IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Il linfoma di Hodgkin recidivato/refrattario

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IRCCS Humanitas, Rozzano

Disclosures of Name Surname

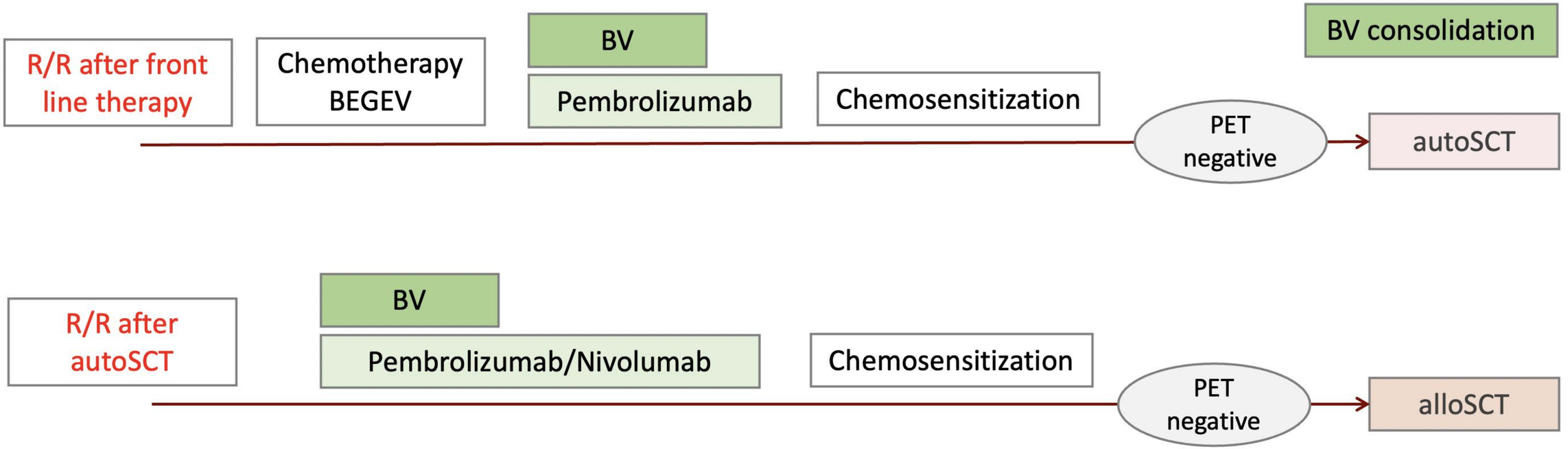
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda						x	

Outline

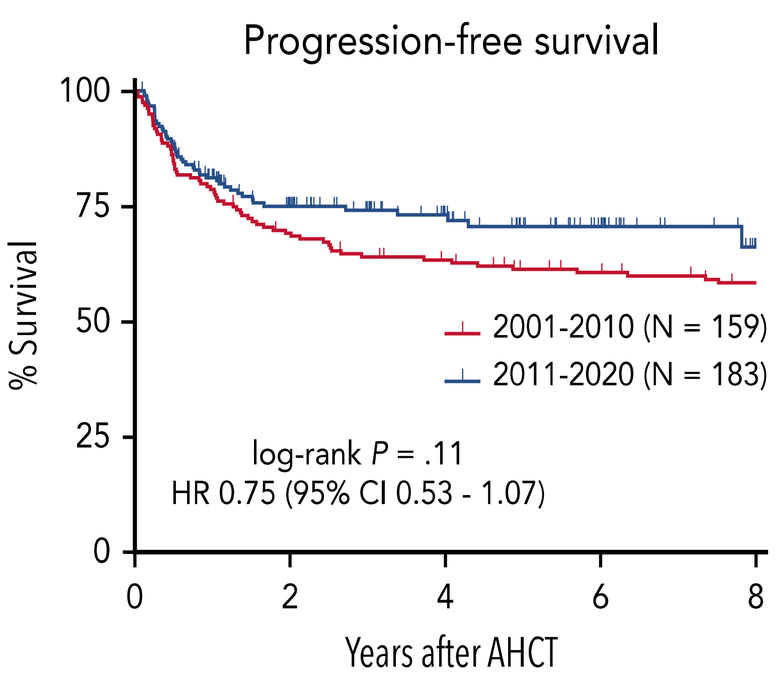
Immunotherapy
in the **standard treatment**

Immunotherapy
in future treatment strategies

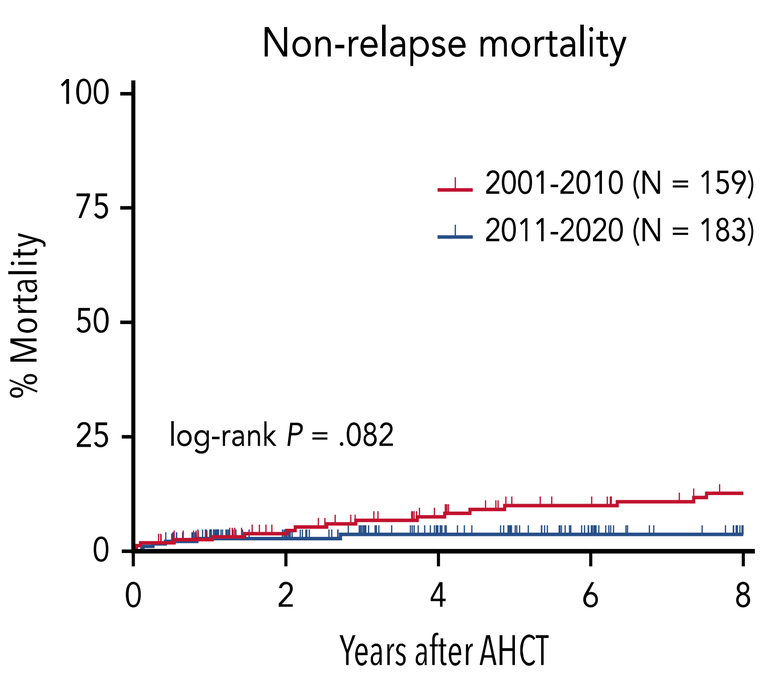
Standard treatment



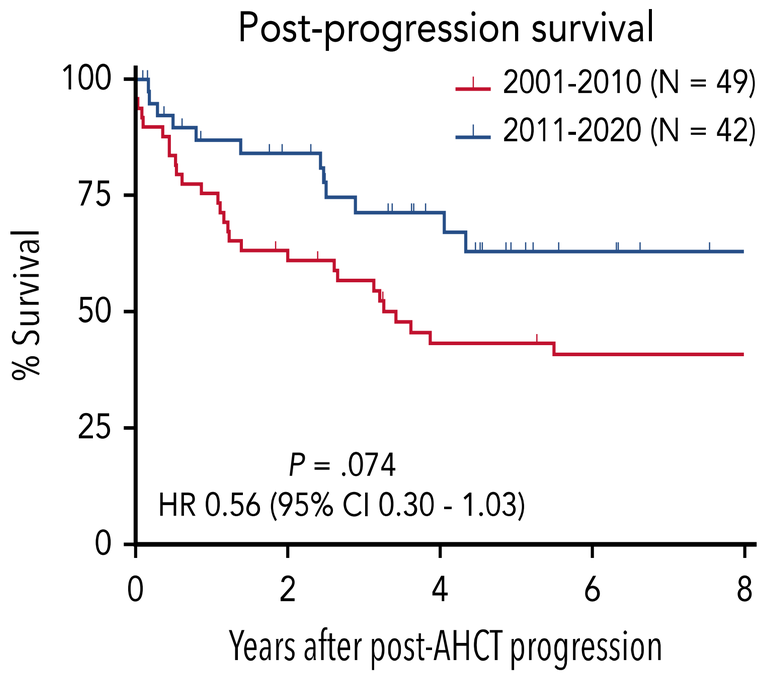
Outcome for r/r HL after autoSCT in the era of novel agents



No. at risk:					
	159	109	96	85	77
	183	101	64	35	11



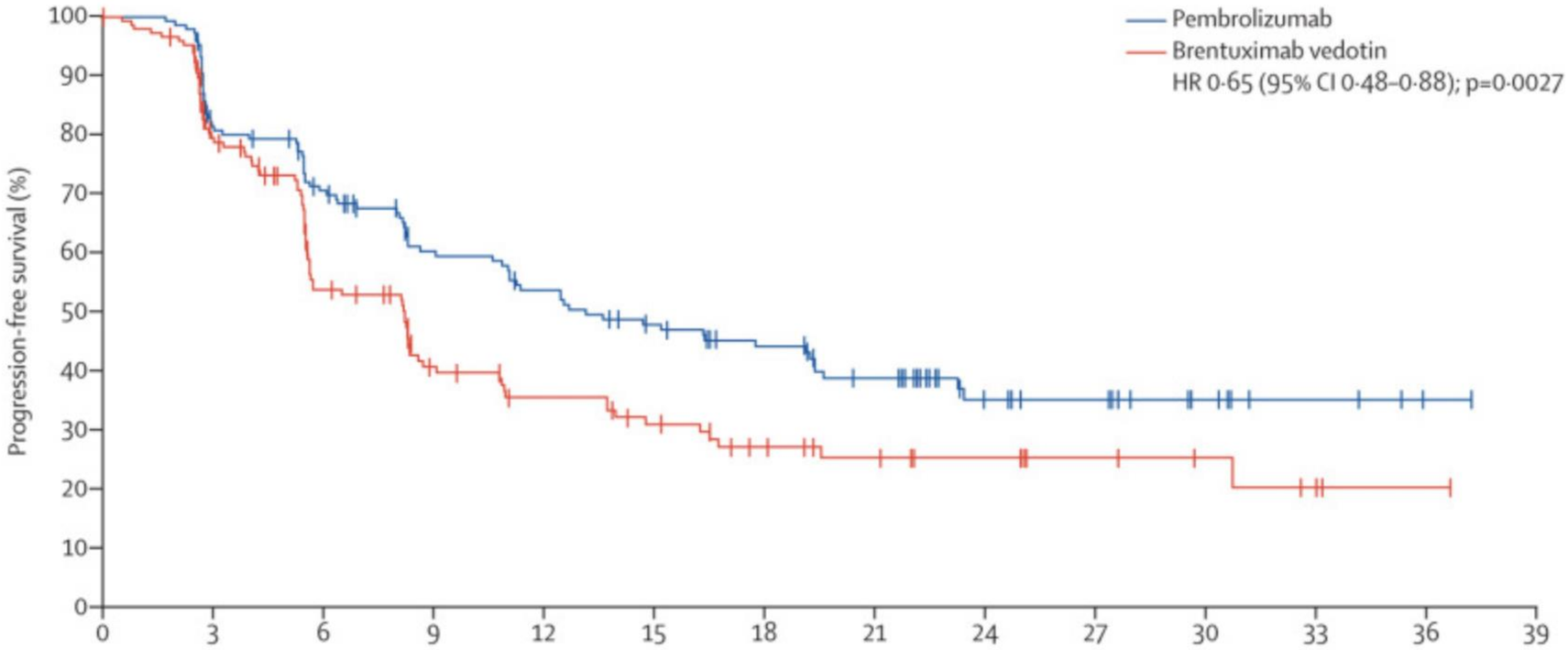
No. at risk:					
	159	137	119	105	95
	183	128	81	42	15



No. at risk:					
	49	31	20	18	18
	42	29	18	8	4

Spinner et al Blood 2023

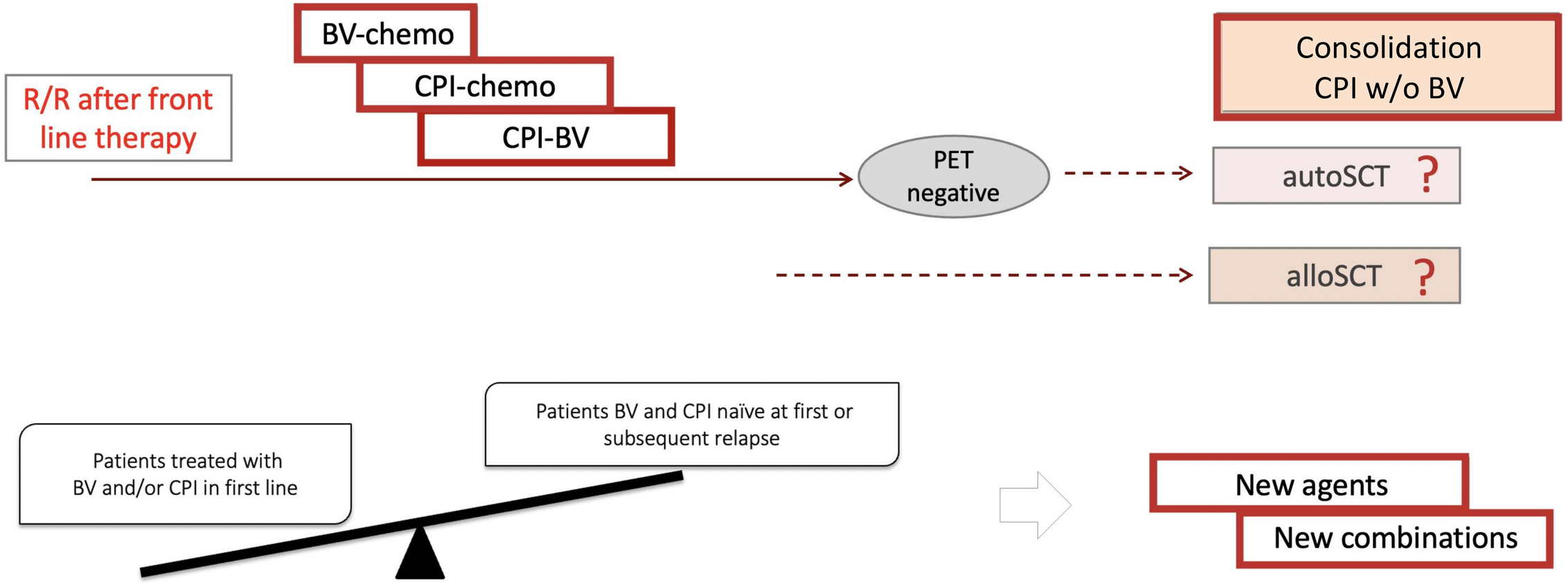
Pembrolizumab vs Brentuximab*:* KEYNOTE-204 - Study Design



Number at risk (number censored)													
Pembrolizumab	151 (0)	116 (9)	96 (13)	74 (22)	65 (23)	55 (26)	44 (33)	35 (37)	18 (52)	15 (55)	9 (61)	4 (66)	1 (69)	0 (70)
Brentuximab vedotin	153 (0)	103 (22)	63 (30)	41 (38)	32 (42)	26 (44)	19 (48)	14 (52)	10 (56)	7 (59)	5 (61)	2 (63)	1 (64)	0 (65)

Kuruvilla et al The Lancet Oncology 2021

Future treatment strategies: the scenario is changing



Brentuximab Vedotin + chemotherapy as first salvage therapy

Regimen	Phase	No.	Primary Refractory, No.	Relapsed, No.	CMR, %	PFS (all patients)	PFS (ASCT cohort)	Reference
BV-based salvage regimens								
BV→augmented ICE	II	45	25	20	76[1]	82% at 3 years	82% at 3 years	Moskowitz et al[19]
BV→salvage therapy	II	57	35	22	74[2]	71% at 2 years	71% at 2 years	Herrera et al[17]
BV + ICE	II	45	29	16	74	80% at 2 years	Not reached	Lynch et al[48]
BV + ESHAP	I/II	66	40	26	70	71% at 30 months	Not reached	Garcia-Sanz et al[49]
BV + DHAP	II	61	23	38	79	76% at 2 years	Not reached	Hagenbeek et al[50]
BV + gemcitabine	I/II	45[4]	29	16	67	Not reached	Not reached	Cole et al[51]
BV + bendamustine	I/II	55	28	27	74	62.6% at 2 years	70% at 2 years	LaCasce et al[52]

Complete metabolic response range between 67% and 79%

Burton et al ASCO Educational Book 2024

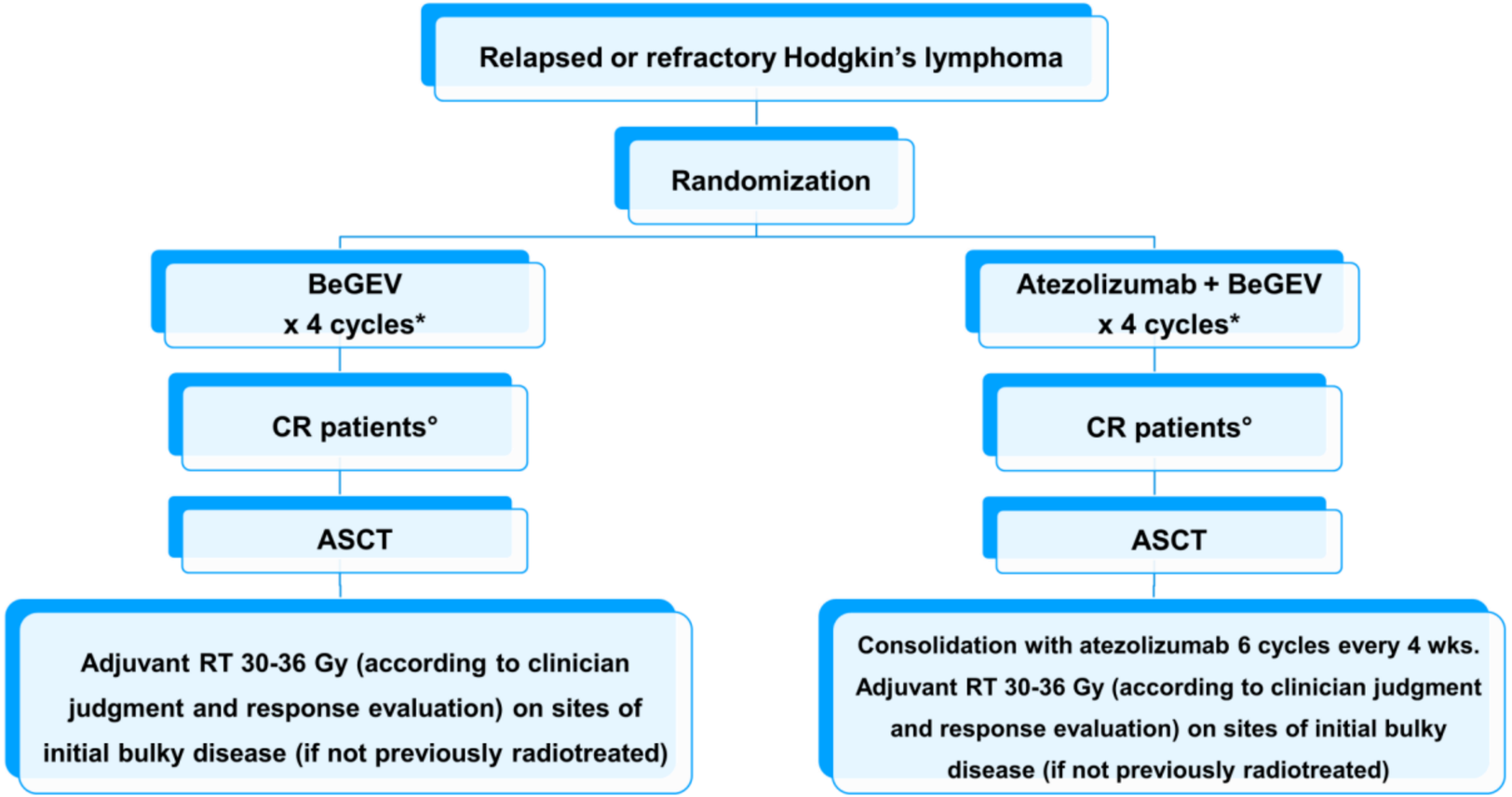
Anti-PD1 + chemotherapy or + BV as first salvage therapy

Combination	Phase	N	Transplanted patients	ORR	CR	PFS	PFS (ASCT cohort)	Median fw	References
Nivolumab+ICE	2	37	76%	93%	91%	72% (2y)	94% (2y)	31 mo	Mei et al Blood 2022
Pembrolizumab+ ICE	2	42	83%°	97.3%	86.5%	87% (2y)	NR	24 mo	Bryan et al Jama Oncol. 2023
Pembrolizumab+GVD	2	39	95%	100%	92.6%	100% (1y)*	100% (1y)	14 mo	Moskpwitzet al JCO 2021
Nivolumab + BV	1/2	93	92%	85%	67%	77% (3y)	91(3y)	34 mo	Advani et al Blood 2021

*One-third of patients received brentuximab vedotin maintenance or brentuximab vedotin plus nivolumab maintenance for a median of five cycles.
° 7% of patients transplanted off protocol

Complete metabolic response range between 86.5% and 95% with CPI+CHT

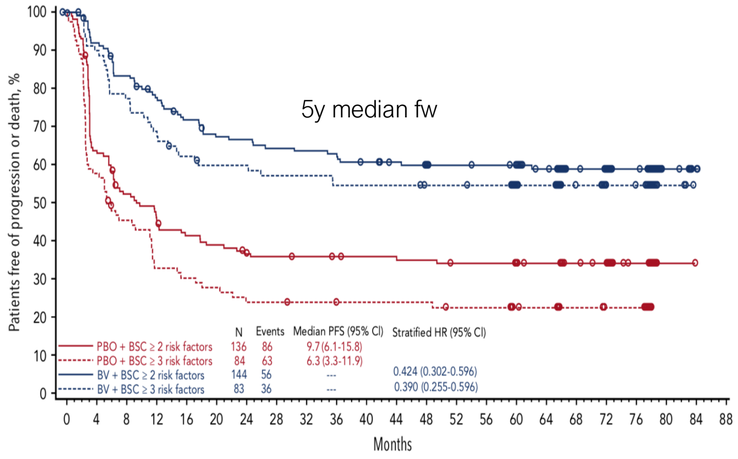
Studio di fase I/II b (controllato randomizzato) su Atezolizumab in combinazione con BEGEV come primo salvataggio in pazienti con linfoma di Hodgkin recidivante o refrattario candidati al trapianto autologo di cellule staminali. EudraCT number: 2020-002927-13



*INTERIM PET WILL BE PERFORMED. PATIENTS WILL REMAIN ON TREATMENT IF DISPLAYING AT LEAST SD
°PATIENTS REACHING PR AFTER FOUR CYCLES OR WITH DOCUMENTED PR AFTER ASCT MAY CONTINUE THE STUDY PROTOCOL ACCORDING TO THE PHYSICIAN JUDGMENT

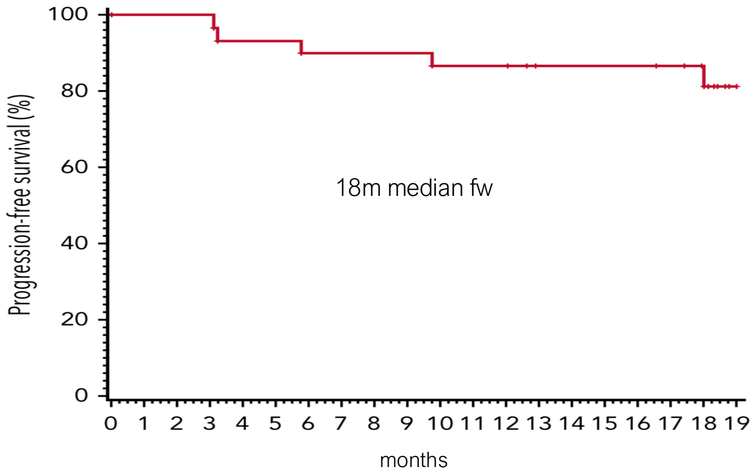
Post-transplant strategies: outcome by consolidation

BV consolidation after ASCT



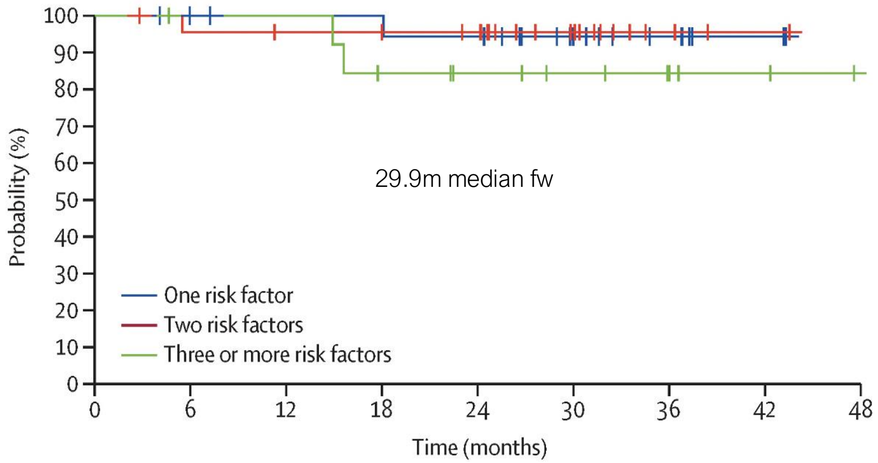
Moskowitz et al, Blood 2018

Pembrolizumab consolidation after ASCT



Armand et al, Blood 2019

Nivo + BV consolidation after ASCT



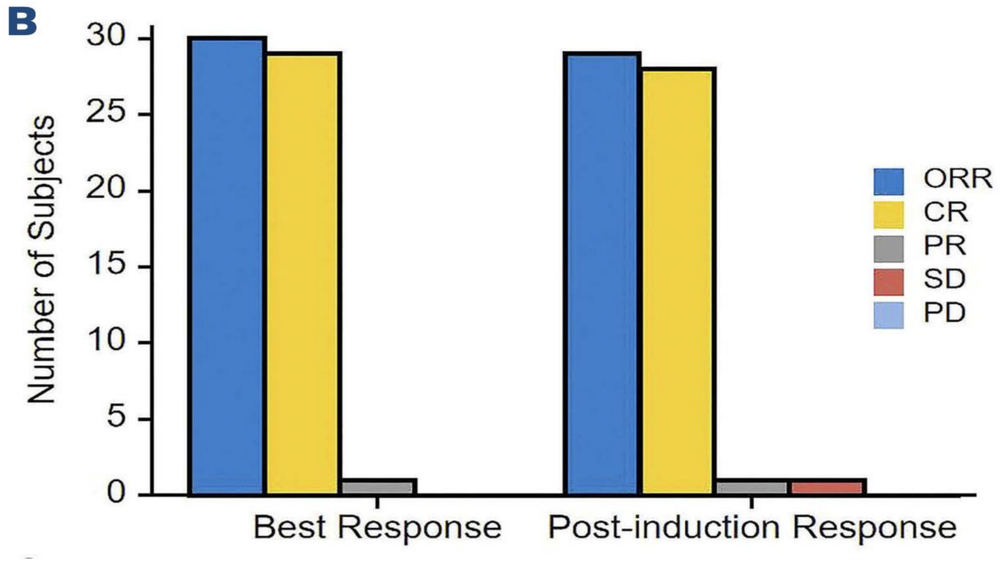
Herrera et al, The Lancet 2023

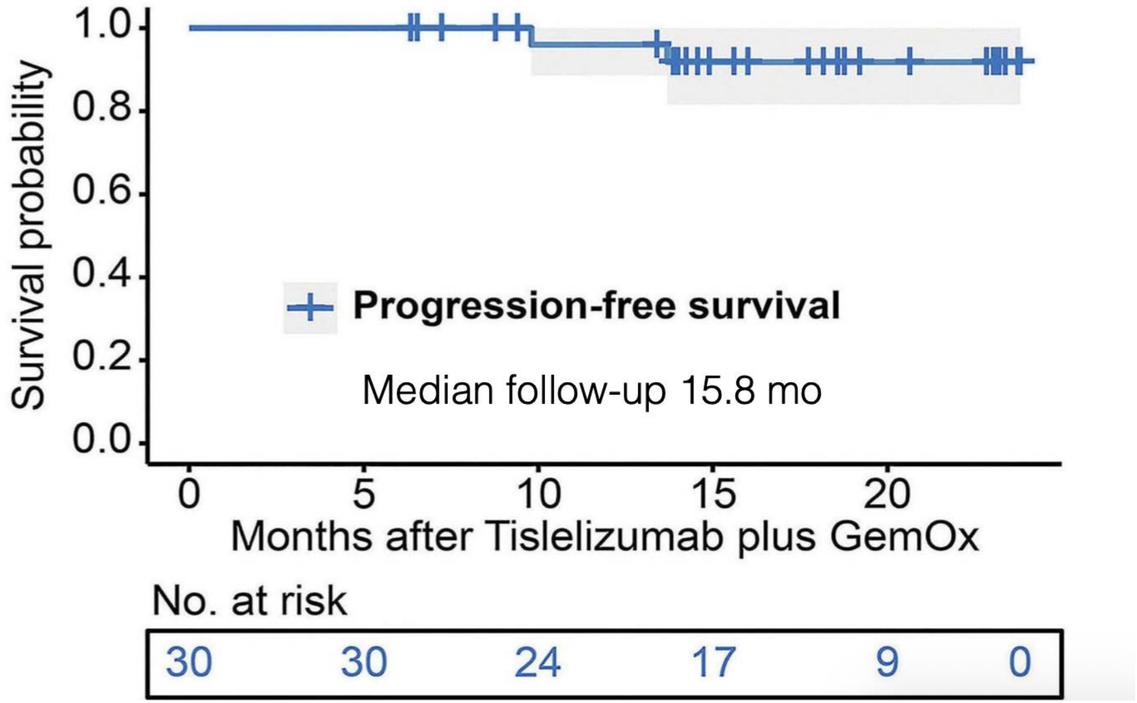
- Novel salvage regimens in the second line setting achived CR rates in 70-95% of patinets
- Highly effective maintenance strategies have been tested succesfully
- The randomized trials that established ASCT as the standard of care for r/r cHL were notably conduced > 20 yrs ago, precdeing the development of BV and PD-1 inhibitors

→ Can ASCT avoided or deferred to later lines of therapy without affect outocome?

Transplant free salvage strategies

Phase II trial: Tislelizumab + gemcitabine + oxaliplatin





Ding et al, Heamatologica 2023

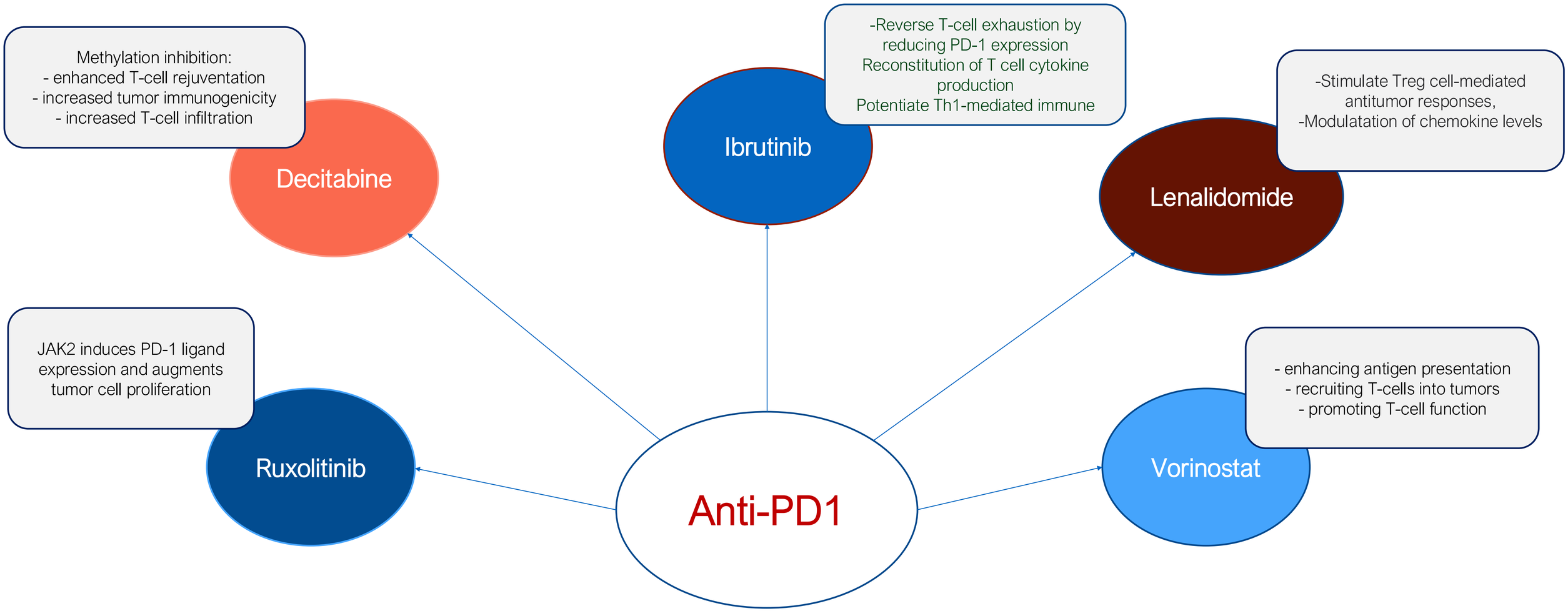
Transplant free salvage strategies

Ongoing trials

Memorial Sloan Kettering (NCT03618550): 4 cycles of pembrolizumab + GVD followed by **13 cycles of pembrolizumab maintenance** without ASCT for pts achieving metabolic CR

City of Hope Medical Center (NCT04561206): BV + Nivolumab for **16 cycles** in lieu of ASCT

New combination strategies

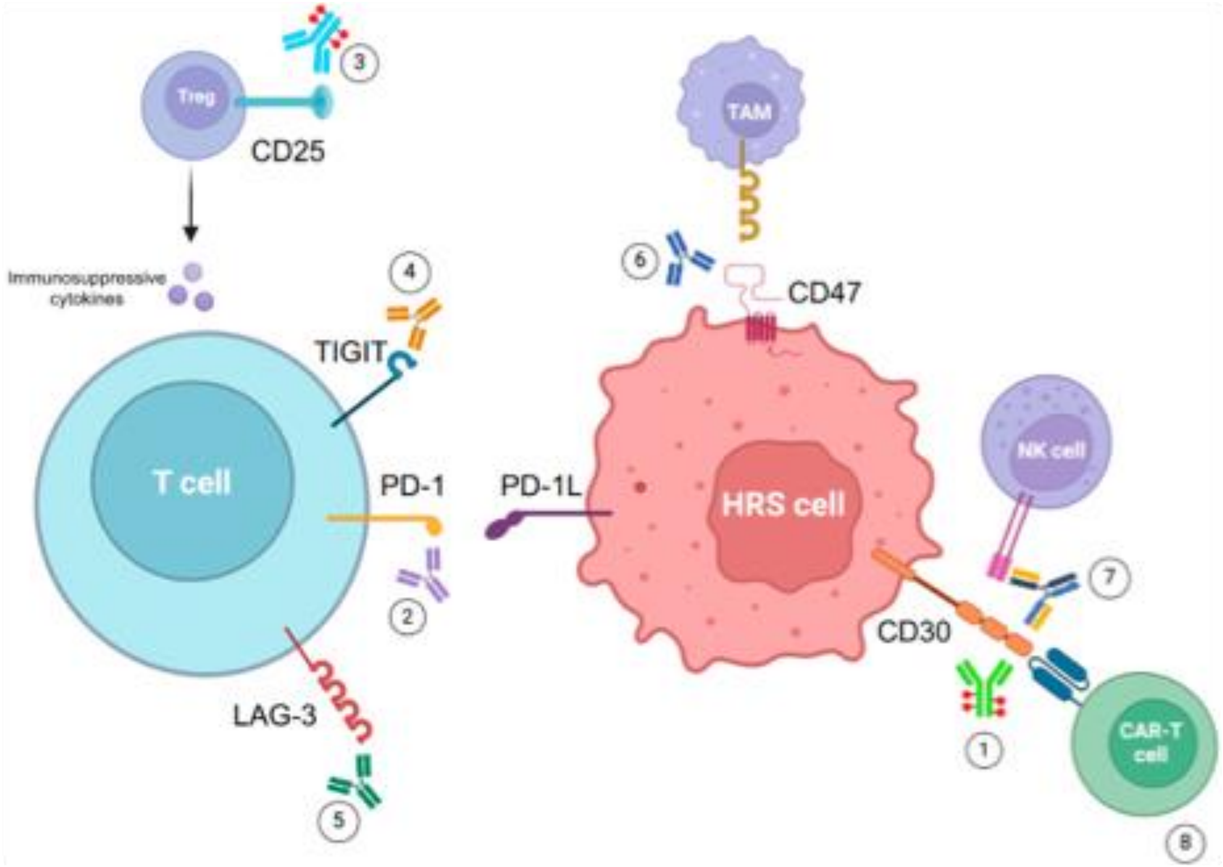


Anti-PD1 based combination may help overcome resistence

COMBINING CPI WITH IMMUNOMODULATORS AND EPIGENETIC MODIFYNG THERAPIES

Regimen	Therapeutic Target(s)	Phase	Patient Population *	N	ORR	CRR	Median PFS	Median f/u
Nivo + lenalidomide	PD1 + CELMoD	1/2	3 prior lines 90% PD1 naïve	10	70%	30%	NR	--
Nivo + ibrutinib	PD1 + BTK/ITK	2	5 prior lines 59% prior PD1	17	52%	29%	17.3 mo.	9 mo.
Nivo + ruxolitinib	PD1 + JAK1/2	1/2	4 prior lines 100% prior PD1	21	42%	26%	16.5 mo.	21 mo.
Camrelizumab + decitabine	PD1 + HMA	2	PD1 naïve	61	95%	71%	NR	15 mo.
Camrelizumab + decitabine	PD1 + HMA	2	PD1 refractory	51	52%	36%	21.6 mo.	39 mo.
Pembro + vorinostat	PD1 + HDACi	1	3 prior lines 78% prior PD1	32	72%	34%	8.9 mo.	33 mo.
Pembro + entinostat	PD1 + HDACi	2	5 prior lines 55% prior PD1	22	86%	45%	NR	8 mo.

Emerging target therapy approaches in cHL

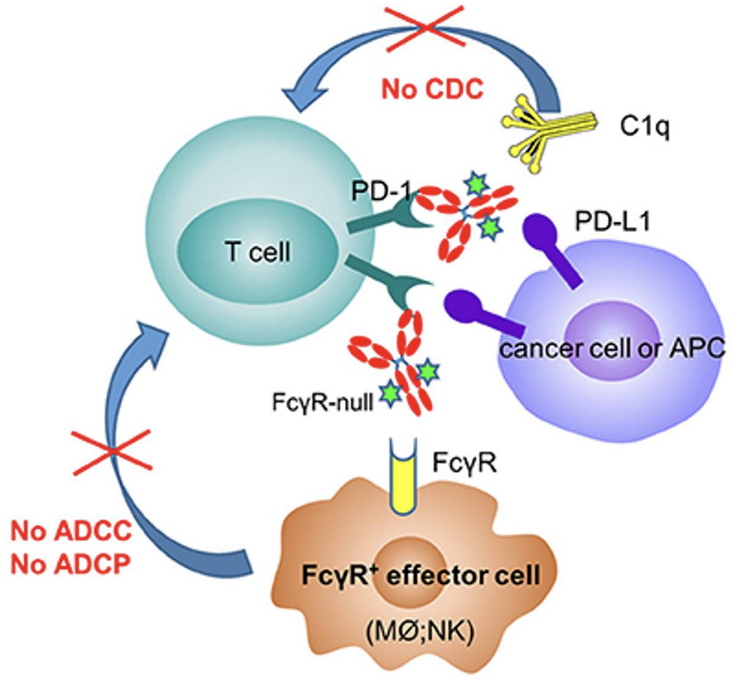


.1: Brentuximab vedotin. 2: Nivolumab, pembrolizumab and other PD-1 inhibitors. 3: Camidanlumab tesirine. 4: Vibostolimab.
5: Favezelimab. 6: Magrolimab. 7: AFM13. 8: anti-CD30 CAR T-cells.

Savelli et al, Cancer 2024

Tislelizumab

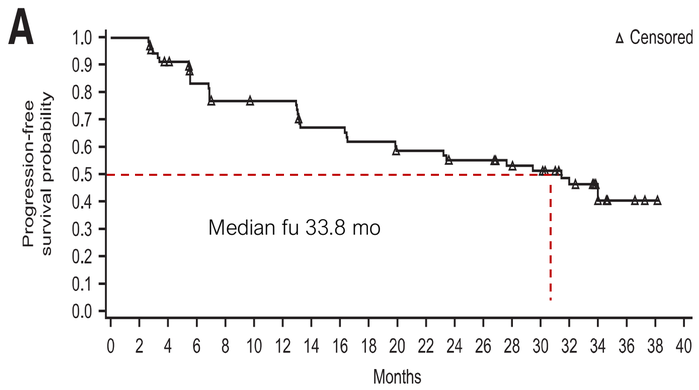
The different FcγR design may have meaningful differences in the clinic

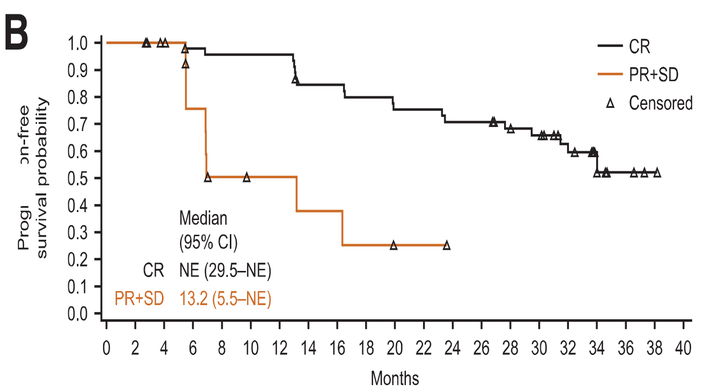


Phase II, open-label, single-arm study:

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

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





Song et al, Clin Cancer Res. 2022

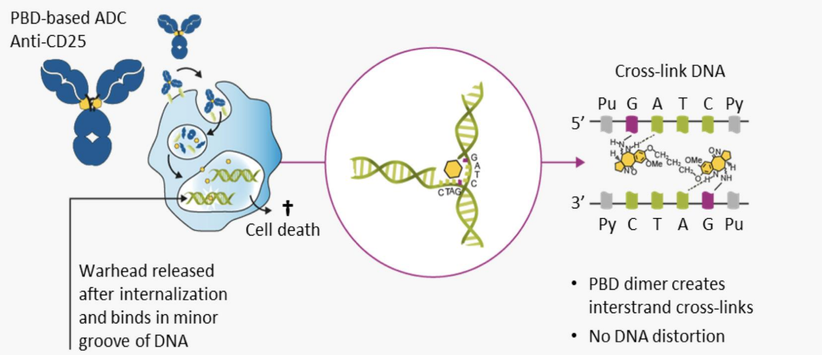
CAMIDANLUMAB TESIRINE (CAMI) - Anti-CD25 antibody drug conjugate

Cami composition

- Human IgG1 anti-CD25 mAb stochastically conjugated to PBD dimer warhead

Mechanism of action[1–3]

- Death of CD25-expressing tumor cells
- Depletion of CD25-expressing T cells in HL tumor microenvironment
- Possible bystander killing of CD25-negative cells



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

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

No. of patients enrolled	Mean (SD) No. of cycles
117	4.6 (2.5)

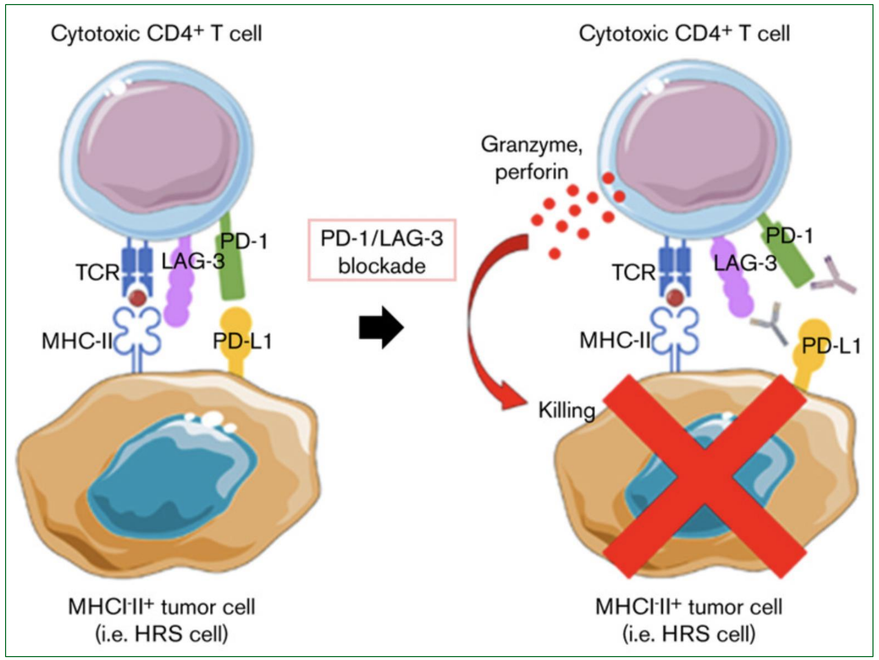
Response	
ORR	70.1%
CR	33.3%
Median PFS	9.13 mo
Median OS	NR
Median fw	20 mo

Safety	
Treatment discontinuation	28.2%
-Skin toxicity	8.5%
-Infections	4.3%
-Nervous system disorders	4.3%
-Guillain-Barré or polyradiculopathy-type events	6.8%

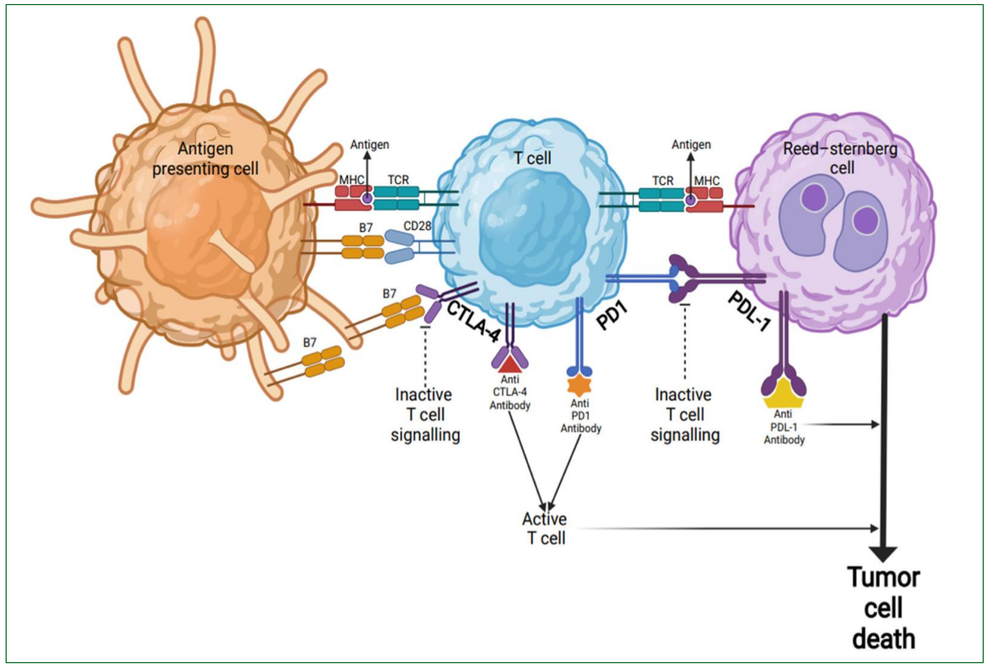
Herrera et al, Blood Advances 2025

OTHERS IMMUNE CHECKPOINT INIBHITORS

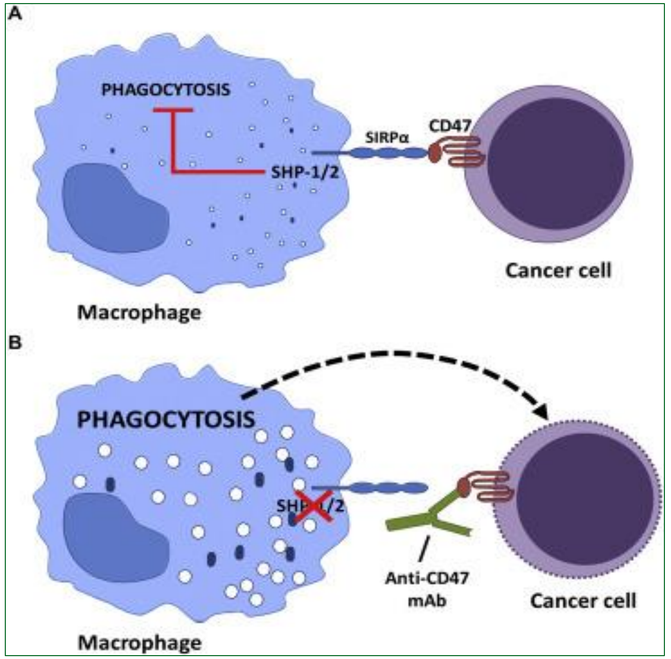
LAG3 blockade



CTL4 blockade



CD47 blockade

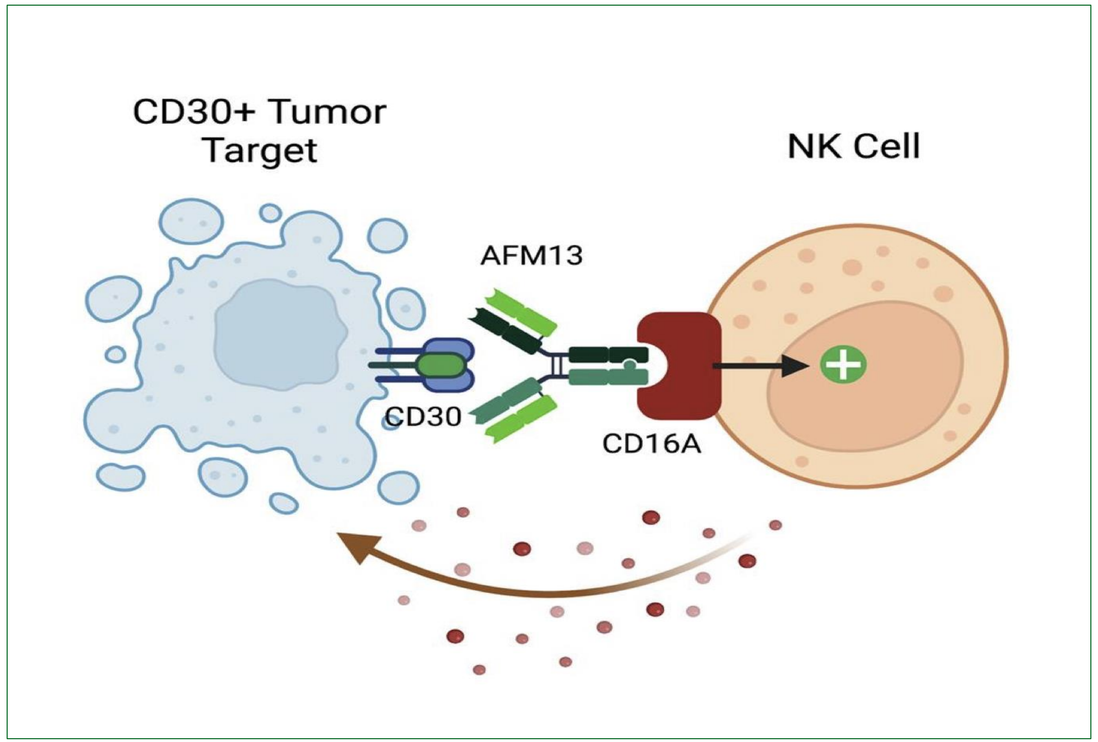


COMBINING IMMUNE CHECKPOINT INIBHITORS

Regimen	Therapeutic target	Phase	Patient Population	N	ORR	CRR	Median PFS	Median f/u
Nivo+ipilimumab Ansell 2016	**PD1+CTL4**	1	4 prior lines All CPI naive	31	74%	23%	NR	18 mo
Nivo+ipilimumab+BV Diefenbach 2020	**PD1+CTL4+CD30**	1/2	2 prior lines All CPI naive	64	82%	73%	NR	20 mo
Pembro+favezelimab Timmerman 2024	**PD1+LAG3**	1/2	CPI naive	30	80%	33%	19.4 mo	32 mo
Pembro+faevzelimab Timmerman 2023	**PD1+LAG3**	1/2	CPI refractory	34	29%	9%	9.7 mo	35 mo
Tislelizumab+IMM01 Song 2024	**PD1+CD47**	2	19 CPI refractory	33	70%	24%	NR	13.8 mo

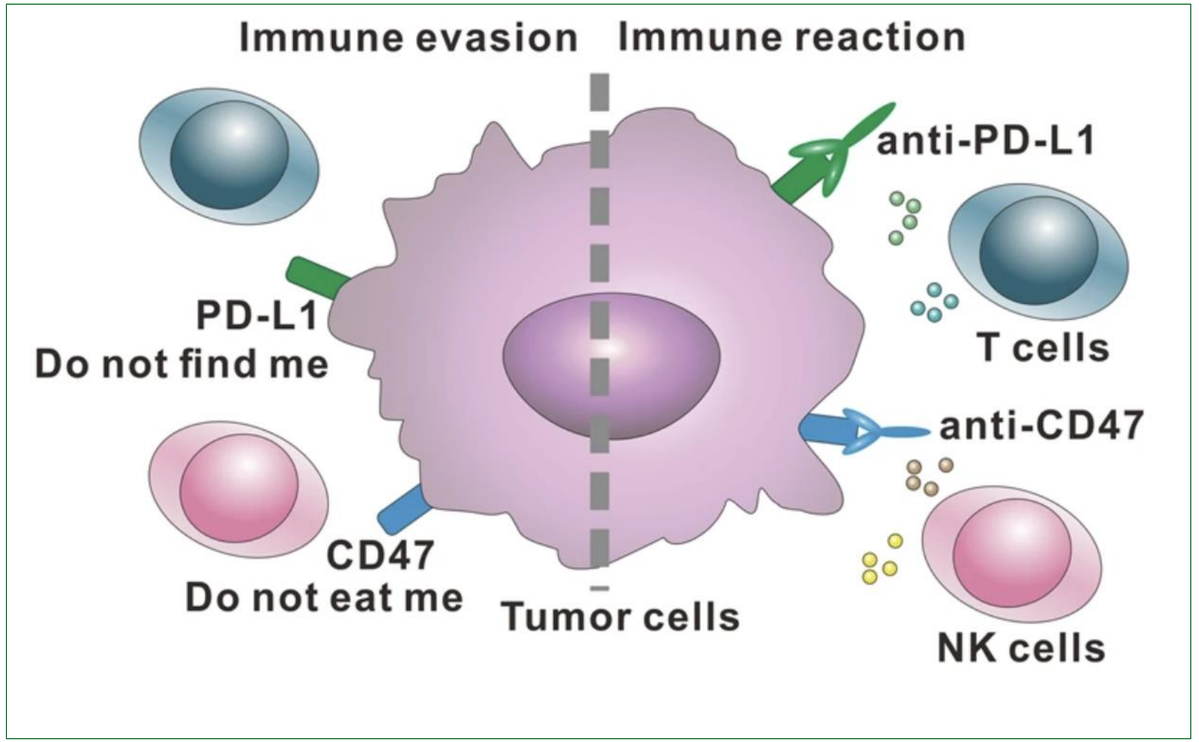
BISPECIFIC ANTIBODIES

CD30/CD16A Bispecific Antibody



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

CD47/PD-L1 Bispecific Antibody



BI322 is a bispecific that antagonize both innate and adaptive immune checkpoint pathways.

CD30/CD16A Bispecific Antibody

CD30/CD16A Bispecific Antibody montherapy Phase II study

Best response to AFM13 (N=26)	Patients, n (%)
CR	0 (0%)
PR	3 (11.5%)
SD	13 (50.0%)
PD	10 (38.5%)

Sasse et al. Leuk Lymphoma 2022

CD30/CD16A Bispecific Antibody combination

Regimen	Therapeutic Target(s)	Phase	Patient Population *	N	ORR	CRR	Median PFS	Median f/u
Pembro + AFM13	PD1 + CD30/CD16A	1	3 prior lines All PD1 naïve	30	83%	37%	--	--
AFM13 + umbilical cord blood derived NK cells	NK cells + CD30/CD16A	1/2	6 prior lines 29% prior PD1	30	97%	63%	NR	8 mo.

Barlett et al. Blood 2020, Nieto et al ASH 2023

CD47/PD-L1 Bispecific Antibody

Phase I study: BI322 (45 mg/kg intravenous Q2W) until unacceptabletoxicity or disease progression, or up to 24 mo

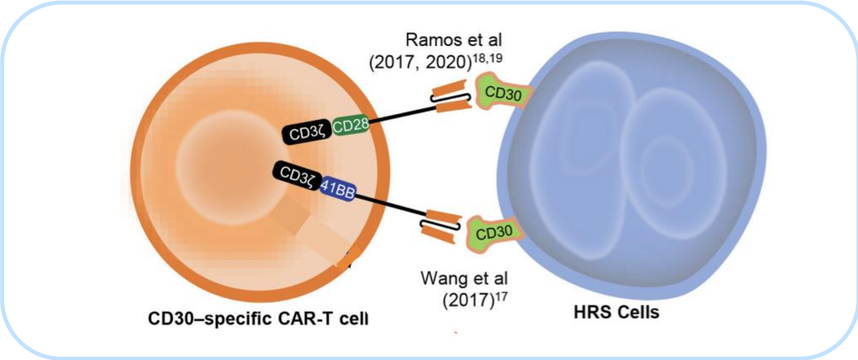
Previous treatments	N=24
CPI Primary resistent	33.3%
CPI Secondary resistent	66.7%

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%

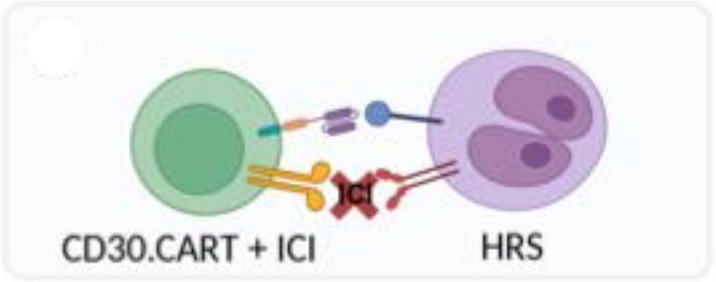
Zhang et al, EHA 2023

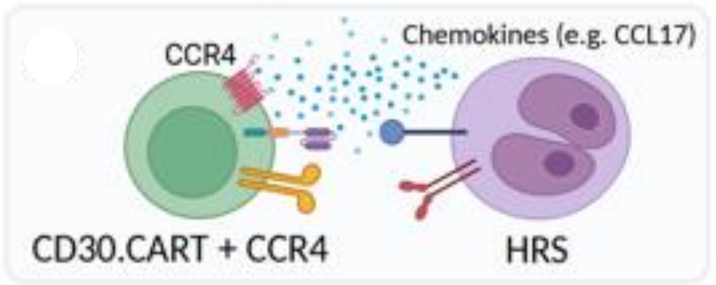
CD30 directed CAR-T cell



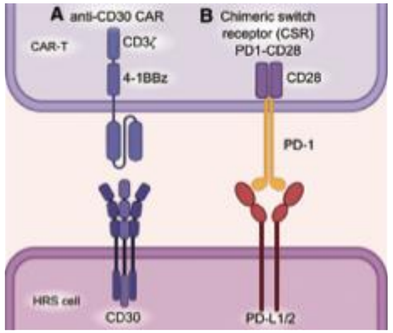
Study	Costimulatory Endodomain	phase	LDC	N	Range of CAR-T Cells	ORR	CR	FW	PFS	OS	CRS & ICANS %(n)
Wang et al 2017	4–1BB (Lenti virus)	1	GEMC (n = 8) Flu + Cy (n = 5) PC (n = 4) Others (n = 4)	17	$1.1–2.1 \times 10^7$ cells/kg	35%	0%	na	14 mo	na	CRS. all grades: 100% CRS. grade ≥3: 0% ICANS. all grades: 0% ICANS. qrade ≥3: 0%
Ramos et al 2017	CD28 (γ- retrovirus)	1	none	7	$0.2–2.0 \times 10^8$ cells/m2	29%	29%	na	na	na	CRS. all grades: 0% CRS. grade ≥3: 0% ICANS. all grades: 0% ICANS. qrade ≥3: 0%
Ramos et al 2021	CD28 (γ- retrovirus)	1/2	Flu + Cy (n = 17) Benda-Flu (n = 17) Benda (n = 8)	42	$0.2–2.0 \times 10^8$ cells/m2	72%	59%	18 mo	36% at 1 y	94% at 1y	CRS. all grades: 24% CRS. grade ≥3: 0% ICANS. all grades: 0% ICANS. grade ≥3: 0%
Sairah et al 2022	CD28 (γ- retrovirus)	2	Benda- Flu	15	$2.0\text{-}2.7 \times 10^8$	73%	60%	na	na	na	CRS. all grades: 6.6 % CRS. grade ≥3: 0% ICANS. all grades: 0% ICANS. grade ≥3: 0%

CD30 directed CAR-T cell





Study	target	phase	LDC	N	ORR	CR	fw	PFS	OS	Toxicity
Sang et al 2022	CD30 + PD1	2	Benda-Flu	12 (9 HL)	92%	50%	21.5 mo	45%	70%	CRS (25%) Gr3 CRS (8%)
Grover et al 2024	CD30 + CCL17	1	Benda-Flu	24	92%	67%	29.6 mo	Median 6.4 mo	NR	CRS (33%) Gr1 CRS (17%) Gr2 CRS (17%)

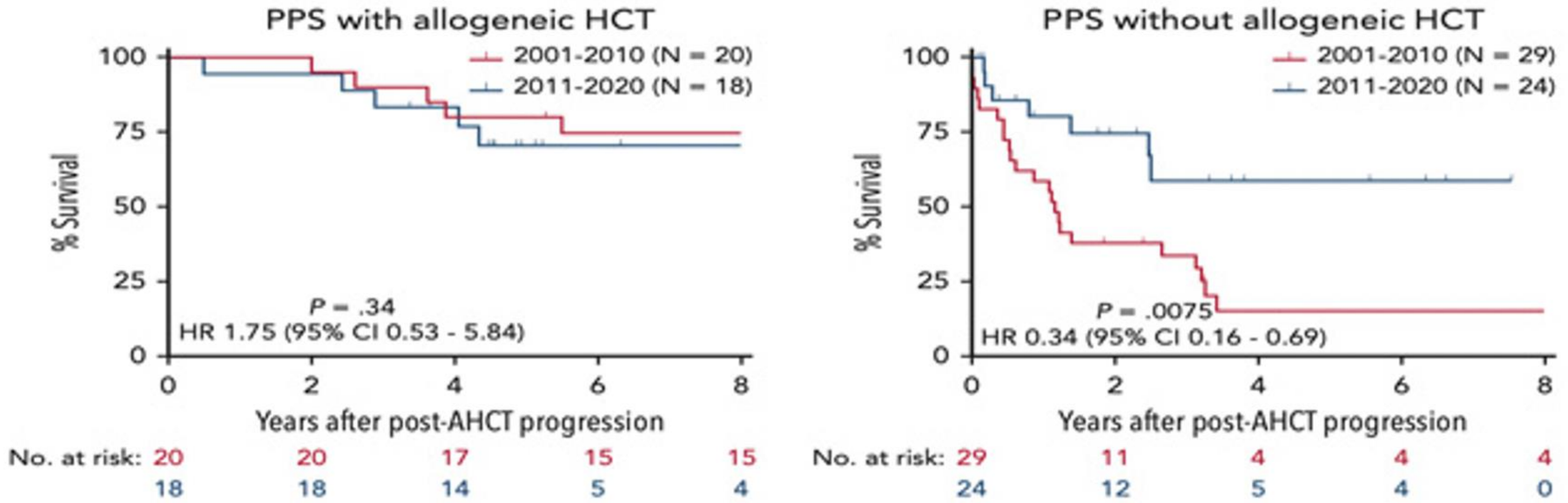


NEW CAR-T

Genetically modified autologous T cells expressing the chimeric CD30 antigen receptor with the chimeric switch receptor PD1-CD28

Allogenic-SCT

What about patients relapsed after ASCT



PPS was similar between eras for parients who underwent allogeneic HCT, among patients who did not undergo allogeneic HCT PPS was superior in the modern era

Spinner et al, Blood 2023

SUMMARY

- The outcome in r/r cHL in the modern era is improved
- ICIs represent a revolutionary approach for HL treatment with significative improval in prognosis with a peculiar but managable toxicity
- ICIs can be effectively combined with chemo, brentuximab-vedotin and small molecules, for salvage treatment pre ASCT
- The impressive results in salvage therapies before ASCT place this standard into question
- Encouraging preliminary data on bispecific abs
- Anti-CD30 CAR-T displayed so far a dismal efficacy for treatment of R/R HL