Taft,[11] Sahar Ansari,[11] Mariana Sacchi,[12] Linda Ho,[11] and Alex F. Herrera[13]

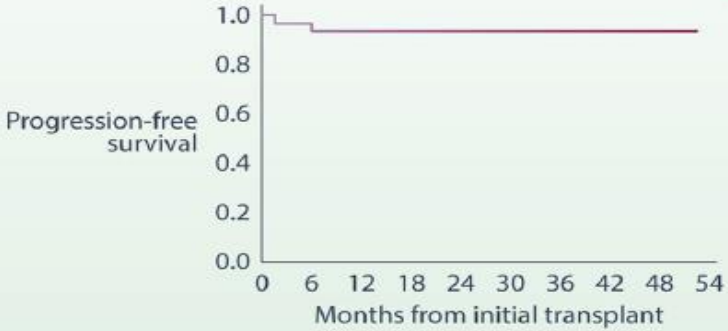






Advani RH et al, Blood 2021

CLINICAL TRIALS AND OBSERVATIONS



Nivolumab + ICE (NICE) is highly effective in patients with relapsed/refractory classical Hodgkin lymphoma

- ORR and CR were 100% and 86% respectively
- 2-year PFS and OS were 88% and 100% respectively
- 2-years PFS and OS post autologous transplant were 94% and 100% respectively

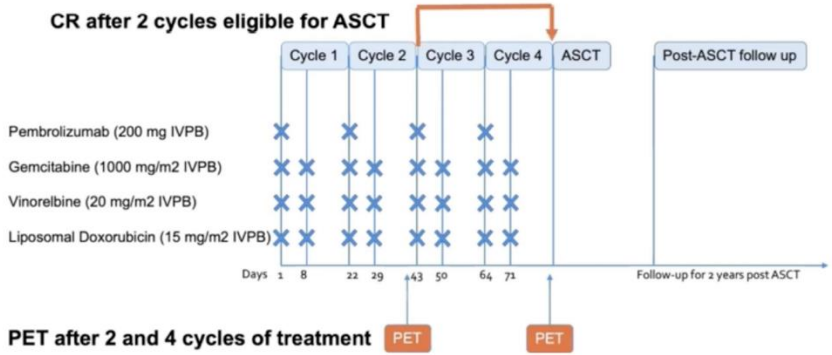
HemaSphere

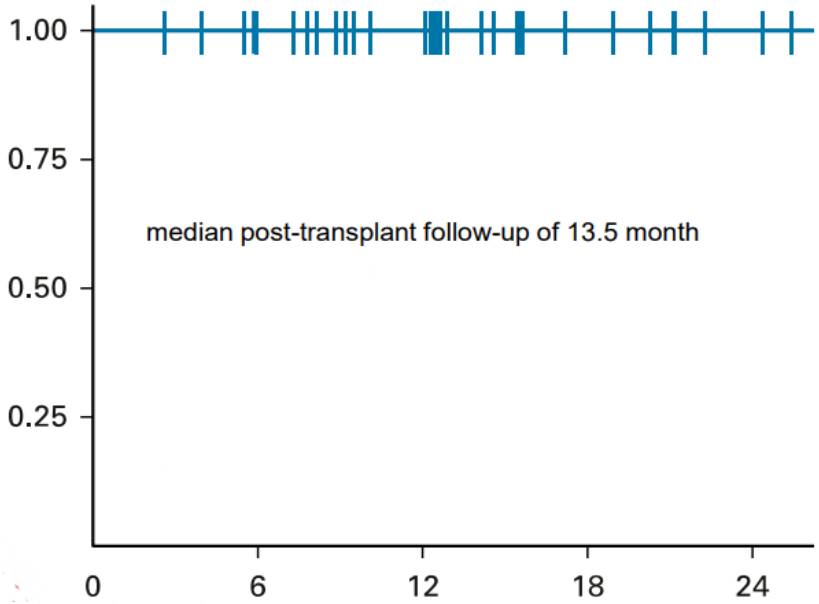
HemaSphere.2025;9:e70126

Phase II Trial of Pembrolizumab Plus Gemcitabine, Vinorelbine, and Liposomal Doxorubicin as Second-Line Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma

Alison J. Moskowitz, MD[1]; Gunjan Shah, MD[2]; Heiko Schöder, MD[1]; Nivetha Ganesan, MPH[1]; Esther Drill, PhD[3]; Helen Hancock, NP[1]; Theresa Davey, PA[1]; Leslie Perez, RN[1]; Sunyoung Ryu, RN[1]; Samia Sohail, MBS[1]; Alayna Santarosa, MPH[1]; Natasha Galasso, MSW[1]; Rachel Neuman, MBA[1]; Brielle Liotta, BS[1]; William Blouin, MBA[1]; Anita Kumar, MD[1]; Oscar Lahoud, MD[1]; Connie L. Batlevi, MD[1]; Paul Hamlin, MD[1]; David J. Straus, MD[1]; Ildefonso Rodriguez-Rivera, MD[1]; Colette Owens, MD[1]; Philip Caron, MD[1]; Andrew M. Intlekofer, MD[1]; Audrey Hamilton, MD[1]; Steven M. Horwitz, MD[1]; Lorenzo Falchi, MD[1]; Erel Joffe, MD[1]; William Johnson, DO[1]; Christina Lee, MD[1]; M. Lia Palomba, MD[1]; Ariela Noy, MD[1]; Matthew J. Matasar, MD[1]; Georgios Pongas, MD[4]; Gilles Salles, MD[1]; Santosha Vardhana, MD[1]; Beatriz Wills Sanin, MD[1]; Gottfried von Keudell, MD[1]; Joachim Yahalom, MD[1]; Ahmet Dogan, MD[1]; Andrew D. Zelenetz, MD[1]; and Craig H. Moskowitz, MD[4]

- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles



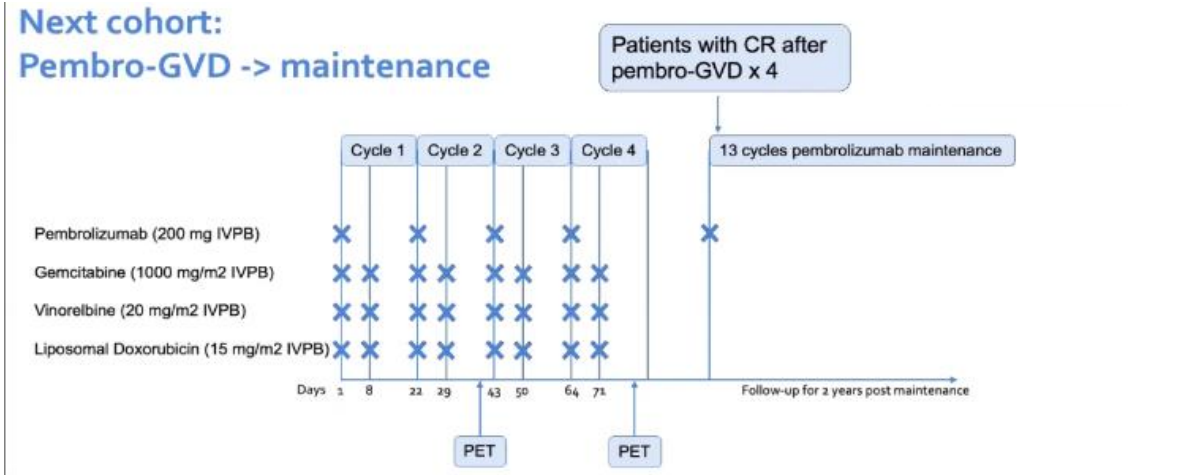


36/38 CR -> 95%

Moskowitz AJ et al, J Clin Oncol 2021

Moving towards an ASCT-free approach?

(patients in CR after Pembro-GVD x 4 will receive 13 cycles of Pembrolizumab manteinance)



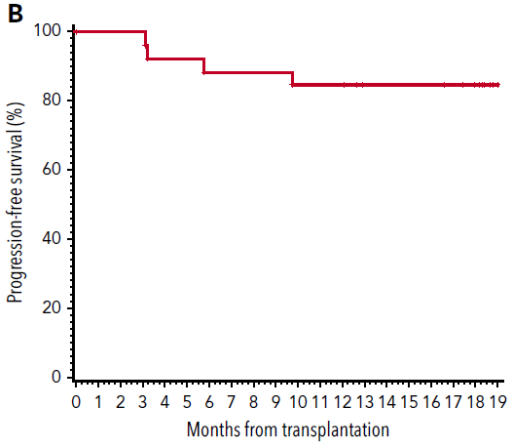
Unprecedented CR rate with pembro GVD

ASCT could be shifted to third line setting for those who need it

Moskowitz AJ et al, ASH 2020

PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation

Philippe Armand,[1] Yi-Bin Chen,[2] Robert A. Redd,[3] Robin M. Joyce,[4] Jad Bsat,[1] Erin Jeter,[1] Reid W. Merryman,[1] Kimberly C. Coleman,[1] Parastoo B. Dahi,[5] Yago Nieto,[6] Ann S. LaCasce,[1] David C. Fisher,[1] Samuel Y. Ng,[1] Oreofe O. Odejide,[1] Arnold S. Freedman,[1] Austin I. Kim,[1] Jennifer L. Crombie,[1] Caron A. Jacobson,[1] Eric D. Jacobsen,[1] Jeffrey L. Wong,[1] Sanjay S. Patel,[7] Jerome Ritz,[1] Scott J. Rodig,[7] Margaret A. Shipp,[1] and Alex F. Herrera[8]



18-mos PFS 82%
18-mos OS 100%
Promising results in HR R/R cHL pts
Need for randomized trial

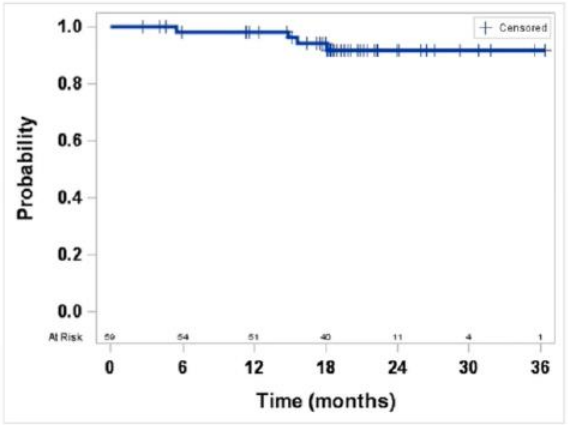
Armand P et al, Blood 2019

AHCT according to institutional standards → 30-75 days after AHCT → **BV 1.8 mg/kg + nivo 3 mg/kg every 21 days for 8 cycles**

If one drug discontinued for toxicity, other could be continued

PET-CT: after AHCT/baseline, Cycle 4 Day 15, EOT, 12 and 18 months after initiation

Progression-free survival



19-month PFS in all patients (n=59): 92% (95 CI 79–97)

BV + Nivo for 8 cycles
→ tolerable approach
→ promising approach

Herrera AF et al, Lancet 2023

New options

Camidanlumab teserine

Anti-PD1 + epigenetic modifiers

Anti-PD1 + AntiLAG3

AntiPD1 + bispecific Ab

AntiCD30+ CART

Diagnosis **First-line** **Second-line** **Consolidation** **Salvage therapy**

ARTICLE OPEN

Check for updates

Outcomes in patients with classic Hodgkin lymphoma refractory or intolerant to brentuximab vedotin and anti-PD-1 therapy: a real world analysis from 15 U.S. academic centers

Timothy J. Voorhees[1✉], Eric M. McLaughlin[2], Pallawi Torka[3], Jorge Florindez[4], Na Hyun Kim[5], Tamara K. Moyo[6], Heather Reves[7], Nuttavut Sumransub[8], Saarang Deshpande[9], Ashley Rose[10], Cassandra Duarte[11], Muhammad Salman Faisal[12], Showkat Hamid[12], Suki Subbiah[13], Sabarish Ayyappan[14], Lauren Shea[15], Matt Cortese[12], Krish Patel[16], Ajay Major[11], Hayder Saeed[10], Jakub Svoboda[9], Sanjal Desai[8], Praveen Ramakrishnan Geethakumari[7], Mehdi Hamadani[5], Natalie Grover[4] and Narendranath Epperla[1,17]

Table 3. Double Refractory Characteristics.

	All patients $n = 173$
Age At DR/INT, (median, range)	40 (19–90)
DR/INT	
Double Refractory	127 (73.4)
Intolerant	46 (26.6)
Years From Diagnosis, (median, range)	3.4 (0.5–23.1)
Prior LOT (median, range)	5 (1–13)
Prior ASCT at DR/INT	
Yes	86 (49.7)
No	87 (50.3)
Treatment After DR/INT	
Yes	153 (88.4)
No	20 (11.6)
BV Therapy After DR/INT	
Yes	41 (23.7)
No	132 (76.3)
Anti-PD-1 Therapy After DR/INT	
Yes	63 (36.4)
No	110 (63.6)

Table 1. Patient Characteristics.

	All Patients $n = 173$	Refractory (DR) $n = 127$	Intolerant (INT) $n = 46$
Age at Diagnosis, median (range)	34 (16–89)	33 (16-89)	40 (18-87)
Sex, *n* (%)			
Male	105 (60.7)	76 (59.8)	29 (63.0)
Female	68 (39.3)	51 (40.2)	17 (37.0)
Race, *n* (%)			
Caucasian	136 (78.6)	100 (78.7)	36 (78.3)
African American	25 (14.5)	18 (14.2)	7 (15.2)
Hispanic	6 (3.5)	5 (3.9)	1 (2.2)
Other	6 (3.5)	5 (3.2)	2 (4.4)
cHL Subtype			
Nodular Sclerosing	118 (68.2)	86 (67.7)	32 (69.6)
Mixed Cellularity	18 (10.4)	10 (7.9)	8 (17.4)
Lymphocyte Rich	1 (0.6)	1 (0.8)	0 (0)
Lymphocyte Deplete	6 (3.5)	6 (4.7)	0 (0)
Unknown	30 (17.3)	24 (18.9)	6 (13.0)
Stage At Diagnosis			
Limited (I-II)	36 (20.8)	29 (22.8)	7 (15.2)
Advanced (III-IV)	132 (76.3)	97 (76.4)	35 (76.1)
Unknown	5 (2.9)	1 (0.8)	4 (8.7)
Front-line Therapy			
ABVD/AVD	134 (77.5)	96 (75.6)	38 (82.6)
BV-AVD	15 (8.7)	12 (9.5)	3 (6.5)
BV + Nivo	5 (2.9)	5 (3.9)	0 (0)
BV +/- Chemo	10 (5.8)	7 (5.5)	3 (6.5)
Other	9 (5.2)	7 (5.5)	2 (4.4)
Front-line CR			
Yes	63 (36.4)	44 (34.7)	19 (41.3)
No	105 (60.7)	81 (63.8)	24 (52.2)
Unknown	5 (2.9)	2 (1.6)	3 (6.5)
Front-line Refractory			
Yes	100 (57.8)	77 (60.6)	23 (50.0)
No	71 (41.0)	49 (38.6)	22 (47.8)
Unknown	2 (1.2)	1 (0.8)	1 (2.2)

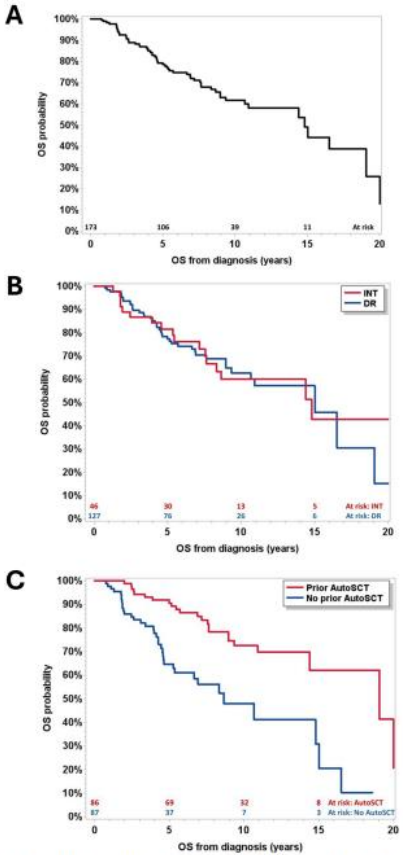


Fig. 1 Overall survival from diagnosis (OS-1). A the full cohort, (**B**) cohort stratified by INT (red) or DR (blue), (**C**) cohort stratified by prior ASCT (red) or no prior ASCT (blue) at the time of DR/INT.

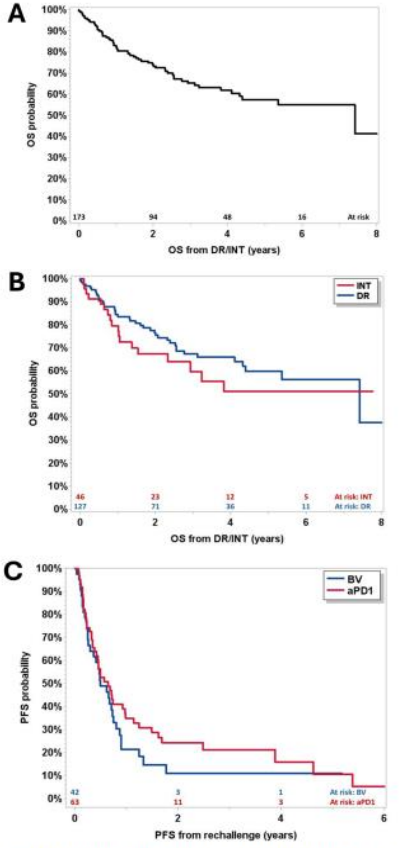


Fig. 2 Overall survival from the time of DR/INT (OS-2). A the full cohort, (**B**) cohort stratified by INT (red) or DR (blue). **C** Progression free survival (PFS) for patients rechallenged with anti-PD-1 based therapy (red) or BV based therapy (blue).

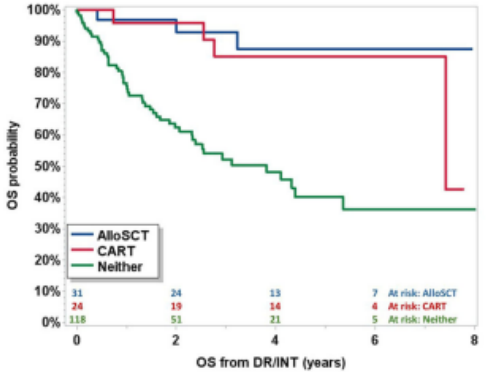


Fig. 3 Overall survival from the time of DR/INT (OS-2) stratified by subsequent AlloSCT (blue), CD30.CAR-T cell therapy (red), or neither therapy (green).

T.J. Voorhees, Blood Cancer Journal ,2025

Treatment Options for Double Refractory Hodgkin lymphoma*

Cytotoxic agents

- Gemcitabine based
- Platinum based
- Vinca Alkaloids
- Bendamustine

Targeted therapies

- Camidanlumab tesirine**
- mTOR inhibitors**
- Lenalidomide**
- HDAC inhibitors**

Transplant and Cellular therapies

- Allogeneic HCT
- CD30.CART-cells**
- EBV CTLs**
- CD16A/CD30 BIKEs**

*Consider Radiation therapy in relapsed/refractory cHL patients with limited treatment options

**Investigational agents for treatment relapsed/refractory cHL

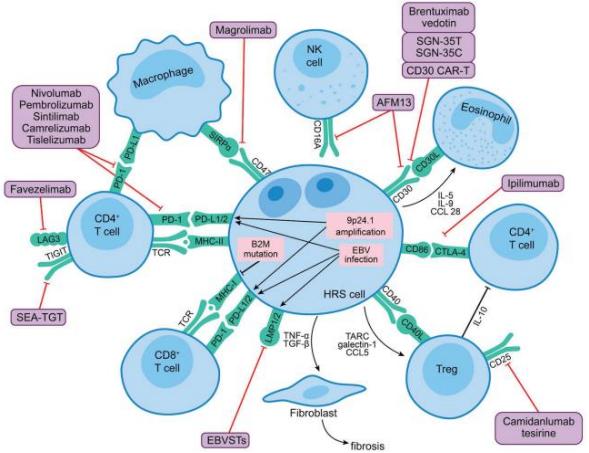


Table 1. Immunotherapies and small molecules in development for classic Hodgkin lymphoma.

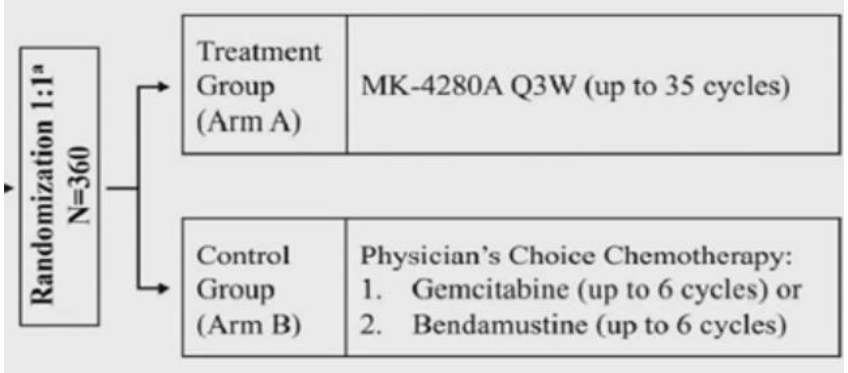
Compound	Company	Structure	Phase	Combinations	Mechanism of action in cHL
Immune checkpoint inhibitors					
Sintilimab	Innovent	Anti-PD-1 mAb	Phase 2	ICE	Enhance CD4+ T-cell responses, withdrawal of pro-survival signals, possible NK cell activation
Camrelizumab	Jiangsu Hengrui		Phase 2	Decitabine, AVD	
Tislelizumab	BeiGene		Phase 2	Gem/Ox, AVD	
Avelumab	Merck	Anti-PD-L1 mAb	Phase 1b	–	
Ipilimumab	Bristol Myers Squibb	Anti-CTLA-4 mAb	Phase 2	Nivolumab, BV	Potentiate T-cell responses
Favezelimab	Merck	Anti-LAG-3 mAb	Phase 2	Pembrolizumab	Overcome T-cell exhaustion
MK-4280A	Merck	Coformulated anti-PD-1 + LAG-3 mAb	Phase 3	–	Overcome T-cell exhaustion, potentiate T-cell responses
Magrolimab	Gilead	Anti-CD47 mAb	Phase 2	Pembrolizumab	Enhance phagocytosis, increase antigen presentation
IMM01	ImmuneOnco Biopharmaceuticals	SIRPα-Fc fusion protein	Phase 2	Tislelizumab	Enhance phagocytosis, increase antigen presentation
SEA-TGT	Seattle Genetics	Anti-TIGIT mAb	Phase 1	BV	Enhance T & NK cell responses
Immunomodulatory agents and small molecules					
Lenalidomide	Bristol Myers Squibb	CELMoD	Phase 2	Nivolumab, temsirolimus	Increase IL-2 production, enhance T & NK cell responses
Ruxolitinib	Incyte	JAK1/2 inhibitor	Phase 2	Nivolumab	Inhibit JAK/STAT signaling, synergize with PD-1 inhibitors
Ibrutinib	AbbVie	BTK/ITK inhibitor	Phase 2	Nivolumab	Enhance Th1 responses
Epigenetic modifying therapies					
Vorinostat	Merck	HDAC inhibitor	Phase 1	Pembrolizumab	Enhance antigen presentation, T-cell recruitment & function
Entinostat	Syndax		Phase 2	Pembrolizumab	
Decitabine	Otsuka	Hypomethylating agent	Phase 2	Camrelizumab	Increase tumor immunogenicity, T-cell infiltration, and overcome resistance to PD-1 inhibitors
Decitabine/cedazuridine (ASTX727)	Astex Pharmaceuticals		Phase 1	Nivolumab	
Azacitidine (CC-486)	Bristol Myers Squibb		Phase 1	Nivolumab	
Antibody-drug conjugates (ADCs)					
Camidanlumab tesirine	ADC Therapeutics	Anti-CD25 ADC	Phase 2	–	Deplete regulatory T cells, target CD25+ HRS cells
SGN-35T	Seattle Genetics	Anti-CD30 ADC	Phase 1	–	Target CD30+ HRS cells with novel linker and MMAE (35T) or camptothecin payload (35C)
SGN-35C	Seattle Genetics		Phase 1	–	
Bispecific antibodies (BsAbs)					
AFM13	Affimed	CD30/CD16A BsAb	Phase 2	Pembrolizumab, AB-101	Recruit NK cells to target CD30+ HRS cells
GEN3017	Genmab	CD30/CD3 BsAb	Phase 1/2	–	Recruit T cells to target CD30+ HRS cells
AZD7789	AstraZeneca	PD-1/TIM-3 BsAb	Phase 1/2	–	Overcome T-cell exhaustion, potentiate T-cell responses
IBI322	Innovent	CD47/PD-L1 BsAb	Phase 1	–	Enhance phagocytosis, increase antigen presentation, potentiate T-cell responses
Cellular therapies					
Autologous CD30 CAR-T	Tessa Therapeutics	Anti-CD30 CAR-T	Phase 2	–	Engineered autologous or allogeneic T cells targeting CD30+ HRS cells
Allogeneic CD30 CAR. EBVSTs (TT11X)	Tessa Therapeutics		Phase 1	–	
Allogeneic UCB-derived NK cells (AB-101)	Artiva	Cytokine-enhanced NK cells	Phase 2	AFM13	Allogeneic NK cell-mediated cytotoxicity, enhanced ADCC

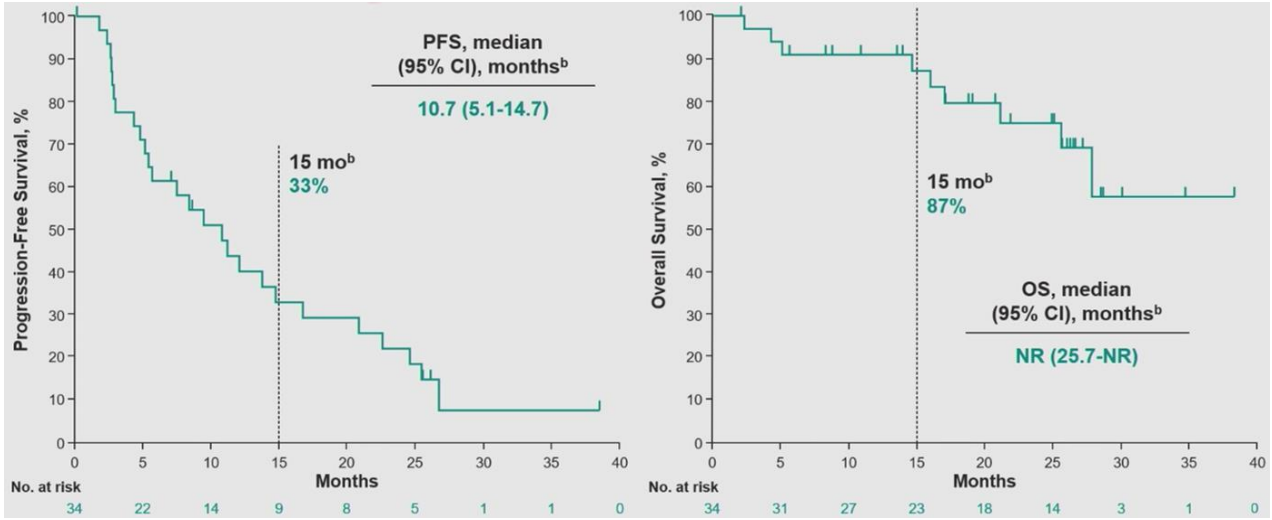
Adapted by Michael A. Spinner & Ranjana H. Advani, **EXPERT OPINION ON EMERGING DRUGS, 2024**

Immune checkpoint inhibitors

Updated Results From an Open-Label Phase 1/2 Study of Favezelimab (anti–LAG-3) Plus Pembrolizumab in Relapsed or Refractory Classical Hodgkin Lymphoma After Anti–PD-1 Treatment

John Timmerman[1]; David Lavie[2]; Nathalie A. Johnson[3]; Abraham Avigdor[4]; Peter Borchmann[5]; Charalambos Andreadis[6]; Ali Bazargan[7]; Gareth P. Gregory[8]; Colm Keane[9]; Inna Tzoran[10]; Vladan Vucinic[11]; Pier Luigi Zinzani[12]; Rachel Marceau West[13]; Pallavi Pillai[13]; Alex F. Herrera[14]



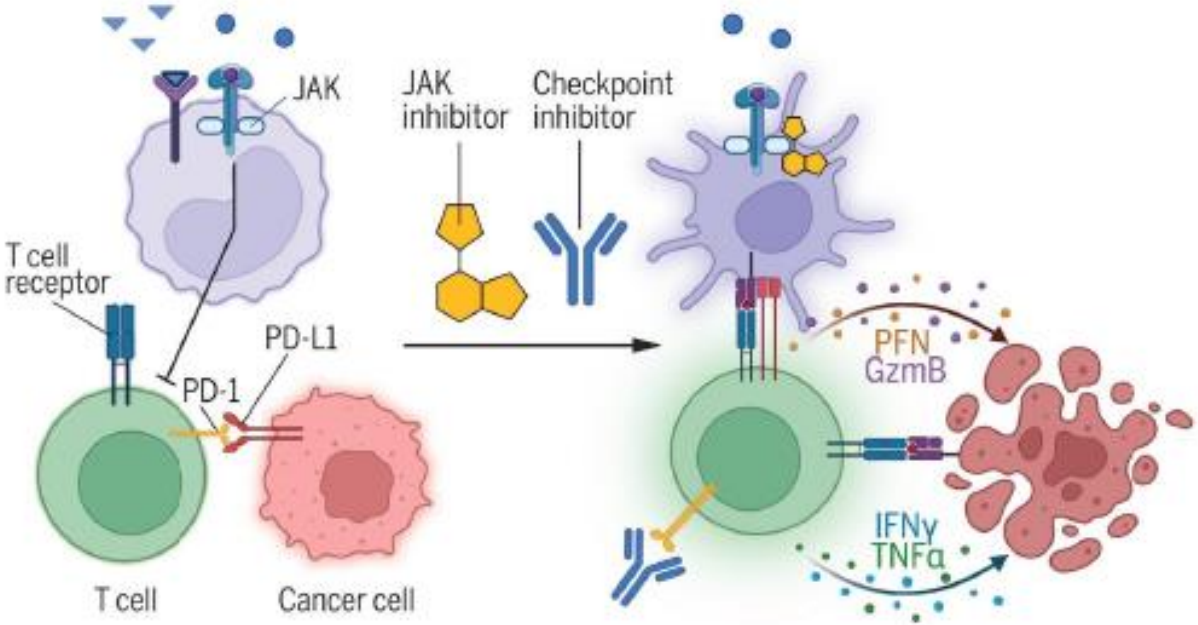


- 28-Day Window
- Informed Consent
- Confirm Eligibility
  - Key Eligibility:
    - PD-1/L1-refractory R/R cHL
    - ECOG PS 0-2
    - Auto-SCT ineligible or failed
    - BV ineligible, failed or discontinued due to toxicity

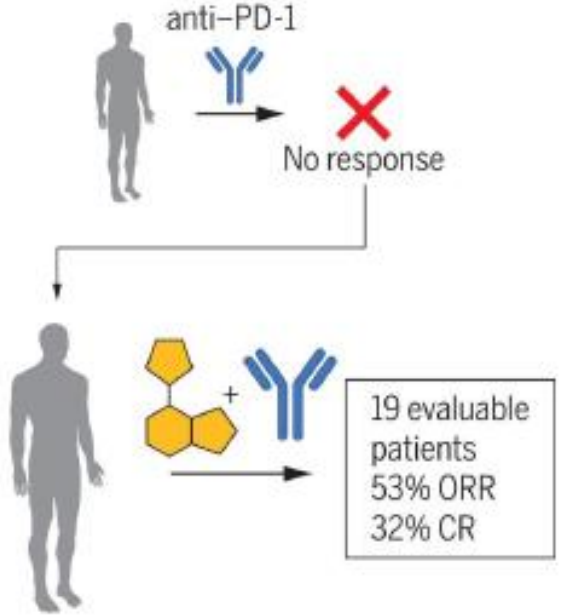
Immunomodulatory agents & small molecules

Ruxolitinib + anti-PD-1

JAK inhibition with checkpoint inhibitors reprograms myeloid cells from a suppressive to an immunostimulatory state



Ruxolitinib with nivolumab in anti–PD-1 relapsed or refractory Classical Hodgkin lymphoma



Jak J et al. Science 2024

Epigenetic modifying therapies

Pembrolizumab plus vorinostat induces responses in patients with Hodgkin lymphoma refractory to prior PD-1 blockade

Background:

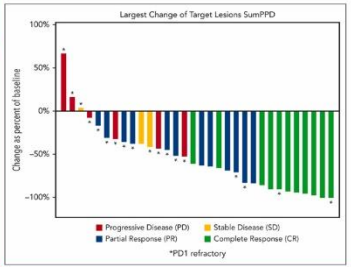
- While most patients with cHL are cured with frontline therapy, 10-30% of subjects will have primary refractory or relapsed (RR) disease. PD-1 blockade is highly effective in cHL, but acquired resistance develops.
- We tested pembrolizumab and vorinostat in patients with cHL, including in patients with PD-1 refractory disease.

Patients and Methods:

- ClinicalTrials.gov Identifier: NCT03150329
- Study design: A phase 1 trial of pembrolizumab plus vorinostat
- Subjects: 32 cHL patients
- Primary outcome measure: Incidence of adverse events
- Secondary outcome measures: Overall response rate (ORR), Complete response rate (CR), duration of response (DOR)

Outcomes:

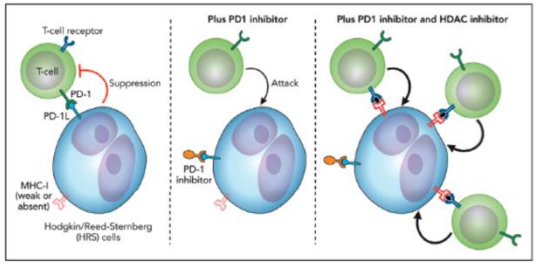
- ORR: 72% (56% in patients with disease refractory to PD-1 blockade)
- CR: 34%
- median DOR: 12.2 months (8.6 months in PD-1 refractory subset)



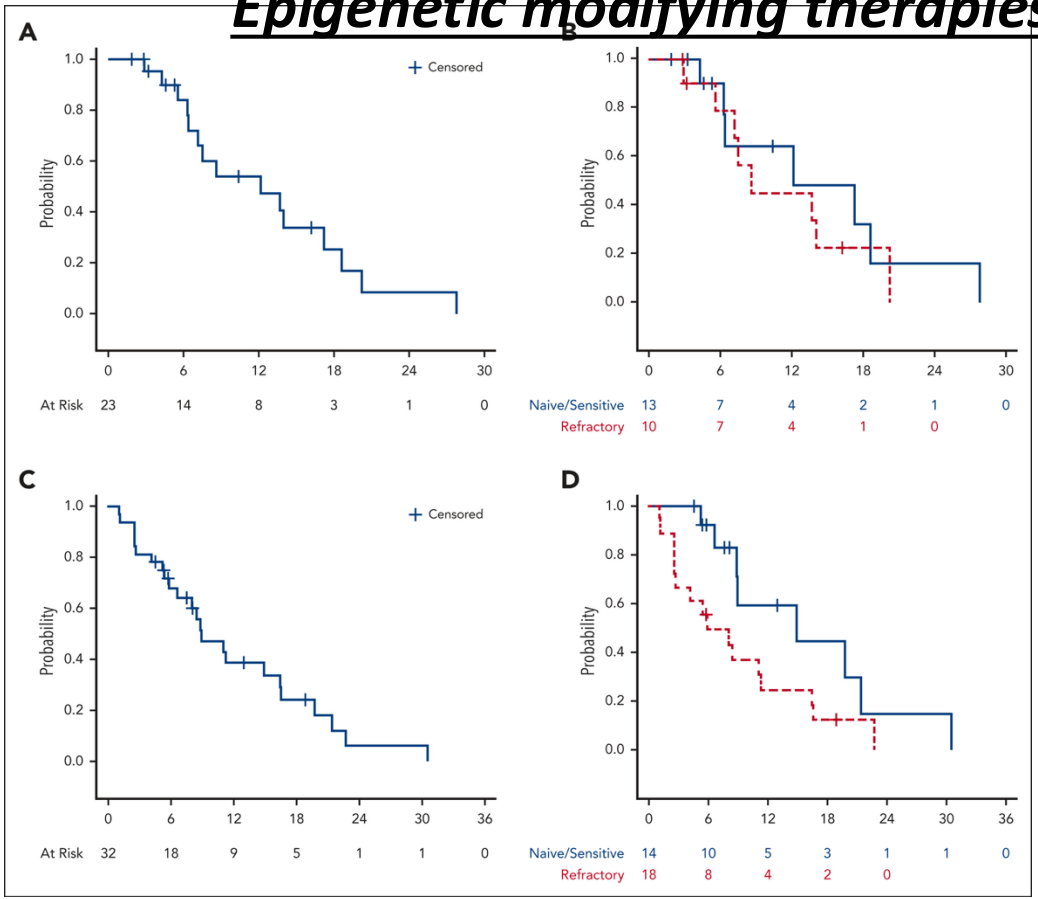
Conclusions: 1) Pembrolizumab and vorinostat were highly effective in patients with RR cHL, including those refractory to prior PD-1 blockade; 2) toxicity was manageable.

*Mei et al. DOI: 10.1182/**blood**.2023020485*

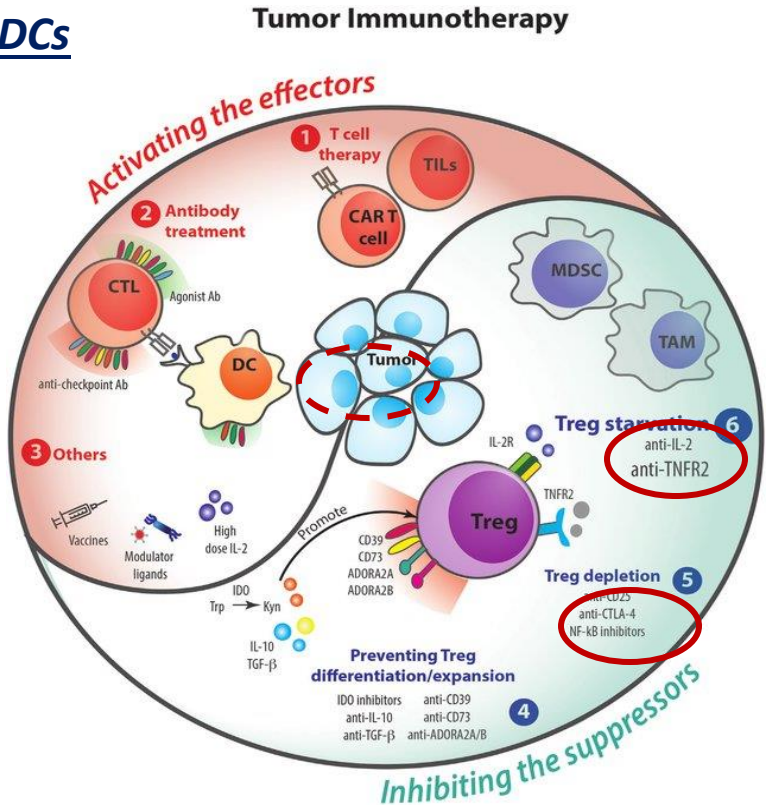
Blood Visual Abstract



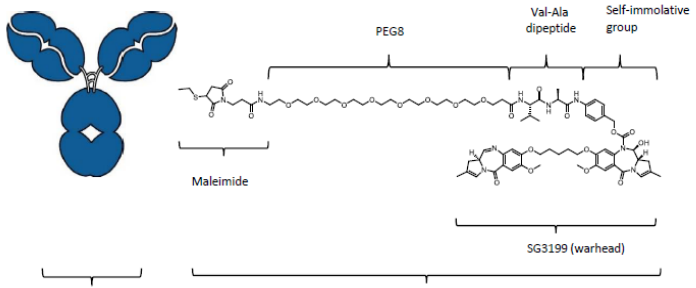
A model showing how the addition of an HDAC inhibitor may enhance the activity of a PD1i in cHL through increased immune receptor expression (such as MHC class I), increased recruitment, and activation of T cells. Professional illustration by Patrick Lane, ScEYEnce Studios.



ADCs

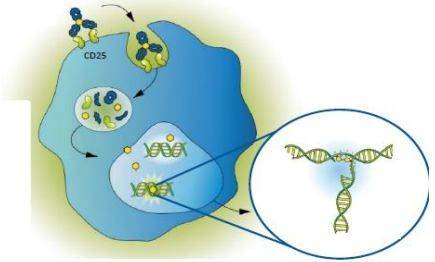


Structure and components of camidanlumab tesirine (Cami)



Immunological rationale

- Targeting of CD25+ Tregs may increase the Teff:Treg → immunologic tumour eradication[1]
- Anti-CD25 therapies synergise with PD-1 blockade to eradicate established tumours[2]



1. Sadiharan NV, et al. *Immunol Cell Biol*. 2018;96:21–33. 2. Arce Vargas F, et al. *Immunity*. 2017;46:577–86. 3. Hartley JA. *Expert Opin Investig Drugs*. 2011;20:733–44. 4. Flynn MJ, et al. *Mol Cancer Ther*. 2016;15:2709–21.
ADC, antibody drug conjugate; CD25, cluster of differentiation 25; PBD, pyrrolobenzodiazepine; Teff, effector T cell; Treg, regulatory T cell; Val-Ala, valine-alanine..

Camidanlumab tesirine: updated efficacy and safety in an open-label, multicenter, phase 2 study of patients with relapsed or refractory classical Hodgkin lymphoma (R/R cHL)

Carmelo Carlo-Stella[1], Stephen Ansell[2], Pier Luigi Zinzani[3], John Radford[4], Kami Maddocks[5], Antonio Pinto[6], Graham P. Collins[7], Veronika Bachanova[8], Nancy Bartlett[9], Isabelle Bence-Bruckler[10], Mehdi Hamadani[11], Justin Kline[12], Jiri Mayer[13], Kerry J. Savage[14], Ranjana Advani[15], Paolo Caimi[16], René-Olivier Casasnovas[17], Tatyana Feldman[18], Brian Hess[19], Mariana Bastos-Oreiro[20], Sunil Iyengar[21], Sandy Eisen[22], Yanina Negievich[22], Luqiang Wang[23], Jens Wuerthner[22], Alex F. Herrera[24]

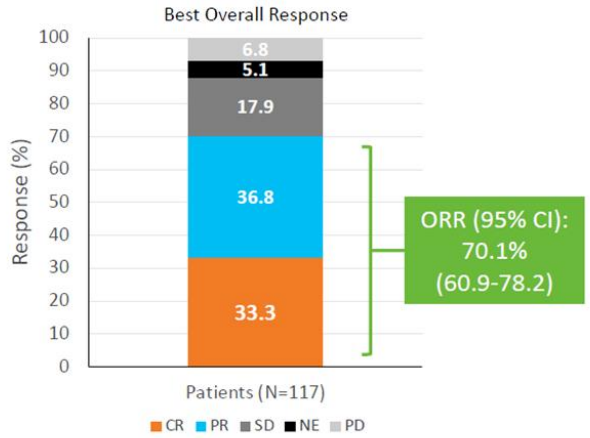
Ongoing, Phase 2, single-arm, multicenter, open-label study in patients with R/R cHL[a]

30-minute IV infusion of Cami on Day 1 of each 3-week cycle

45 µg/kg → 30 µg/kg

Cycles 1 & 2 — Cycle 3 onwards, up to 1 year[b]

Efficacy – Overall Response Rate[a]



Best Overall Response in Patients with or without prior SCT

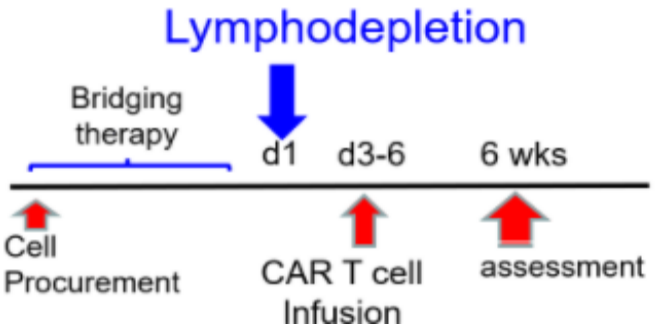
Best Overall response, n (%)[b]	BV and CHPi With Prior SCT (n=73), n (%)	BV and CHPi Without Prior SCT (n=43), n (%)
CR	30 (41.1)	8 (18.6)
PR	24 (32.9)	19 (44.2)
SD	13 (17.8)	8 (18.6)
NE[c]	3 (4.1)	3 (7.0)
PD	3 (4.1)	5 (11.6)
ORR 95% CI for ORR	54 (74.0) 62.4-83.5	27 (62.8) 46.7-77.0

- Primary endpoint: ORR (per 2014 Lugano classification) assessed by central review
- Secondary endpoints: DoR, PFS, safety (frequency and severity of adverse events)
- As of November 1, 2021, enrollment was complete **(N=117)**

Society of Hematologic Oncology Congress, September 28-October 1, 2022
Session Date & Time: 30 September 2022 5:49 PM – 5:58 PM CDT

cellular therapy

Anti-CD30 CAR-T



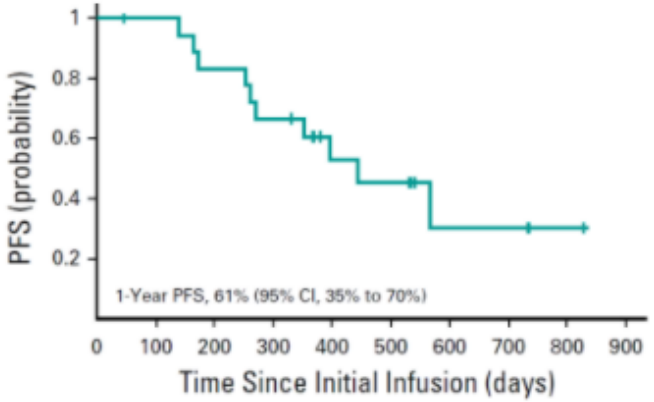
- Phase 1 trials run in parallel at BCM and UNC
- 41 HL, Median 35 yrs (range 17-69)
  - Median 7 regimens (range 2 -23)
  - BV (38; 90%), CPI (34; 81%), SCT (32; 76%), Allo (10; 24%)
- Primary Objective: safety
- Secondary: response per Lugano
  - Initial assessment at week 6

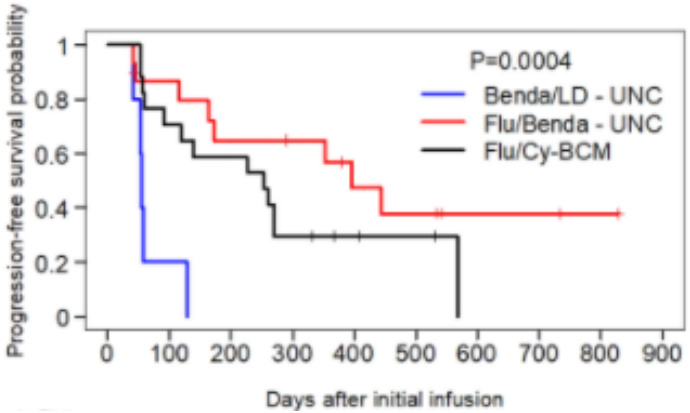
Bendamustine (90 mg/m^2/day) x 2 days
or
Bendamustine (70 mg/m^2/day) x 3 days
Fludarabine (30 mg/m^2/day) x 3 days

Cyclophosphamide (500 mg/m^2/day) x 3 days
Fludarabine (30 mg/m^2/day) x 3 days

Characteristics	All patients N=42
Prior BV	38 (90%)
Progression on BV	32 (84%)
Prior CPI	34 (81%)
Prior ASCT	32 (76%)
Prior AlloSCT	10 (24%)

Ramos et al, JCO 2020



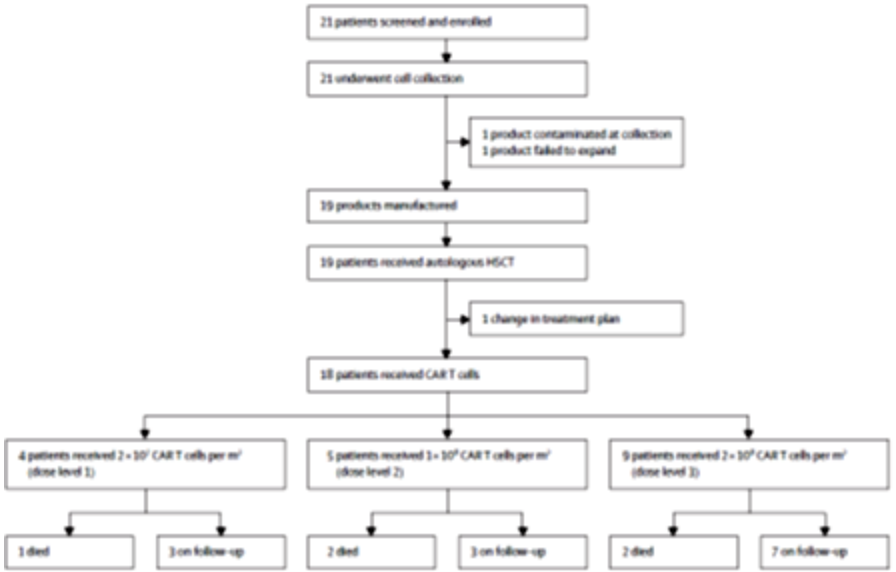


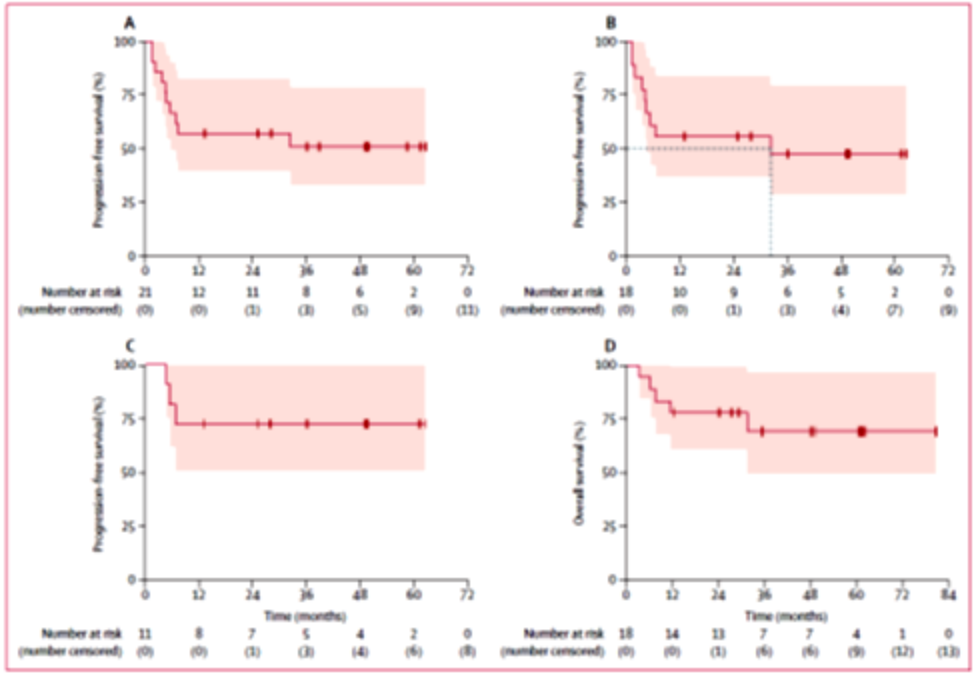
Adverse Event	All Patients (N= 42)[a]	Benda (n = 8)[a]	Benda-Flu (n = 17)	Cy-Flu (n = 17)[a]
Lymphopenia	42 (100)	8 (100)	17 (100)	17 (100)
Leukopenia	24 (57)	3 (38)	8 (47)	13 (76)
Anemia	5 (12)	0	2 (12)	3 (18)
Hypoalbuminemia	3 (7)	0	0	3 (18)
Hyponatremia	2 (5)	0	0	2 (12)
Hyperkalemia	0	0	0	1 (6)
Dyspnea	1 (2)	0	0	1 (6)
Rash (any grade)	20 (48)	2 (25)	4 (24)	14 (82)
Headache	1 (2)	0	0	1 (6)
Pharyngitis	1 (2)	0	1 (6)	0
Lung infection	1 (2)	0	1 (6)	0
Neutropenia	20 (48)	2 (25)	7 (41)	11 (65)
Grade 3/4 neutropenia not resolved by day 28	4 (10)	0	2 (12)	2 (12)
Prolonged grade 3/4 neutropenia (not resolved by month 3)[b]	0	0	0	0
Thrombocytopenia	11 (26)	1 (13)	7 (41)	3 (18)
Grade 3/4 thrombocytopenia not resolved by day 28	10 (24)	0	7 (41)	3 (18)
Prolonged grade 3/4 thrombocytopenia (not resolved by month 3)[b]	4 (10)	0	3 (18)	1 (6)
Cytokine release syndrome (all grade 1)	10 (24)	1 (13)	2 (12)	7 (41)

Ramos et al, JCO 2020

Anti-CD30 CAR T cells as consolidation after autologous haematopoietic stem-cell transplantation in patients with high-risk CD30⁺ lymphoma: a phase 1 study

Natalie S Grover, George Hucks, Marcie L Riches, Anastasia Ivanova, Dominic T Moore, Thomas C Shea, Mary Beth Seegars, Paul M Armistead, Kimberly A Kasow, Anne W Beaven, Christopher Dittus, James M Coghill, Katarzyna J Jamieson, Benjamin G Vincent, William A Wood, Catherine Cheng, Julia Kaitlin Morrison, John West, Tammy Cavallo, Gianpietro Dotti, Jonathan S Serody, Barbara Savoldo





Lancet Haematol 2024;
11: e358–67

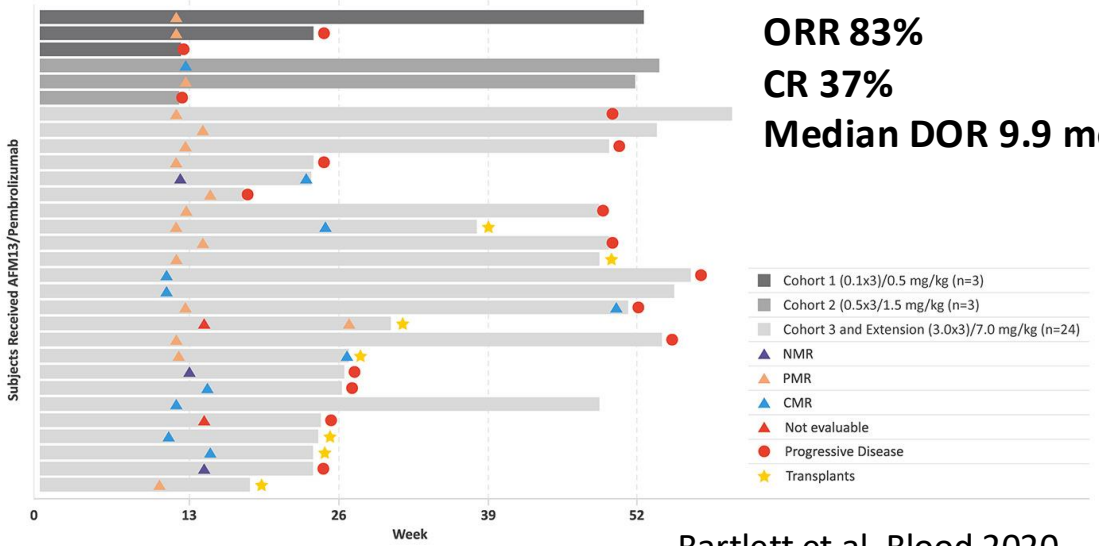
A phase 1b study of AFM13 in combination with pembrolizumab in patients with R/R HL

→ AFM13 is a bispecific, tetravalent innate cell engager that activates NK cells and macrophages via CD16A to target CD30+ lymphoma cells

→ AFM13 in combination with pembrolizumab for HL patients was well-tolerated with adverse events that were generally manageable

Characteristics	N=30
Median age (range)	33.5 (18, 73)
Relapsed	13 (43%)
Refractory	17 (57%)
Prior lines of therapy ≥ 4	16 (53%)
Prior ASCT	12 (40%)
BV as last prior therapy	13 (43%)

*prior anti PD1 excluded



ORR 83%
CR 37%
Median DOR 9.9 mo

Bartlett et al, Blood 2020

Conclusions – The expanding role of antibody-based therapy

- **Antibody-based therapies** have transformed Hodgkin lymphoma from a chemotherapy-driven to an **immunotherapy-driven disease**.

- **Brentuximab vedotin (anti-CD30)** and **anti–PD-1 antibodies** are now core components of first-line and second-line strategies

- **PD-1–based combinations** (with chemo or ADCs) achieve **deep, durable remissions** and high pre-transplant CR rates.

- **Next-generation antibodies** (anti-CD25 ADCs, bispecifics, and CAR-T) are promising for post–PD-1/brentuximab resistant disease.

- **Future direction:** toward **chemo-free, biomarker-guided immunotherapy**—achieving cure with minimal late toxicity.