4th Cuneo City ImmunoTherapy Conference (CCITC)

Immunotherapy in Hematological Malignancies 2024

CUNEO
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Spazio Incontri Fondazione CRC

NEWS AND VIEWS IN HODGKIN LYMPHOMA

Chiara Rusconi
Division of Hematology and Bone Marrow Transplantation
Fondazione IRCCS Istituto Nazionale Tumori
Milano

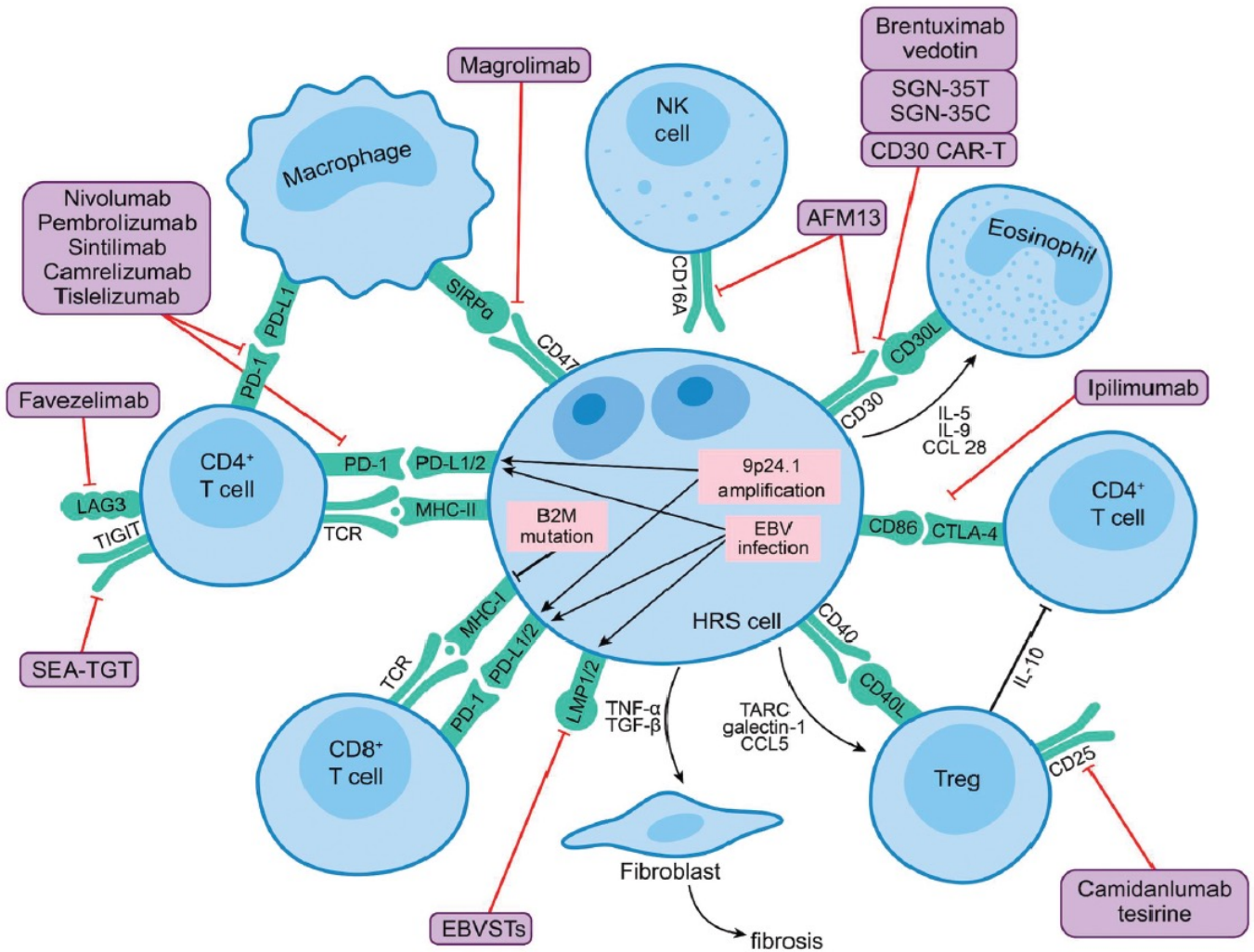
Organized by Prof. Massimo Massaia, SC Ematologia AO S.Croce e Carle, Cuneo - Italy and
Centro Interdipartimentale di Biotecnologie Molecolari "Guido Tarone" (MBC), Torino - Italy

Immunotherapy in Hematological Malignancies 2024

Disclosures of Chiara Rusconi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda						X	X
Lilly						X	
Gilead							X
Novartis							X

Immunotherapy in Hematological Malignancies 2024

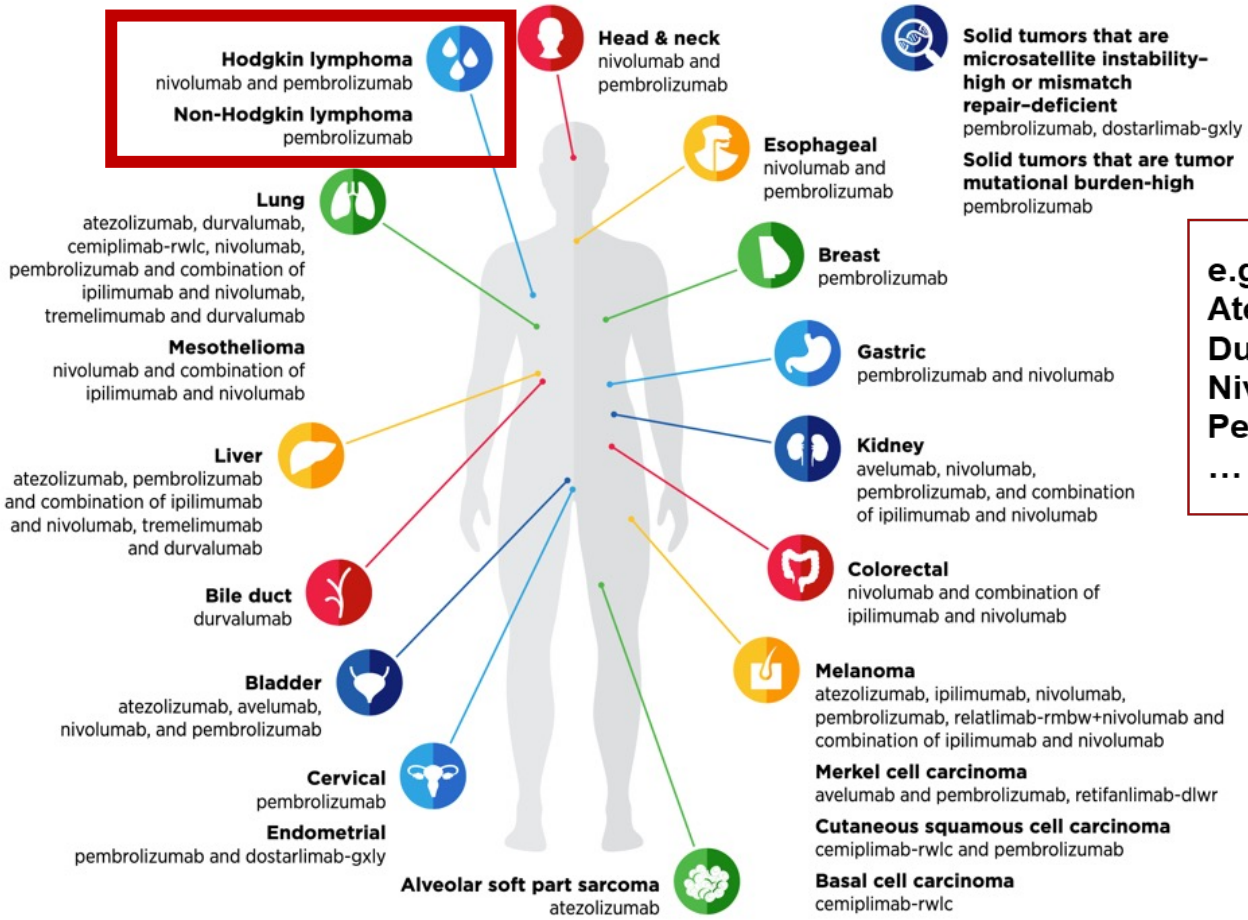


Hodgkin lymphoma: the king of immune evasion

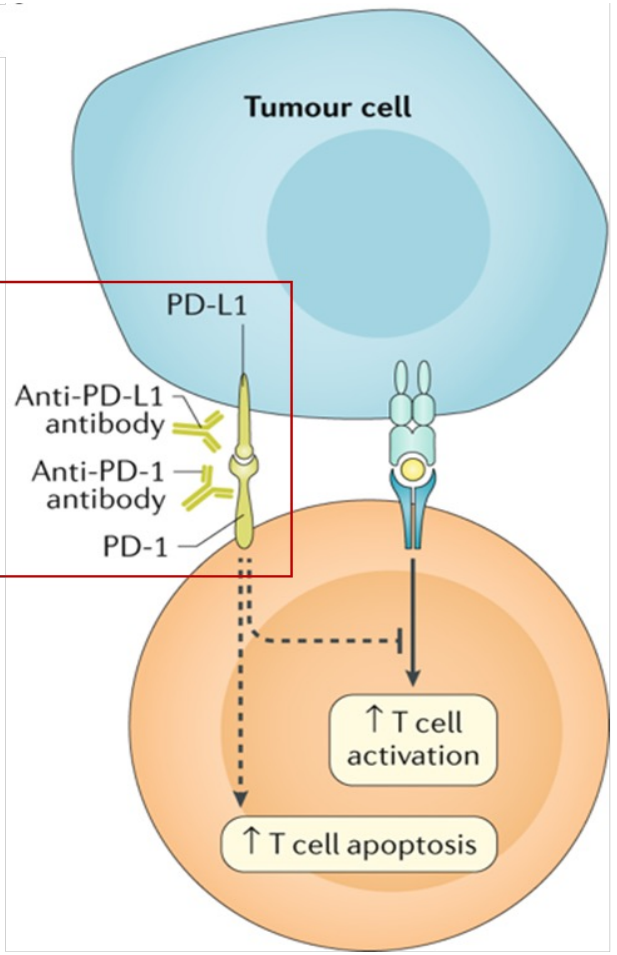
- PDL1 and PDL2 overexpression→T-cell exhaustion
- Loss of MHC class I-II expression→»invisible» tumor
- Immunosoppressive tumor microenvironment

Modified from Spinner MA and Advani RA, Exp Opinion on Emerging Drugs 2024

Immunotherapy in Hematological Malignancies 2024



e.g.
Atezolizumab
Durvalumab
Nivolumab
Pembrolizumab
…



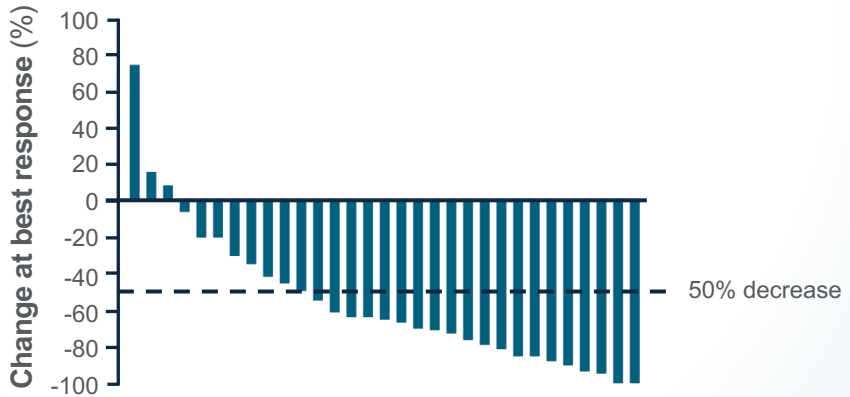
Ramos-Casals et al. Nat Rev Dis Prim 2020

ICIs as a single agent for r/r HL

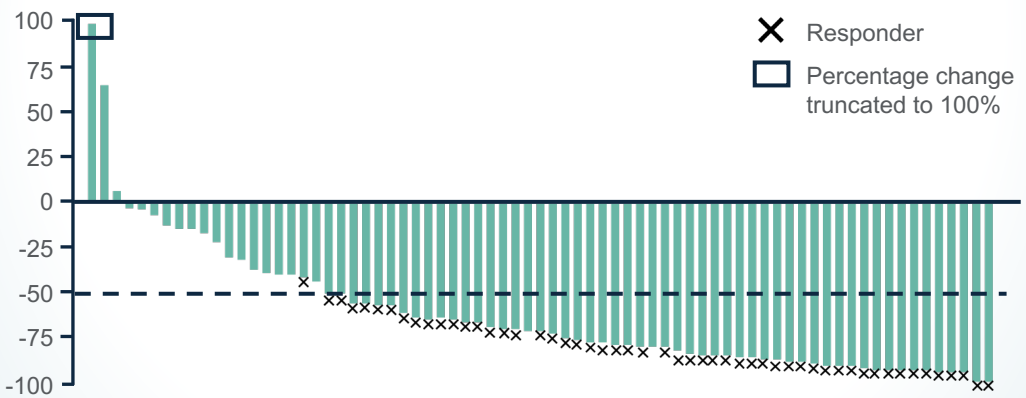
Nivolumab and pembrolizumab in r/r HL[1]

Study	Study type	Setting	No. of patients	Regimen used, including ICIs	AEs	Efficacy
Armand et al. CheckMate 205	Phase 2	r/r HL after ASCT, 3 cohorts: Cohort A: BV naïve Cohort B: BV received after ASCT Cohort C: BV received before and/or after ASCT	243	Nivolumab, 3 mg/kg every 2 weeks until disease progression/ unacceptable toxicity	Most common Grade III/IV AEs were lipase increases (5%), neutropenia (3%), and ALT increases (3%)	ORR: 69% (Cohort A: 65%, Cohort B: 68%, Cohort C: 73%) CR: 16% (Cohort A: 29%, Cohort B: 13%, Cohort C: 12%)
Chen et al. KEYNOTE-087	Phase 2	r/r HL, 3 cohorts: Cohort 1: Progression after ASCT and BV Cohort 2: Progression after salvage chemotherapy and BV (ASCT ineligible) Cohort 3: Progression after ASCT without BV	210	Pembrolizumab, 200 mg every 3 weeks for up to 2 years or until disease progression/ unacceptable toxicity	Grade 3 AEs in 11%. Most common were neutropenia and diarrhea	ORR: 71.9% (Cohort 1: 76.8%, Cohort 2: 66.7%, Cohort 3: 73.3%) CR: 27.6% (Cohort 1: 26.1%, Cohort 2: 25.9%, Cohort 3: 31.7%)

Pembrolizumab[2]



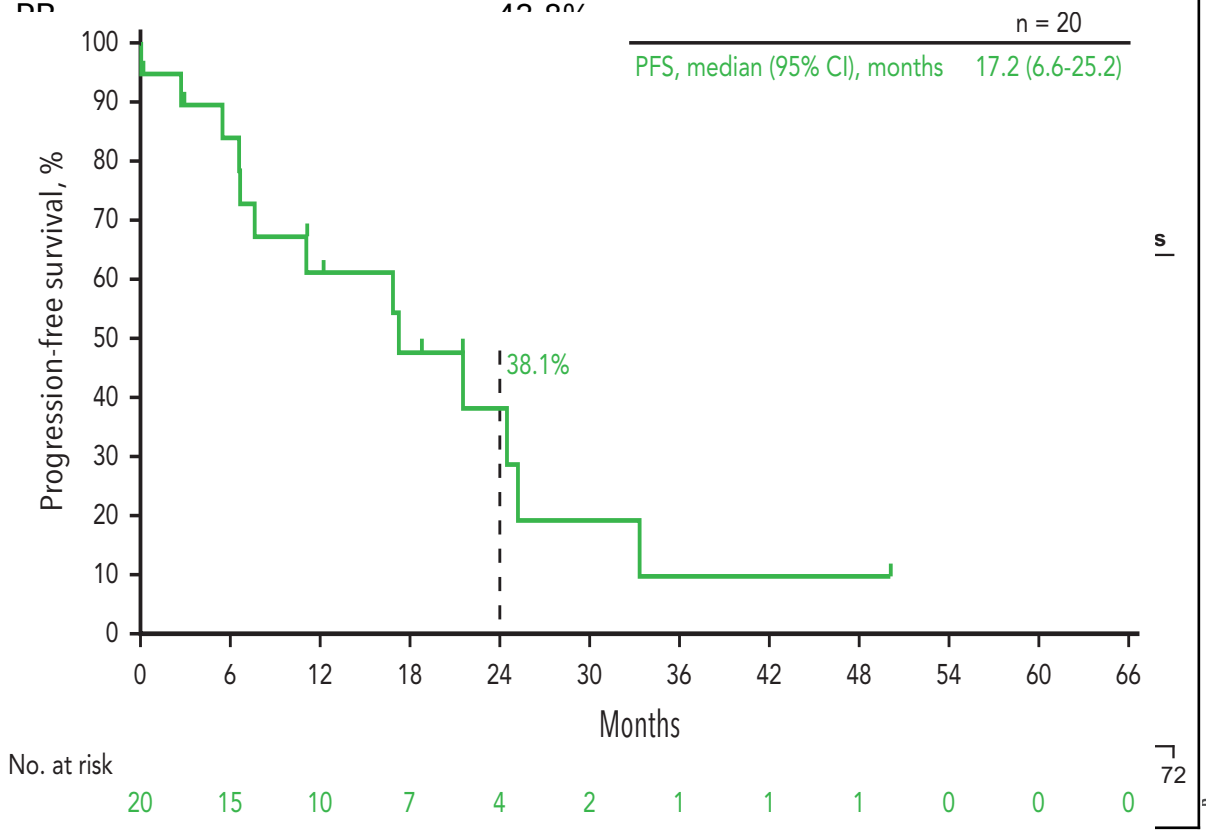
Nivolumab[3]



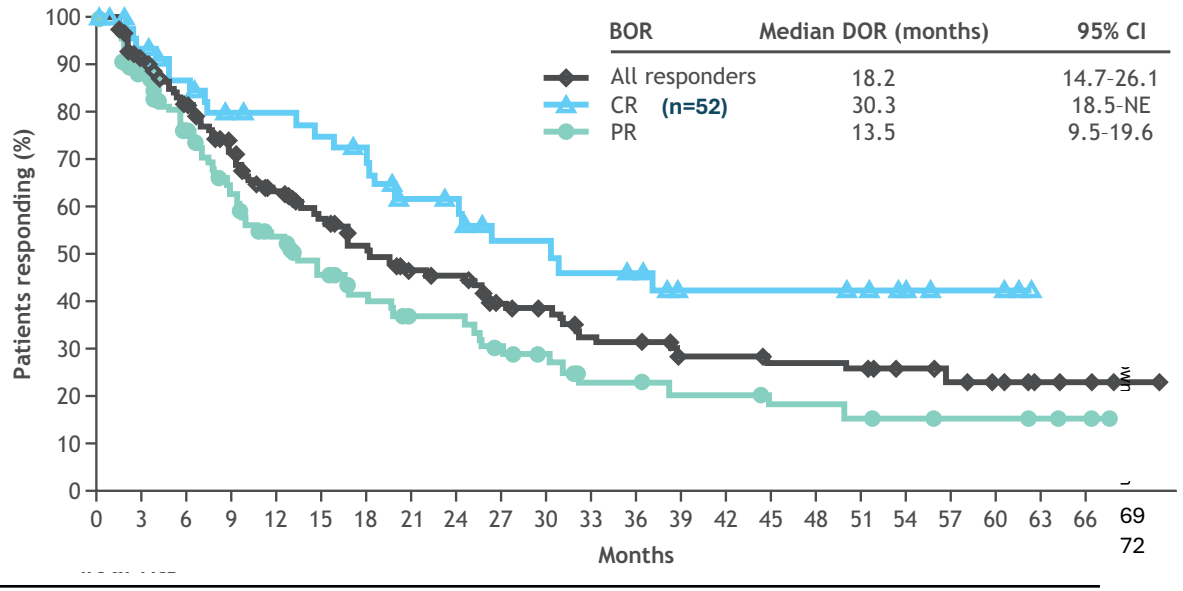
Five-year follow-up of KEYNOTE-087 and CHECKMATE 205

Outcome **Keynote – 087 (Pembrolizumab)**

20 patients who achieved CR and experienced PD received a second-course pembrolizumab

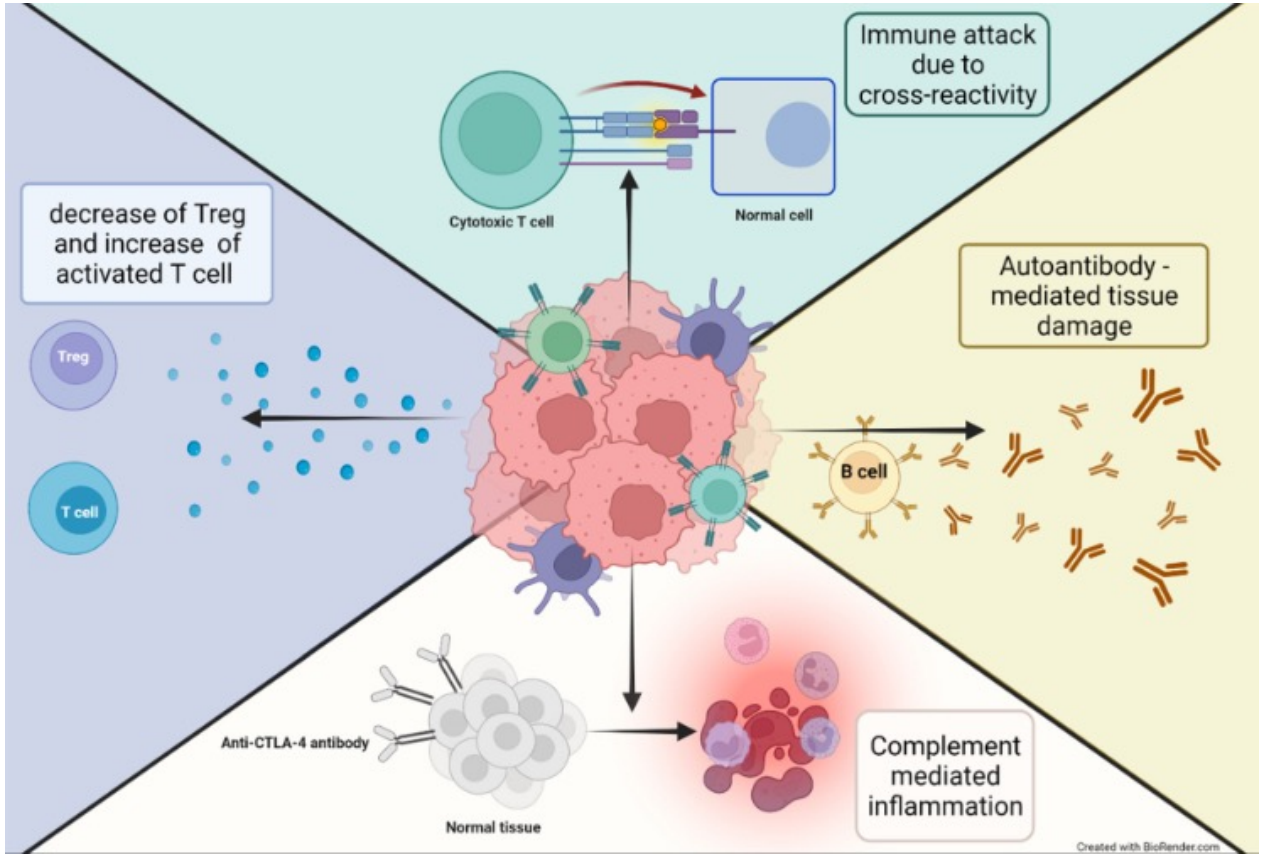


Response	**CheckMate 205 (Nivolumab)**
ORR	71.2%
CR	21.4%
PR	49.8%
Median DOR	18.2 mo

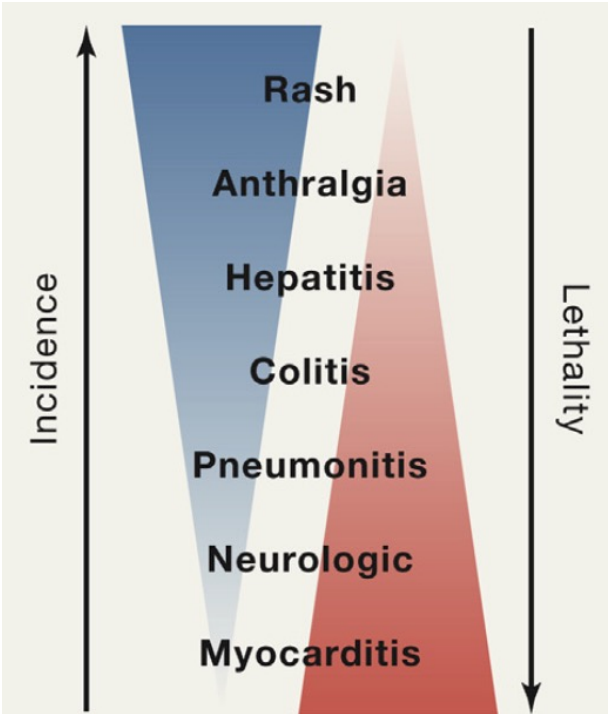


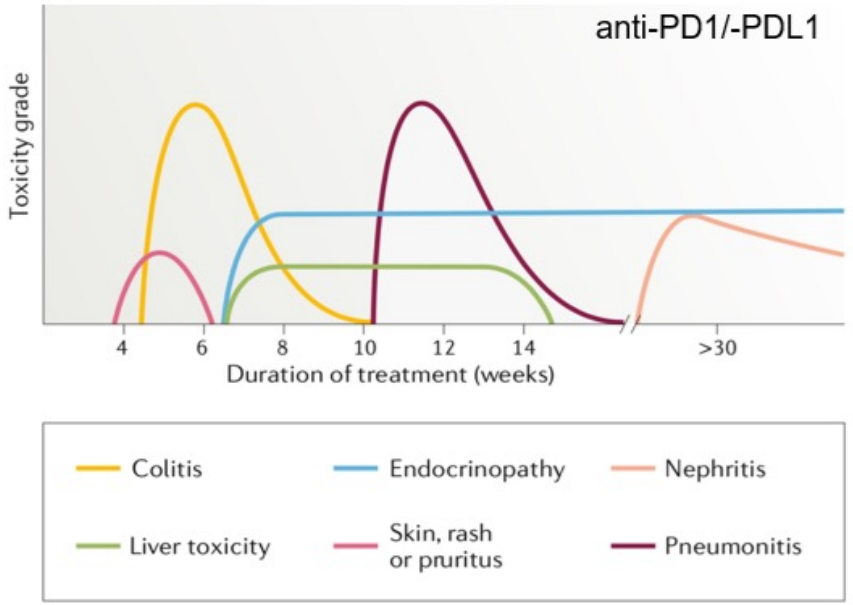
Armand P et al, Blood 2023; Ansell S et al, Blood Advances 2023

Immune check-points inhibitors: toxicity



Moral G et al, Cell Rev 2021





ICI combination therapy for r/r HL

Second-line therapy (first salvage) with ICIs

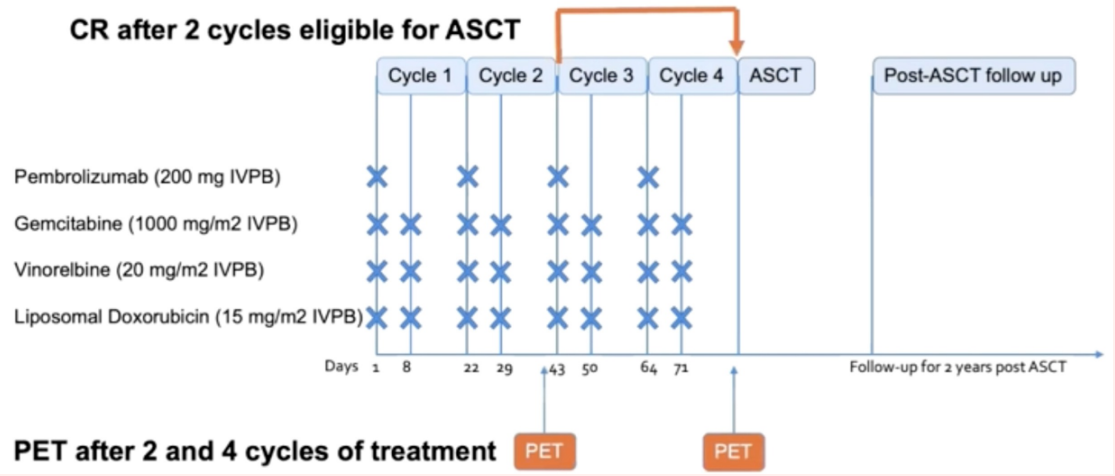
Study	Study type	Setting	No. of patients	Regimen used, including ICIs	AEs	Efficacy
Moskowitz et al.	Phase 1/2	Initial salvage for r/r HL	91	BV (1.8 mg/kg) and nivolumab (3 mg/kg) in 3-week cycles for up to 4 cycles	Most common Grade 3 AEs were anemia, FN, hypophosphatemia and neutropenia (all at 3%); 14% of patients had irAEs requiring treatment with systemic steroid	ORR: 85% CR: 67%
Herrera et al.	Phase 2	Initial salvage for r/r HL	39	Nivolumab 3 mg/kg Q2W for up to 6 cycles. After Cycle 6, if CR, proceed to ASCT; if not, N-ICE for 2 cycles	Most common AEs related to nivolumab alone were fatigue (28%), rash (18%), fever (15%), thrombocytopenia (10%), and dyspnea (10%). All Grade 1–2	ORR: Nivolumab alone (78%) after N-ICE (100%) CR: Nivolumab alone (70%) after N-ICE (86%)
Moskowitz et al.	Phase 2	Initial salvage for r/r HL,	18	Pembrolizumab 200 mg and GVD Q3W for 2–4 cycles. After Cycle 2, if CR, proceed to ASCT; if not, 2 more cycles	Most common AE was elevated liver enzymes (13%)	ORR: 100% CR: 93%
Bryan et al.	Phase 2	Initial salvage for r/r HL	23	Pembrolizumab 200 mg and ICE Q3W for 2 cycles followed by pembrolizumab 200 mg for 1 more cycle. After Cycle 2, if CR, proceed to ASCT	Most common AEs were cytopenias, mucositis, diarrhea and FN	CR: 97% (2 patients with positive PET had negative biopsy)

ICI partners: BV or polychemotherapy (ICE, GDP…)

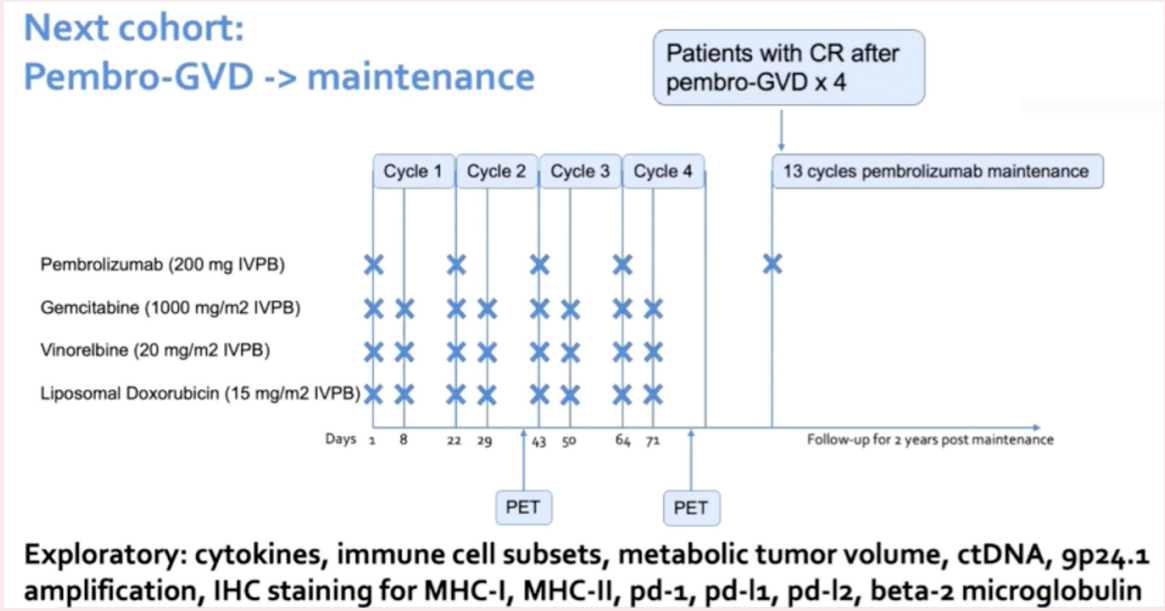
Pembro-GVD as first salvage

Part I study: 39 pts

- **Eligibility**: relapsed or refractory cHL following 1-line of therapy
- **Primary endpoint**: CR (by Deauville 3) rate after 2-4 cycles



Part II study: 33 pts



Moskowitz AJ et al, JCO 2021; Moskowitz AJ et al, ISHL 2022

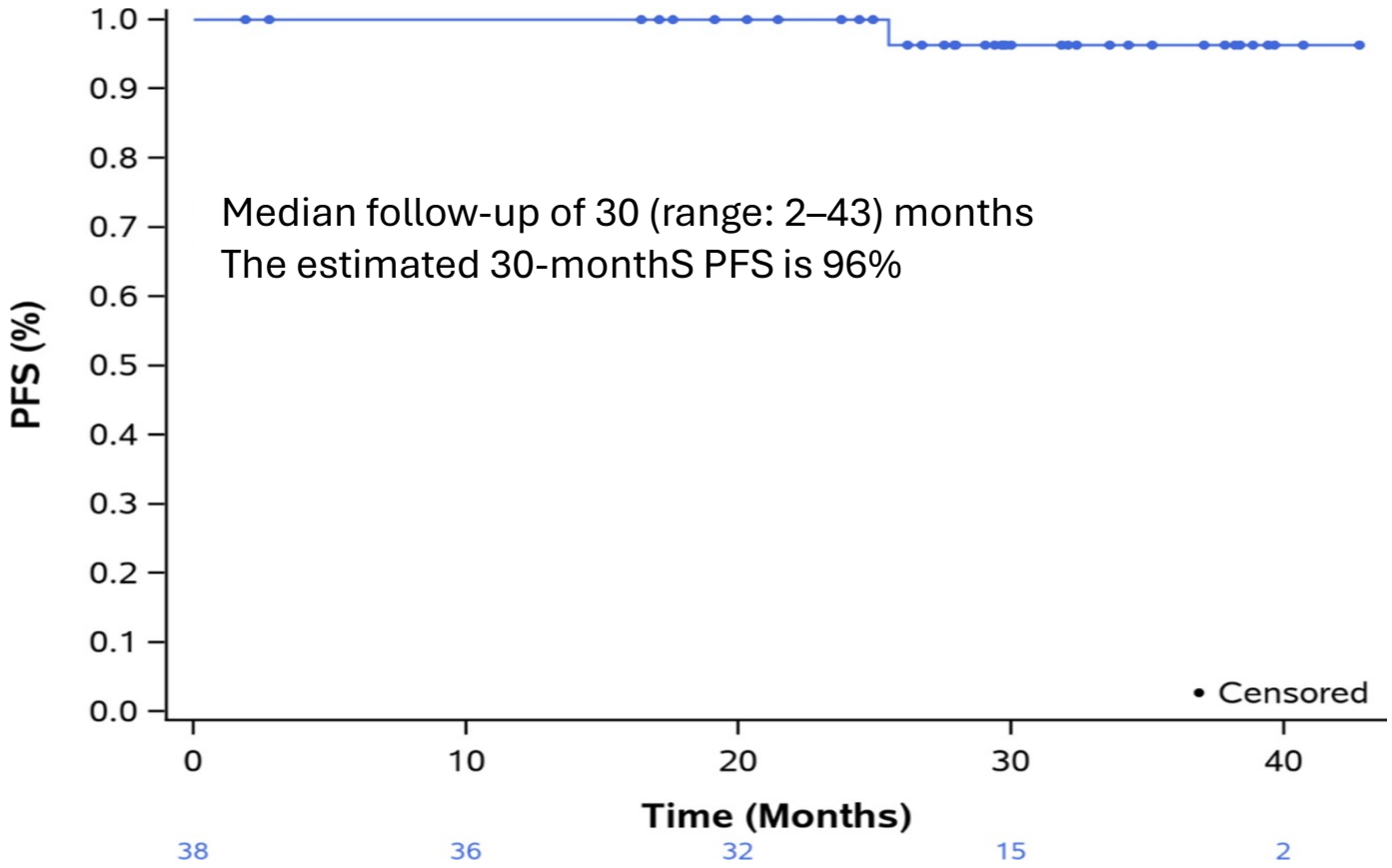
Pembro-GVD as first salvage

Response	(%)
CR	92.6%
ORR	100%

Toxicity	N (%)
Toxicity G 4-5	2 (3%)
-sepsis	1 (1.5%)
-pneumonitis	1 (1.5%)†
Toxicity G3	29 (40.5%)
-neutropenia	9 (12.5%)
-AST/ALT	7 (10%)
-mucositis	5 (7%)
-anemia	4 (5%)
-lung infection	2 (3%)
-rash	2 (3%)

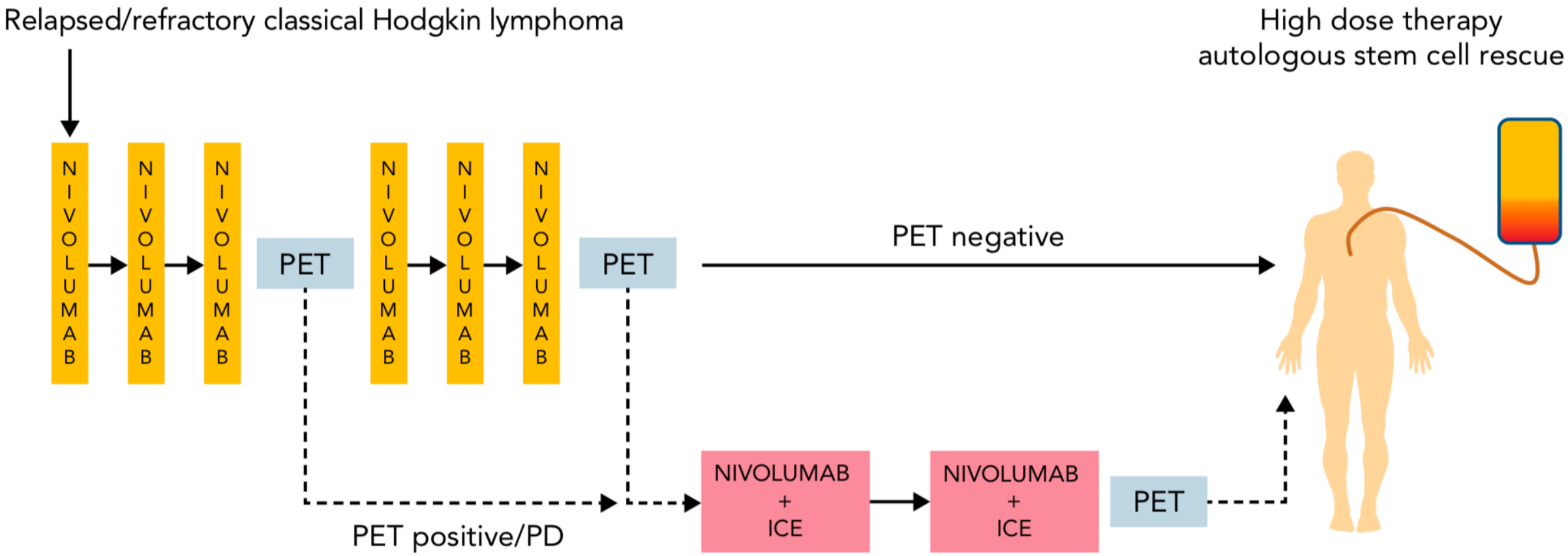
* 68 pts evaluable

PFS (part I= ASCT consolidation)



Moskowitz AJ et al, JCO 2021; Moskowitz AJ et al, ISHL 2022

Nivo-ICE as first salvage



Mei et al, Blood 2022

Nivo-ICE: efficacy

OUTCOME	
End of protocol therapy (43 pts)	
ORR	93%
CR	91%
End of Nivo response (43 pts)	
ORR	81%
CR	71%
End of Nivo+ICE response (9 pts)	
ORR	100%
CR	89%
2y PFS all patients	72%
2y PFS transplanted patients*	94%
Median follow-up	30.7 months

* 33 PTS (26 AFTER NIVO MONOTHERAPY)

Mei et al, Blood 2022

ICI combination therapy for first-line HL

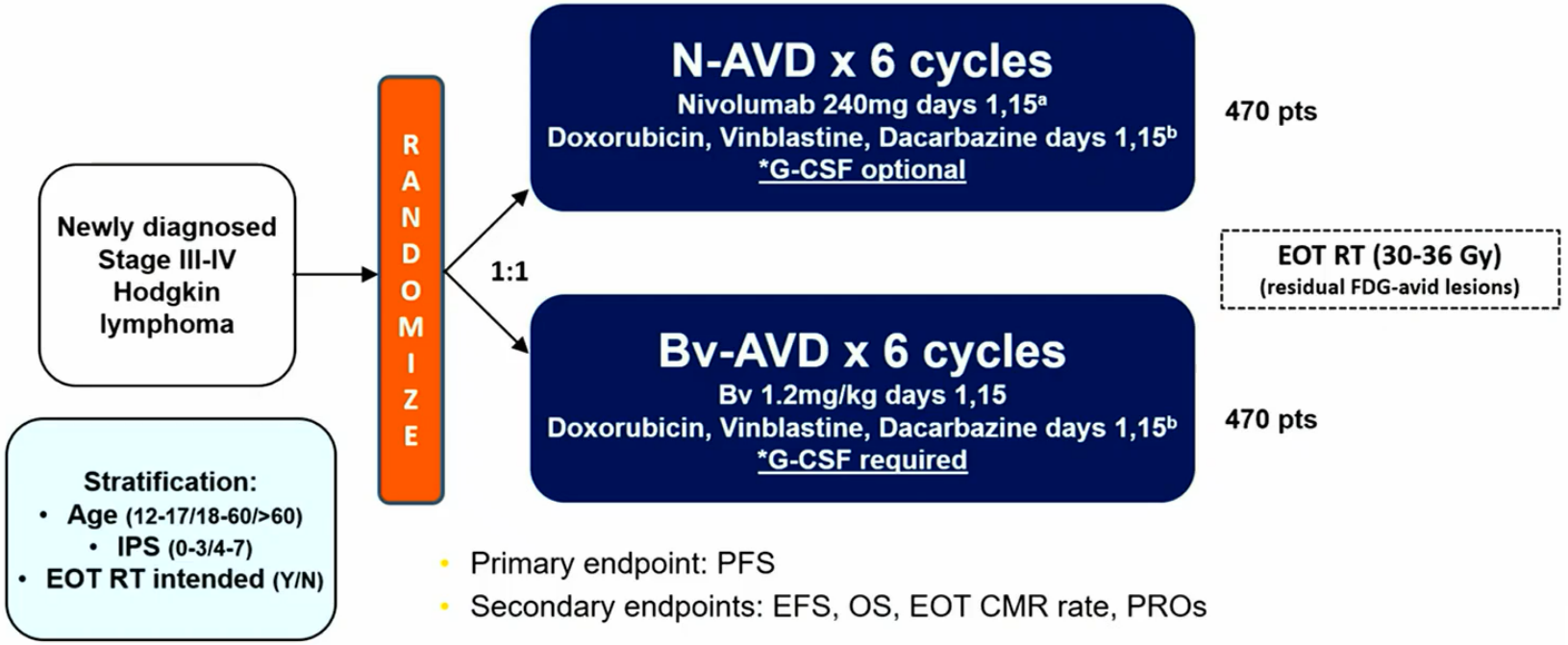
Frontline trials of ICIs

Study	Study type	Setting	No. of patients	Regimen used, including ICIs	AEs	Efficacy
Ramchandren et al.	Phase 2	Newly diagnosed advanced-stage HL	51	Nivolumab monotherapy (240 mg Q2W for 4 doses) then N+AVD, 6 combination cycles (12 doses, Q2W) (nivolumab, 240 mg; doxorubicin, 25 mg/m^2; vinblastine, 6 mg/m^2; and dacarbazine, 375 mg/m^2)	Grade 3/4 occurred in 59%. Most common were neutropenia (49%) and FN (10%)	ORR: 84% CR: 80%
Allen et al.	Phase 2	Newly diagnosed HL Stages I–IV	30	Three cycles of pembrolizumab, 200 mg Q3W; subsequently, 4–6 cycles of AVD based on initial stage	Grade IV AEs were neutropenia (33%), transaminitis (3%), and sepsis (3%)	CR: 37% CR after 2 cycles of AVD: 100%
Bröckelmann et al.	Phase 2	Newly diagnosed early-stage unfavorable HL, <60 years	110	Group A: 4 cycles of N+AVD (Days 1 and 15 of each 28-day cycle) Group B: Sequential therapy, starting with 4x nivolumab in 2-weekly intervals, followed by 2 cycles of N+AVD and 2x AVD. Both groups received 30 Gy ISRT	Grade III/IV AEs were observed in 76% (Group A) and 80% (Group B). Most common were hematological toxicities: Anemia, leukopenia, thrombocytopenia or infection	ORR: Group A (100%), Group B (98%) CR: Group A (83%), Group B (84%)
Yasenchak et al.	Phase 2	Newly diagnosed elderly (≥60 years) HL	21	BV, 1.8 mg/kg + nivolumab, 3 mg/kg Q3W for 16 cycles	Most common Grade 3 AEs were elevated lipase (19%) and peripheral motor neuropathy (14%)	ORR: 100% CR: 72%
Cheson et al.	Phase 2	Newly diagnosed elderly (≥60 years) HL or unsuitable for ABVD	46	BV, 1.8 mg/kg + nivolumab, 3 mg/kg Q3W for 8 cycles	Most common Grade 3 AEs were neutropenia (17%) and PN (11%)	ORR: 61% CR: 46%

ICI partners: BV or polychemotherapy (mainly AVD)

SWOG 1826 trial

S1826 Study Design



Key Inclusion

- Age ≥ 12 years old
- HIV+ eligible, if controlled
- Zubrod PS 0-2 (Peds: Lansky)
- LVEF ≥ 50% (or SF ≥ 27%)
- CrCl ≥ 30 mL/min (Peds: CrCl/GFR ≥ 70, SCr ≤ 1.5 ULN)
- Tbili ≤ 2 x ULN and AST/ ALT ≤ 3 x ULN

Herrera AF et al, ICML 2023

SWOG 1826 trial: baseline characteristics

Baseline characteristics	N+AVD n=489 N (%)	BV+AVD n=487 N (%)
Age, median (range)	27 (12–83)	26 (12–81)
12–17 years	120 (25)	117 (24)
18–60 years	323 (66)	323 (66)
≥61 years	46 (9)	47 (10)
Female sex	218 (45)	213 (44)
Race		
White	375 (77)	364 (75)
Black	57 (12)	56 (11)
Asian	11 (2)	17 (3)
Other/Unknown	46 (9)	50 (10)
Hispanic	68 (14)	59 (12)

Baseline characteristics	N+AVD n=489 N (%)	BV+AVD n=487 N (%)
Stage		
III	187 (38)	167 (34)
IV	301 (62)	317 (65)
Not reported	1 (0.2)	3 (1)
B-symptoms present	286 (58)	274 (56)
IPS score		
0–3	331 (68)	330 (68)
4–7	158 (32)	157 (32)
Bulky disease >10 cm	155 (32)	131 (27)
HIV+	10 (2)	5 (1)

Representative study, inclusive of high-risk patients

Herrera AF et al, ICML 2023

BV+AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; HIV, human immunodeficiency virus; IPS, International Prognostic Score; N+AVD, nivolumab, doxorubicin, vinblastine, dacarbazine.
Herrera AF. Presented at the American Society for Clinical Oncology Annual Meeting, 2–6 June 2023, Chicago, IL: Oral presentation LBA4.

SWOG 1826 trial: toxicity

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Neutropenia	268 (55%)	227 (47%)	152 (32%)	118 (25%)
Anemia	185 (38%)	29 (6%)	207 (44%)	42 (9%)
Thrombocytopenia	48 (10%)	8 (2%)	82 (17%)	15 (3%)
Received G-CSF	265 (54%)		463 (98%)	
Bone pain	39 (8%)		94 (20%)	

More neutropenia after N-AVD
More growth factor use, bone pain in Bv-AVD arm

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Gr N (%)	Gr ≥ 3 N (%)	Any Gr N (%)	Gr ≥ 3 N (%)
Peripheral sensory neuropathy	138 (29%)	6 (1%)	262 (55%)	37 (8%)
Peripheral motor neuropathy	20 (4%)	1 (0%)	35 (7%)	6 (1%)

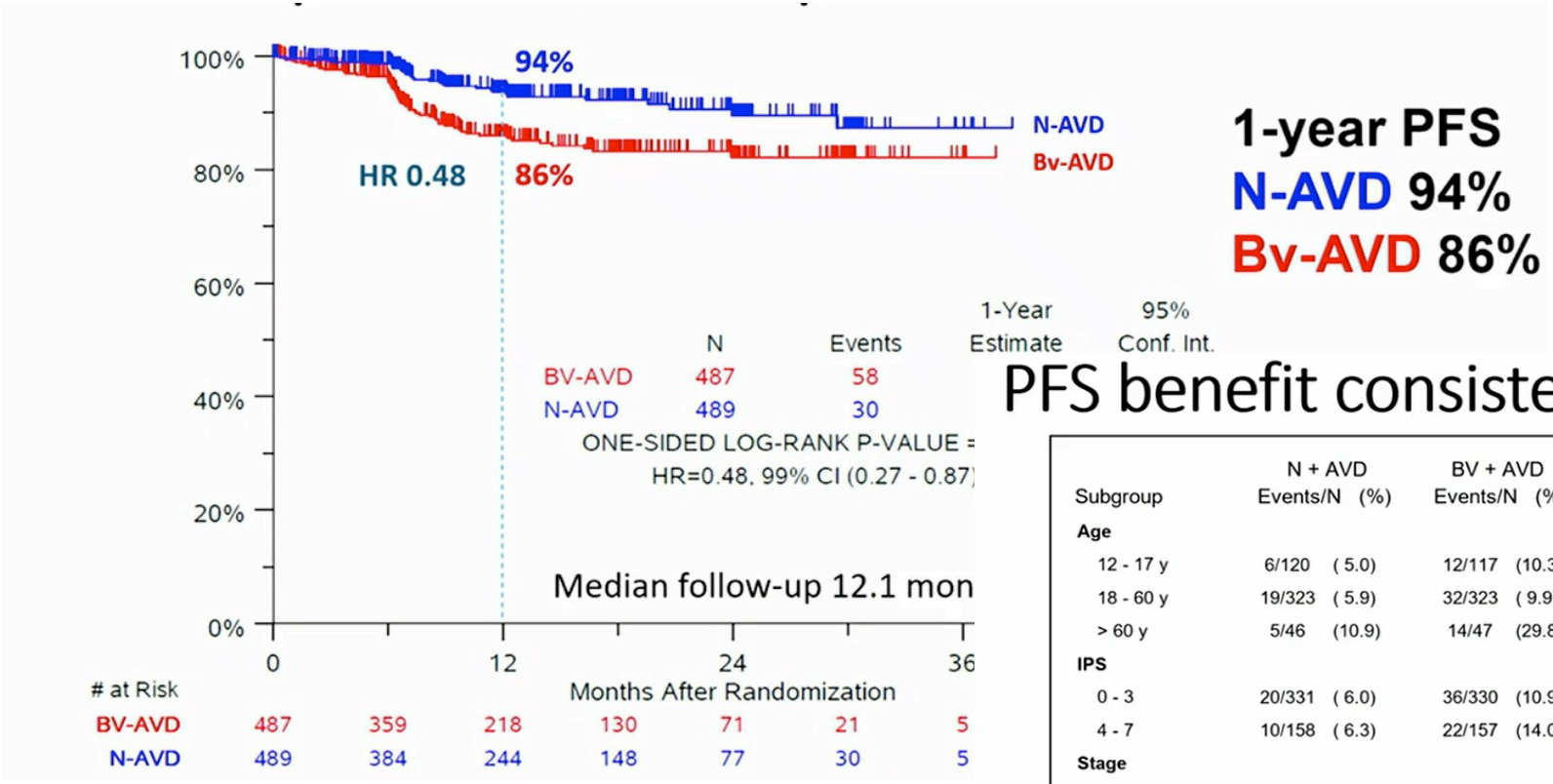
More neuropathy in Bv-AVD arm

Toxicity	N-AVD n = 483		Bv-AVD n = 473	
	Any Grade No (%)	Grade ≥ 3 No (%)	Any Grade No (%)	Grade ≥ 3 No (%)
ALT increased	156 (32%)	22 (5%)	194 (41%)	22 (5%)
AST increased	120 (25%)	12 (2%)	153 (32%)	13 (3%)
Rash maculo-papular	51 (11%)	4 (1%)	58 (12%)	0 (0)
Hypothyroidism	33 (7%)	1 (0%)	3 (1%)	0 (0)
Rash acneiform	18 (4%)	0 (0)	12 (3%)	0 (0)
Pneumonitis	10 (2%)	2 (0%)	15 (3%)	10 (2%)
Gastritis	10 (2%)	3 (1%)	8 (2%)	0 (0)
Hyperthyroidism	14 (3%)	0 (0)	0 (0)	0 (0)
Colitis	5 (1%)	1 (0%)	6 (1%)	4 (1%)

Low rates of immune-related adverse events

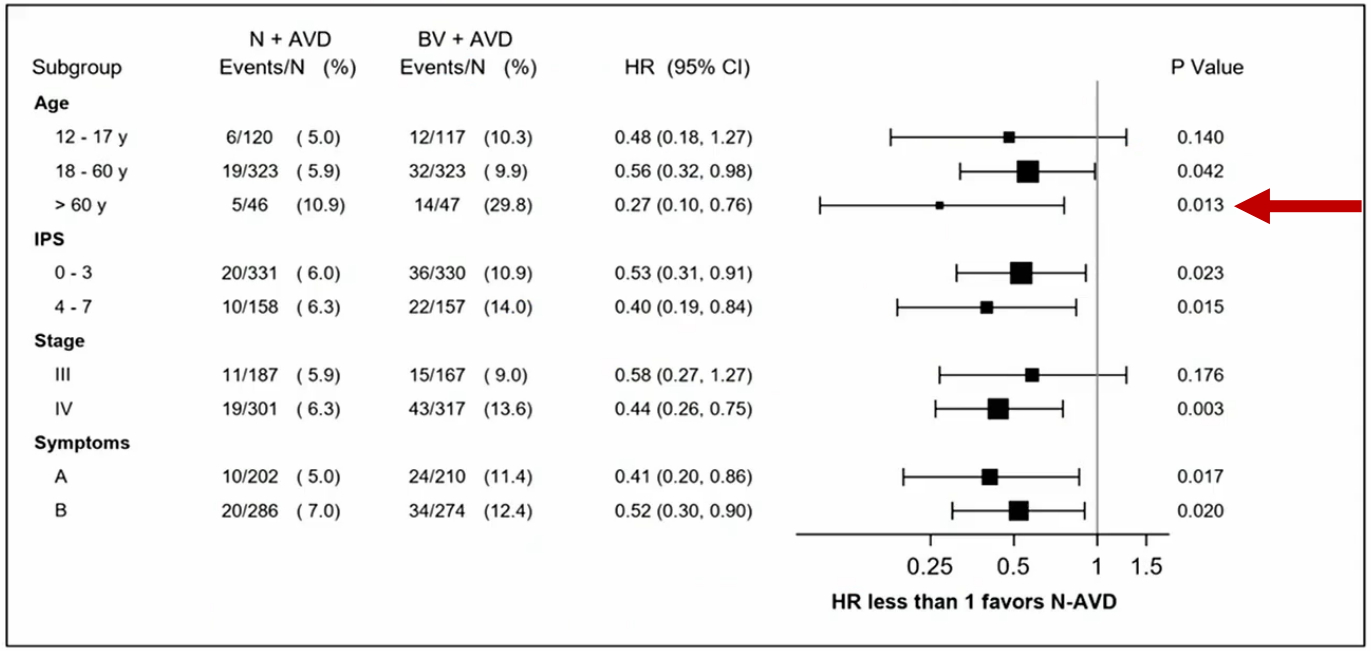
Herrera AF et al, ICML 2023

SWOG 1826 trial: survival



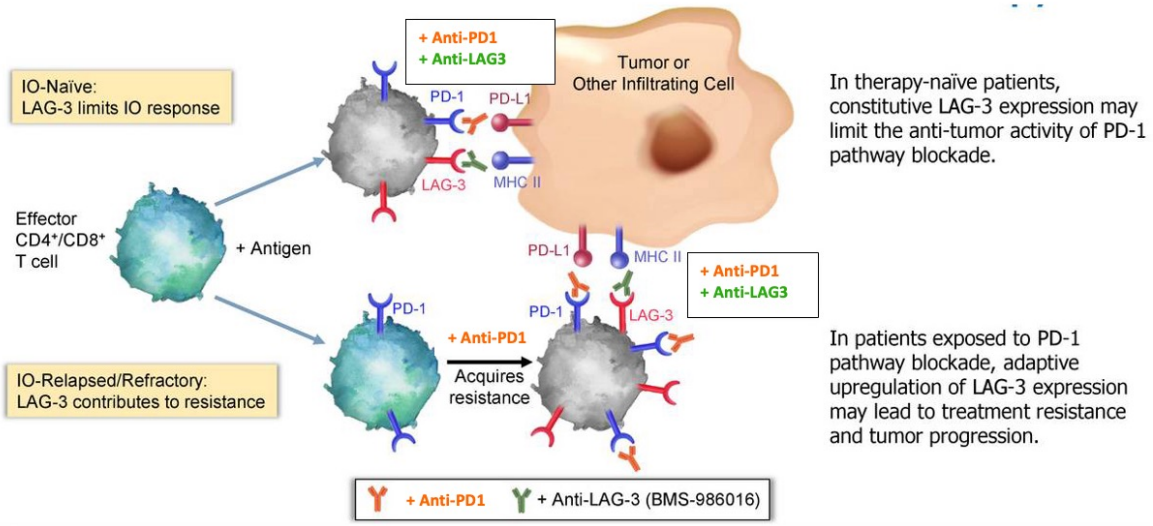
1-year PFS
N-AVD 94%
Bv-AVD 86%

PFS benefit consistent across subgroups



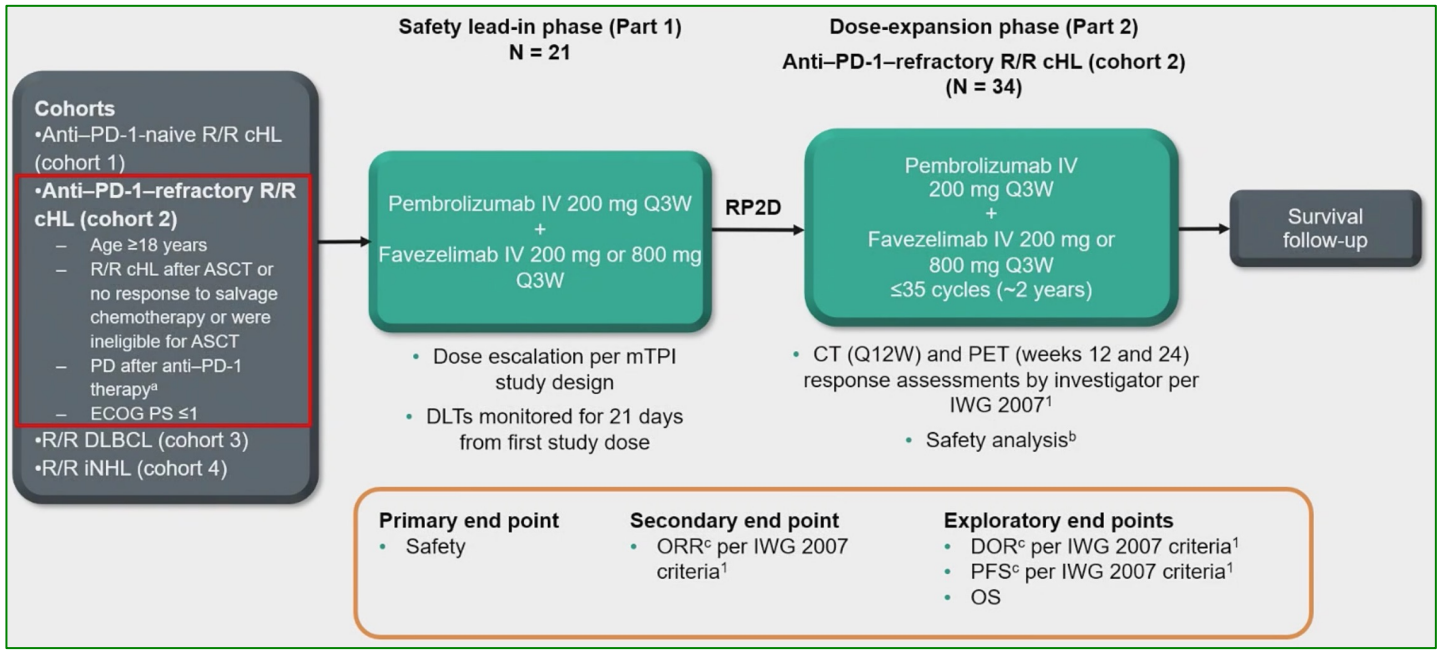
Herrera AF et al, ICML 2023

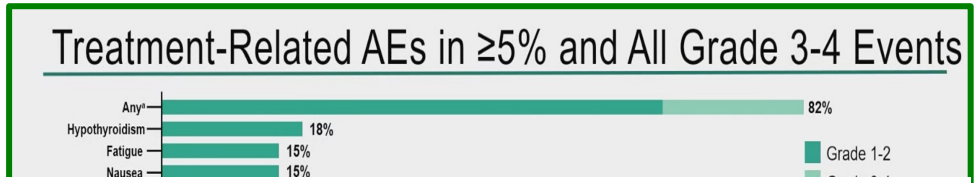
New combos: Favezelimab (anti-LAG-3) + Pembrolizumab



In therapy-naïve patients, constitutive LAG-3 expression may limit the anti-tumor activity of PD-1 pathway blockade.

In patients exposed to PD-1 pathway blockade, adaptive upregulation of LAG-3 expression may lead to treatment resistance and tumor progression.



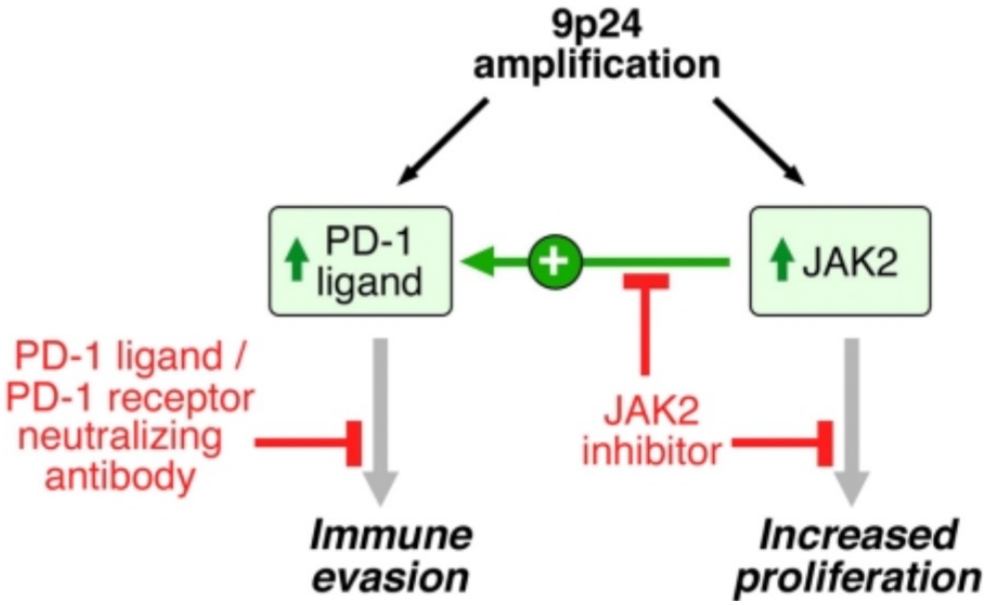


Response	Cohort 1 (N=30) Anti-PD1 naive	Cohort 2 (N=34) Anti-PD1 refractory
ORR per IWG 2007	22 (73%)	10 (30%)
CR	7 (23%)	3 (9%)
PR	15 (50%)	7 (21%)
SD	11 (32%)	11 (32%)
PD	7 (21%)	7 (21%)
NA	5 (15%)	5 (15%)
Median fw	13.5 mo	29.3 mo
Median PFS	19 mo	10.7 mo
Median OS	Not reached	Not reached
Median DOR	Not reached	21.9 mo

Timmermann et al, ASH 2023

New combos: Nivolumab + Ruxolitinib

- **Phase I/II multicenter, open-label, dose escalation/dose-expansion study:** Ruxolitinib was administered at 3 dose levels: 10, 15 or 20 mg orally twice a day continually with nivolumab at fixed dose 3 mg/kg IV every 2 weeks

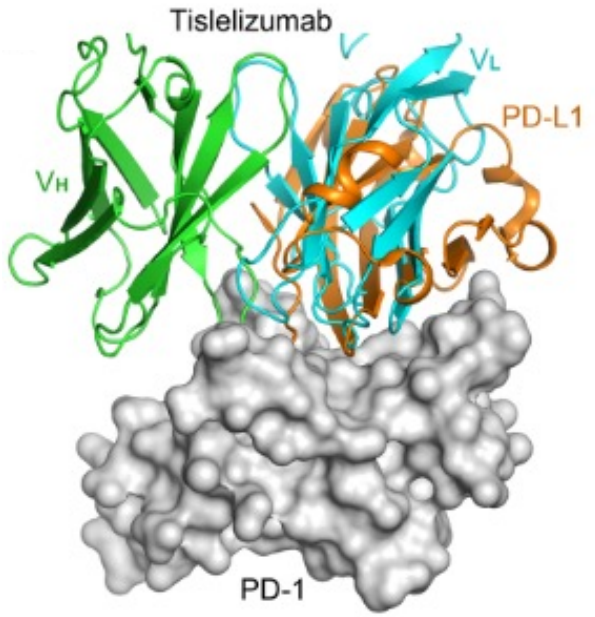


Previous treatments	N=24
CPI	100%
CPI refractory	78%

Response	N=19
ORR	42%
CR	26%
PR	16%
SD	16%
Median DOR	16.5 mo
Median fw	20.7 mo
PFS at 2y	45%

Bachanova V et al, Hematol Oncol 2023

New CPI: Tislelizumab

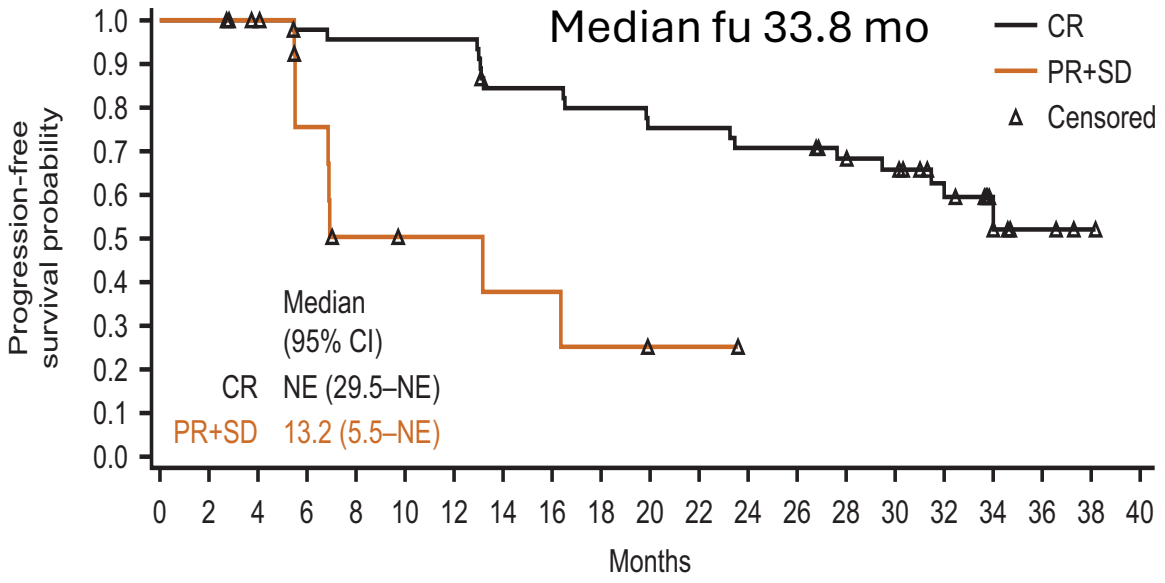


Phase II, open-label, single-arm study:

70 r/r cHL patients: Tislelizumab 200 mg iv, every 3 wks until PD, unacceptable toxicity, or study termination.

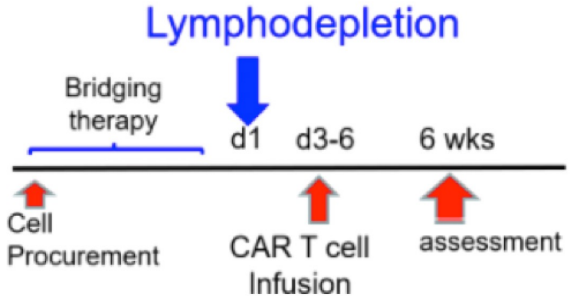
Response: ORR 87.1%; CR 62.9% *(Song et al. Leukemia 2020)*

- BGB-A317
- humanized IgG4 mAb
- high affinity and specificity for programmed cell death protein 1 (PD1)
- superior antitumor activity compared to nivolumab in mice

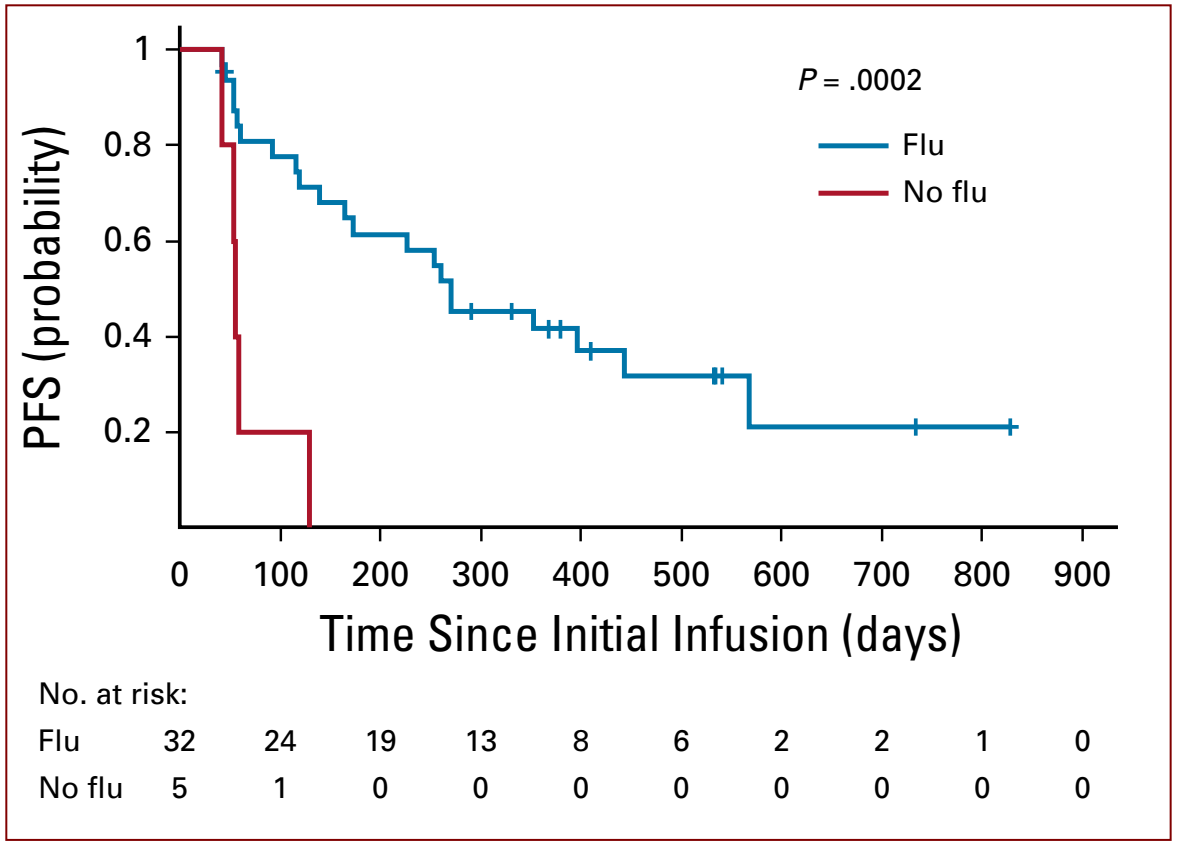


Song et al, Clin Cancer Res. 2022

Anti-CD30 CAR-T Cell Therapy in R/R HL



Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
ORR				
CR + PR	23 (62)	0 (0)	12 (80)	11 (65)
Response rate				
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)
SD	4 (11)	1 (20)	1 (7)	2 (11)
PD	10 (27)	4 (80)	2 (13)	4 (24)



Median follow-up: 533 days; 1-year PFS 36%; 1-year OS 94%

Ramos C 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

High-risk defined by:
primary refractory disease or relapse within 12 months of initial therapy or extranodal involvement at the start of pre-transplantation salvage therapy

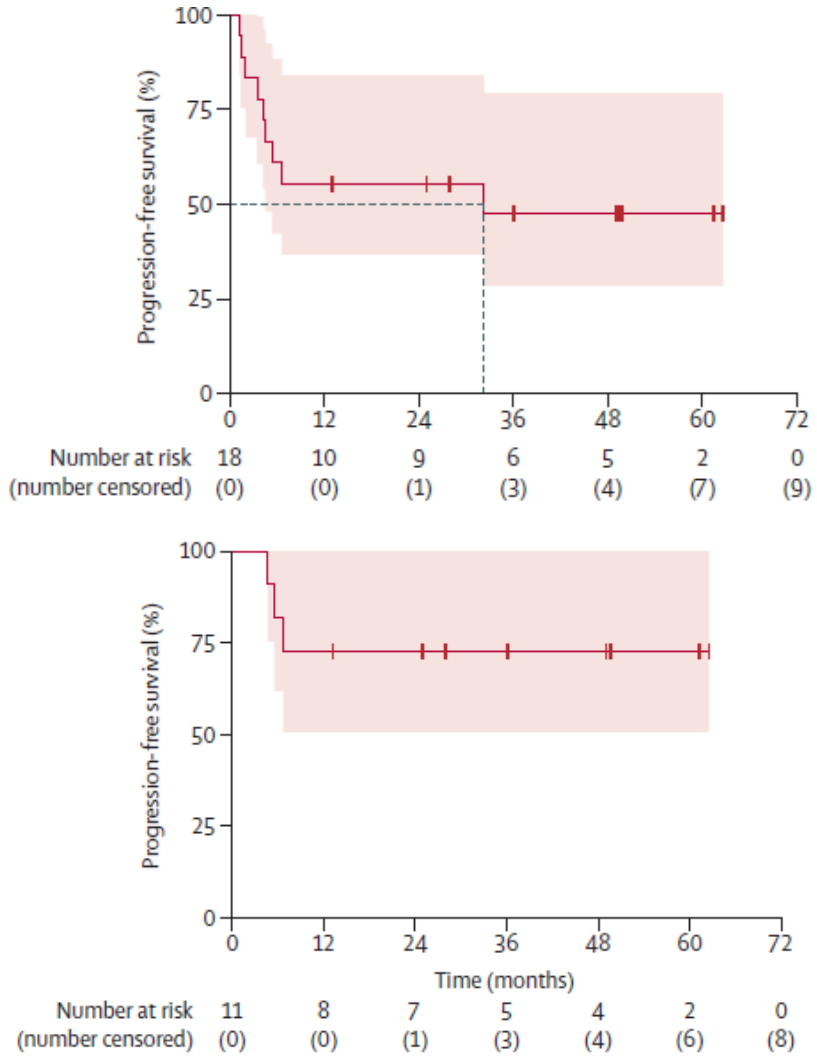
Patients were eligible to receive anti-CD30 CAR T-cell infusion following trilineage haematopoietic engraftment after BEAM and autologous HSCT

After haematopoietic engraftment, patients received a single intravenous dose of CAR T cells on one of three dose levels:
dose level 1: 2×10^7 CAR T cells per m^2
dose level 2: 1×10^8 CAR T cells per m^2
dose level 3: 2×10^8 CAR T cells per m^2

Grover NS et al, Lancet Hematol 2024

Anti-CD30 CART as post ASCT consolidation

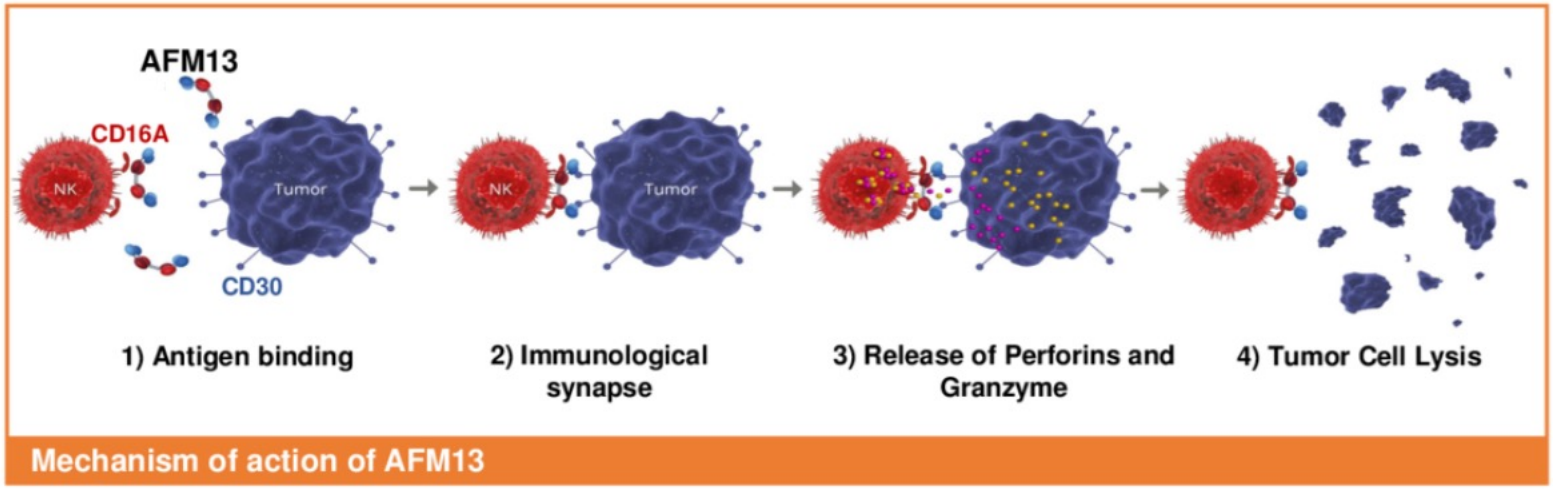
	Grade 1–2	Grade 3	Grade 4
Anaemia	1 (6%)	1 (6%)	0
Aspartate aminotransferase increased	4 (22%)	0	0
Cytokine release syndrome	1 (6%)	0	0
Diarrhoea	3 (17%)	0	0
Dizziness	2 (11%)	0	0
Fatigue	3 (17%)	0	0
Headache	2 (11%)	0	0
Hypocalcaemia	2 (11%)	0	0
Lymphocyte count decreased	6 (33%)	2 (11%)	0
Nausea	6 (33%)	0	0
Neutrophil count decreased	3 (17%)	0	1 (6%)
Platelet count decreased	4 (22%)	1 (6%)	0
Rash maculopapular	1 (6%)	1 (6%)	0
Vomiting	2 (11%)	0	0
White blood cell count decreased	4 (22%)	2 (11%)	0



Grover NS et al, Lancet Hematol 2024

AFM13 and Pembrolizumab

- AFM13 is a CD16A/CD30 tetravalent, bispecific antibody stimulating innate immune cells, such as natural killer (NK) cells and macrophages
- AFM13 binds CD16A on innate cells and binds CD30 on HL cells, acting as a bridge to recruit and activate innate immune cells in close proximity to tumor cells
- By engaging CD16A-positive NK cells, AFM13 leads to NK-cells mediated killing of CD30-positive lymphoma cells

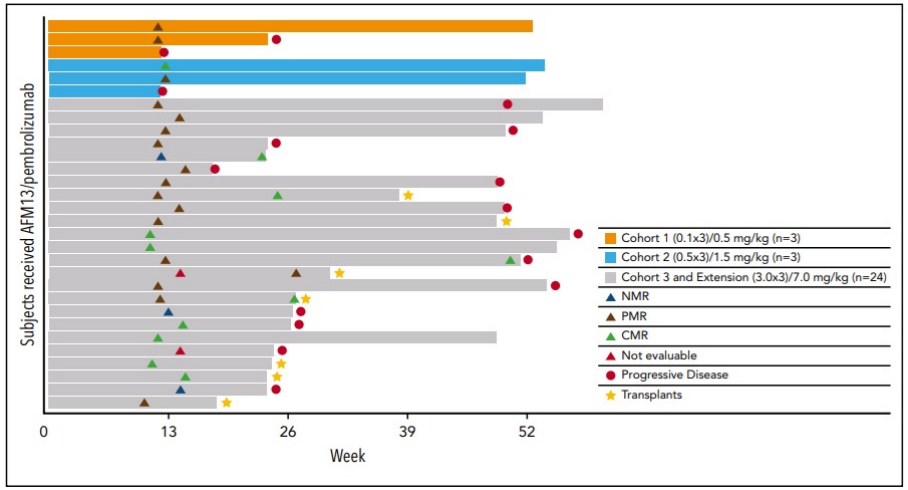


Mechanism of action of AFM13

Population Characteristics

Characteristic	Total Patient Population (N=30) N Number (%)
Age, years, median (range)	34 (18 to 73)
Gender	Female 10 (33%); Male 20 (67%)
Prior therapies, no.	
Unknown	1 (3%)
3	14 (47%)
4	6 (20%)
5	3 (10%)
6	4 (13%)
7	2 (7%)
Prior auto. stem cell transplant.	11 (37%)
Prior brentuximab vedotin (BV)	30 (100%)
BV as last therapy	13 (43%)
Refractory vs. relapsed	57% vs. 43%

Demographic and baseline characteristics, safety population



Bartlett N et al, Blood 2020

New drugs: CD47/PD-L1 Bispecific Antibody

IBI322 is an anti-CD47/PD-L1 bispecific antibody that blocks both the PD-1/PD-L1 and CD47/SIRP-α pathways

CD47-SIRPα

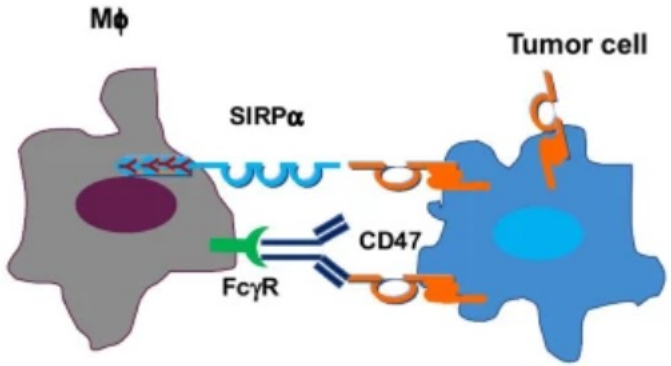
CD47 — Integrin associated protein (IAP)

- Ig-like protein
- 5 membrane spanning segments
- Short cytoplasmic tail
- Ubiquitous expression including T, B, RBC, platelet, HSC

SIRPα — Signal regulatory protein

- Ig-like protein
- Single transmembrane domain
- Long cytoplasmic region with 4 Y-sites
- High in Mϕ, DC, neutrophils, neurons,
- Low in fibroblasts and endothelial cells.

"Don't eat me" signal versus "eat me" signal



- **Hematopoietic cells and solid tumor cells express high levels of CD47.**
- **High CD47 expression correlates with more aggressive disease and poorer clinical outcomes.**
- **CD47 delivers an inhibitory "don't eat me" signal to macrophages via binding to SIRPα.**
- **Fc-FcγR engagement activates "eat me" signal to macrophages.**

"Don't eat me" signal versus "eat me" signal

Lian et al, Sci Rep 2019

CD47/PD-L1 BISPECIFIC ANTIBODY (IBI322) IN ANTI-PD-1 OR PD-L1 TREATMENT-RESISTANT CLASSICAL HODGKIN LYMPHOMA: A PHASE I STUDY

Phase I study: IBI322 (45 mg/kg intravenous Q2W) until unacceptable toxicity or disease progression, or up to 24 mo

Previous treatments	N=24
CPI Primary resistent	33.3%
CPI Secondary resistent	66.7%

Safety	All grade	Grade >3
TRAE	91.7%	41.7%
lymphopenia	62.5%	29.2%
anemia	62.5%	
leukopenia	20.8%	
trombocytopenia	20.8%	
irAEs	16.7%	

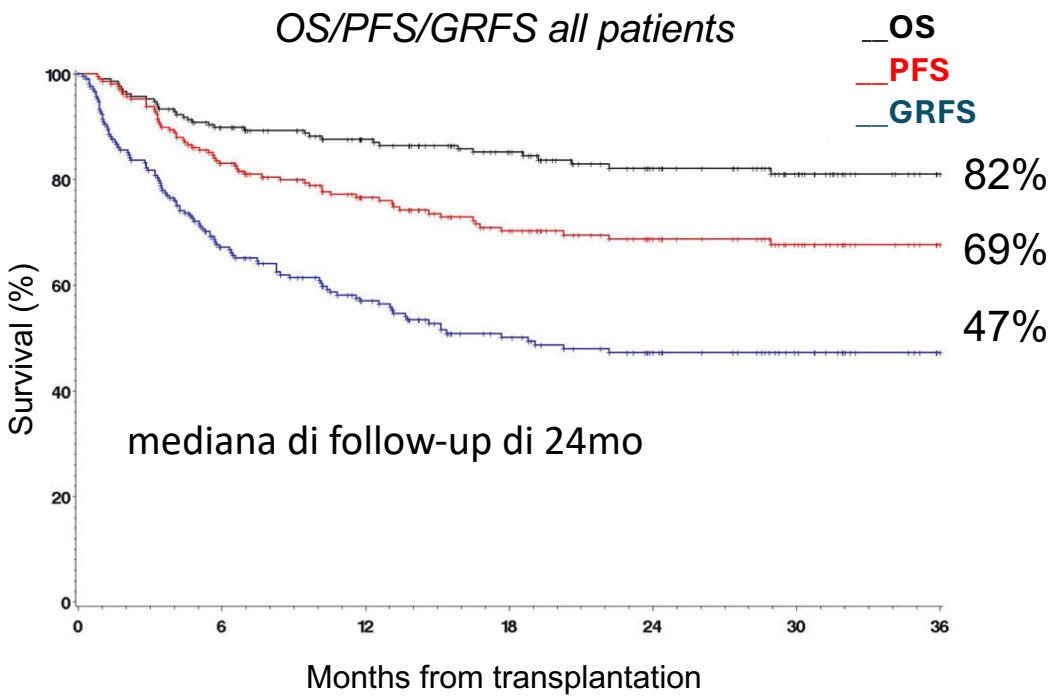
Response	ALL N=23	Primary resistent N=7
ORR	47.8%	57.1%
CR	17.4%	42.9%
PR	30.4%	14.2%
SD	43.5%	28.6%
PD	8.7%	14.3%
DCR	91.3%	85.7%

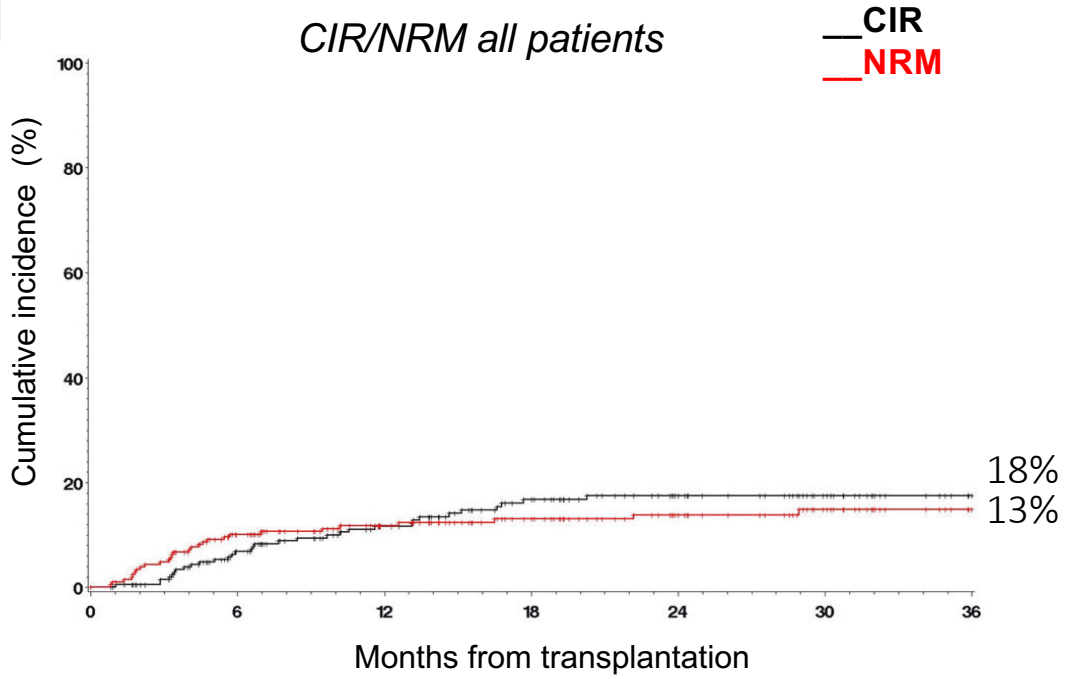
Zhang et al, EHA 2023

Does Allogeneic-SCT still play a role in the era of new drugs?

Auto-SCT failure: Anti-PD1 as bridge to allo-SCT

- 209 patients
- AlloSCT after a median of 10 (range 1-74) doses of AntiPd1
- Median time from last dose of CPIs to alloSCT: 81 days (range 17-1029)
- Haploidentical (44%), matched sibiling (23%), MUD (27%)
- PTCy as part of their GVHD prophylaxis regimen 56%





Recipients of PTCy

-Lower 2y CI of cGVHD (25% vs. 46%, p = 0.002)

-Similar rate of severe aGVHD

An interval **of > 80** days from PD-1 to alloHCT (the median value in this cohort) was associated with a **lower risk of grade grade 3–4 aGVHD** (9% vs 21%) (HR 0.4, p = 0.01)

Merryman et al. Leukemia, 2021

Summary

- ICIs represent a revolutionary approach for HL treatment with significative improval in prognosis with a peculiar but managable toxicity
- ICIs as single agents for R/R HL allowed an excellent disease control and re-treatment for responding patients can be an option, but concerns about definitive cure rate still remain
- ICIs can be effectively combined with chemo, brentuximab-vedotin and small molecules, both for salvage and first line treatment
- Anti-CD30 CAR-T displayed so far a dismal efficacy for treatment of R/R HL; promising data on post-ASCT consolidation and new cellular products are under developement
- Encouraging preliminary data on bispecific abs
- Do not forget allogeneic stem cell transplantation, that is the oldest and, so far, the only potentially curative immunotherapy approach for HL

Thanks for your attention!

Agenda

- CPI:
  - update on nivolumab and pembrolizumab as single agents or in combination (with chemo or small molecules)
  - new CPIs
- CAR-T
- Bispecific antibodies
- Allotx

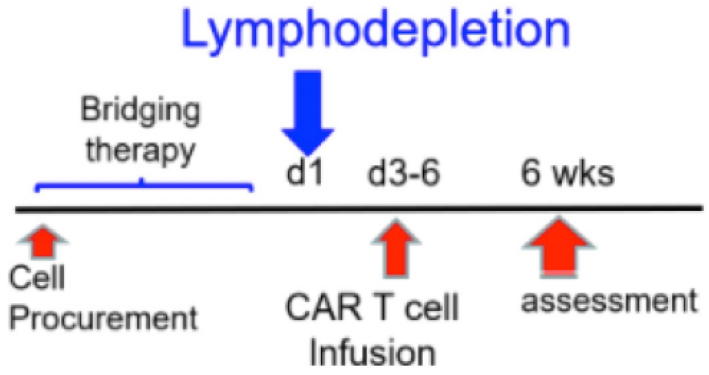
Anti-CD30 CAR-T cells co-expressing CCR4

Phase I clinical trial

Key inclusion criteria

HL or CD30 CTCL; Age ≥ 18 years; 2 prior lines of therapy including BV

Primary objective: safety; Secondary objectives: efficacy - PFS, OS and ORR



Lymphodepletion

Bendamustine 70 mg/m^2/day) x days

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

Safety

No dose limiting toxicities

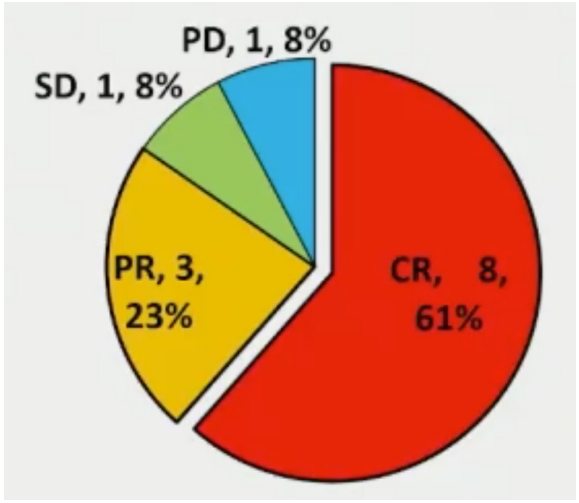
No ICANS

3 pts with CRS

- 2 G2 witch resolved with TCL
- 1 self-limiting G1 CRS
- Onset day 13-19

Grover NS et al, ASH 2021

Anti-CD30 CAR-T cells co-expressing CCR4



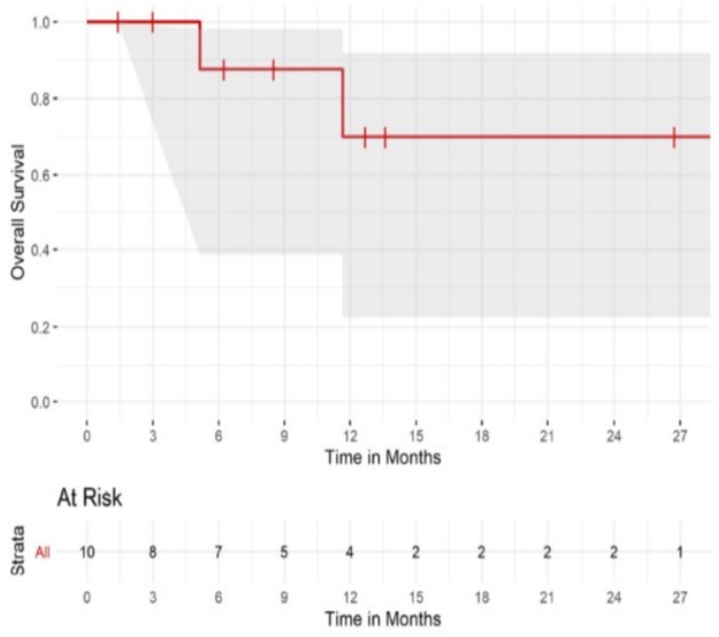


Figure 1: Overall Survival for All Patients

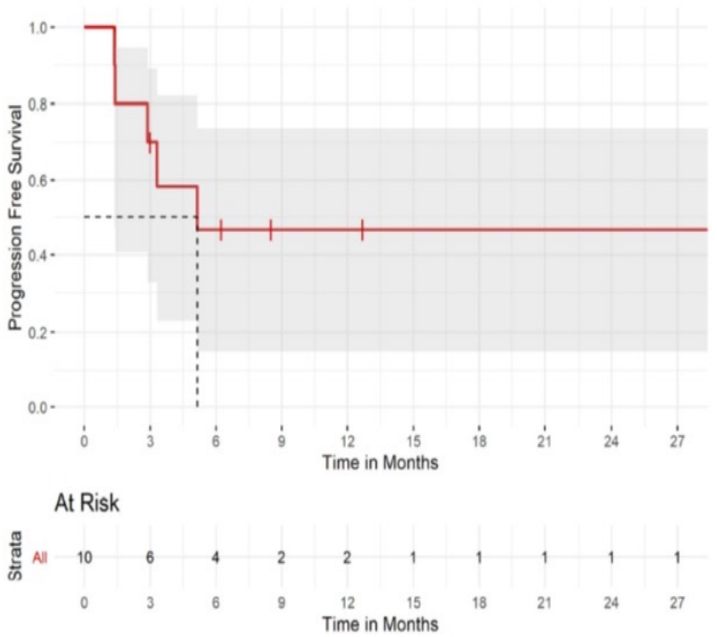
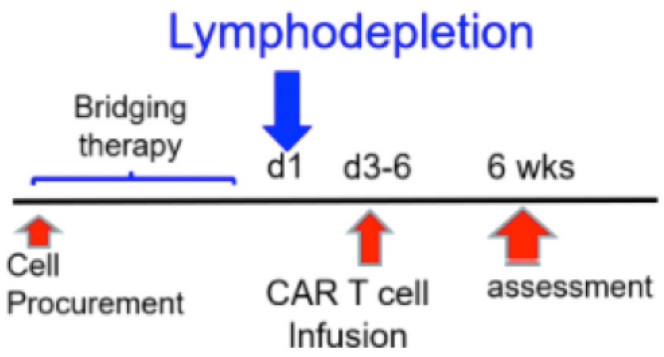


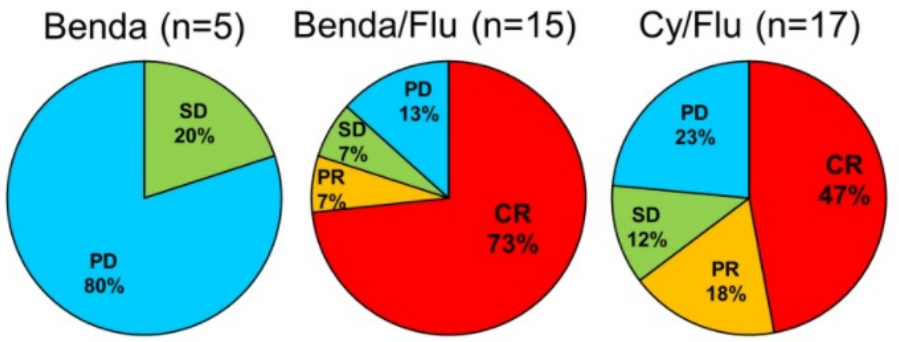
Figure 2: Progression Free Survival for All Patients

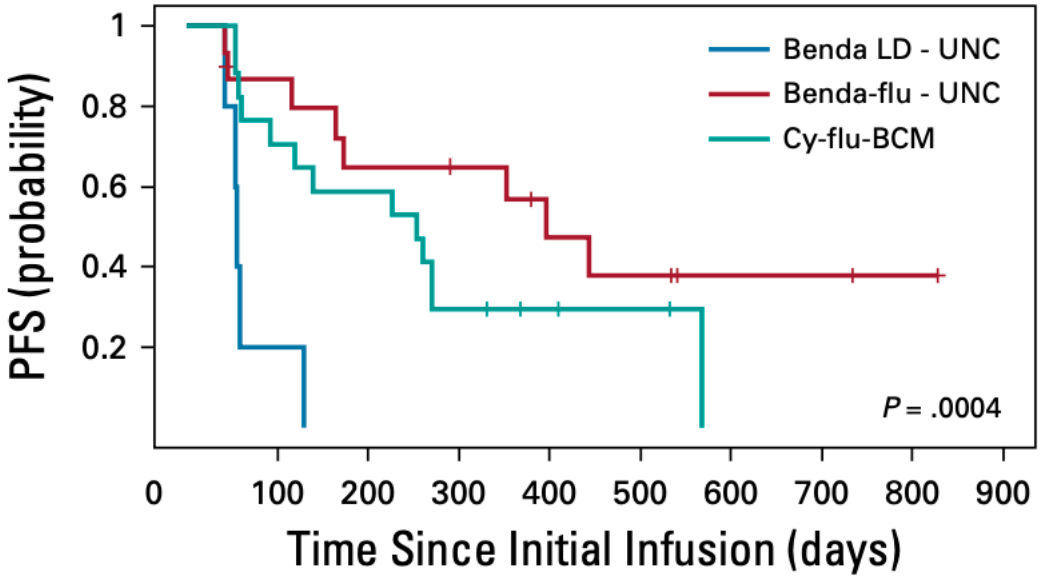
Grover NS et al, ASH 2021

New agents: CD30 directed CAR-T cells



Bendamustine (90 mg/m^2/day) x 2 days
or
Bendamustine 70 mg/m^2/day) x days
Fludarabine (30 mg/m^2/day) x 3 days
or
Cyclophosphamide (500 mg/m^2/day) x 3 days
Fludarabine (30 mg /m^2/day) x 3 days



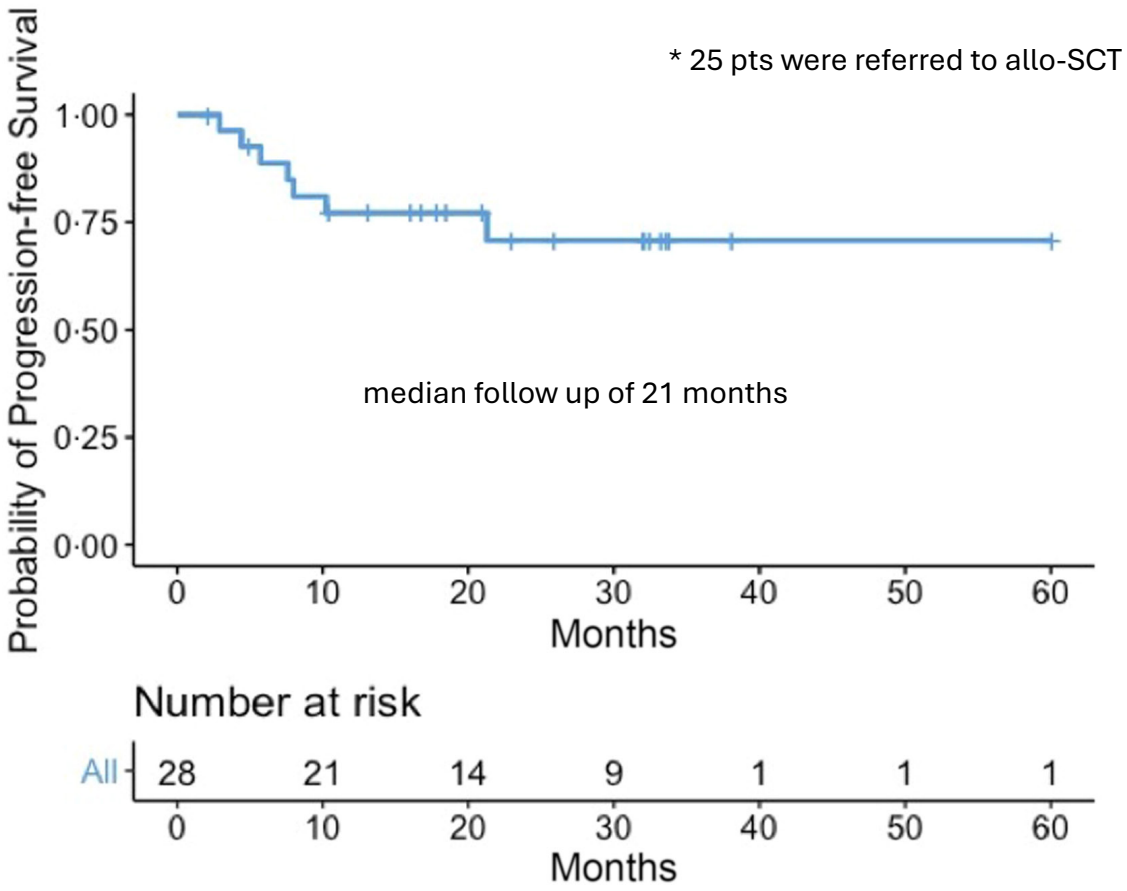


Ramos C et al, JCO 2020

Chemosensitization after CPI

	All *n* = 28
Gender	
Male	21 (75%)
Female	7 (25%)
Median age (range)	29 (19–71)
Stage prior to anti-PD1 therapy	
I–II	6 (21%)
III–IV	22 (79%)
Extranodal disease prior to anti-PD1 therapy	21 (75%)
B symptoms prior to anti-PD1 therapy	10 (36%)
Bulky disease prior to anti-PD1 therapy	6 (21%)
Response to anti PD-1 therapy	
Refractory	10 (36%)*
Responsive	18 (64%)
Median number of anti PD-1 cycles (range)	13 (3–72)
Median duration of anti PD-1 therapy (mos)	6 (2–34)
Median number of prior therapies (range)	4 (2–11)
Prior BV	28 (100%)
Prior ASCT	18 (64%)
Prior RT	14 (50%)
Response to last chemotherapy prior to anti-PD1 therapy	
Refractory	26 (92%)
Responsive	2 (8%)

Response rate: 93% ORR - 82% CR - 11% PR

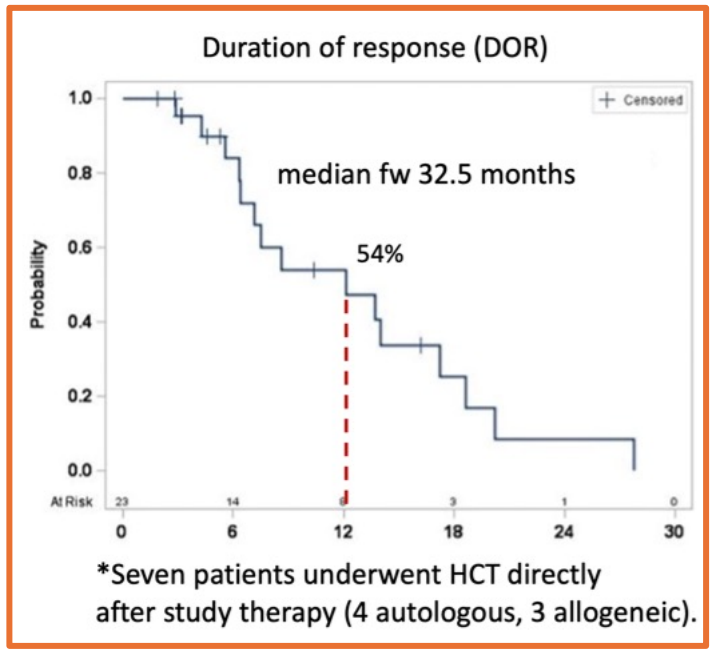


Calabretta E et al, BJH 2022

New combos: Pembrolizumab + Vorinostat

Baseline Characteristics	N (%)
Total	32 (100)
Age (median/range)	35 (18-79)
Prior lines (median/range)	3 (2-10)
Male	22 (69)
Stage I-II	8 (25)
Stage III-IV	24 (75)
B symptoms	4 (13)
Bulky disease (> 5cm)	6 (19)
Extranodal involvement	14 (44)
EBV+	4 (13)
EBV-	16 (50)
EBV unknown	12 (37)
Primary refractory	22 (69)
Refractory to most recent therapy	17 (53)
Prior BV	30 (94)
BV refractory	21 (66)
Prior PD1 blockade	25 (78)
PD1 refractory	18 (56)

Response	PD1 naïve (n=7)	PD1 Exposed Sensitive (n=7)	PD1 refractory (n=18)	Total (n=32)
Overall	7 (100)	6 (86)	10 (56)	23 (72)
CR	4 (57)	5 (71)	2 (11)	11 (34)
PR	3 (43)	1 (14)	8 (44)	12 (38)
SD	0 (0)	1 (14)	2 (11)	3 (9)
PD	0 (0)	0 (0)	6 (33)	6 (19)



Mei et al, Blood 2023