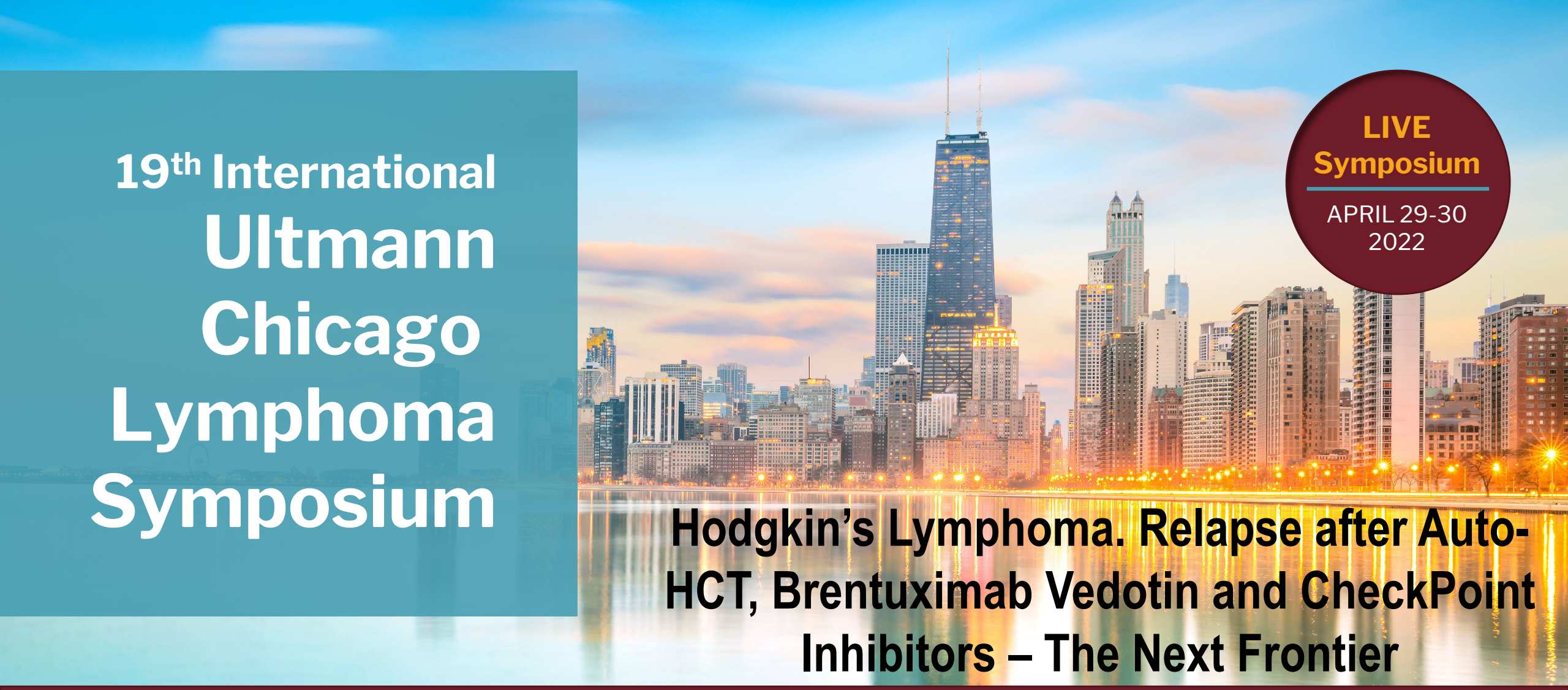


19th International Ultmann Chicago Lymphoma Symposium

LIVE Symposium

APRIL 29-30 2022

Hodgkin's Lymphoma. Relapse after Auto-HCT, Brentuximab Vedotin and CheckPoint Inhibitors – The Next Frontier

Anna Sureda. Hematology Department,
Institut Català d'Oncologia – Hospitalet,
Barcelona, Spain

19TH ULTMANN

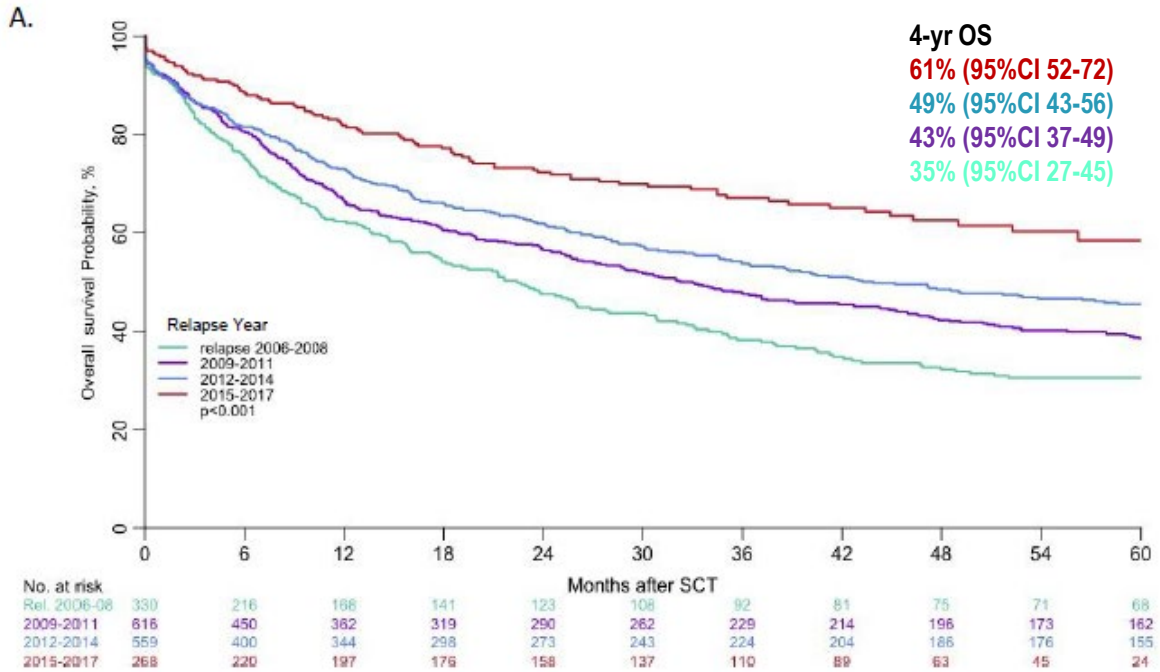
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Disclosures

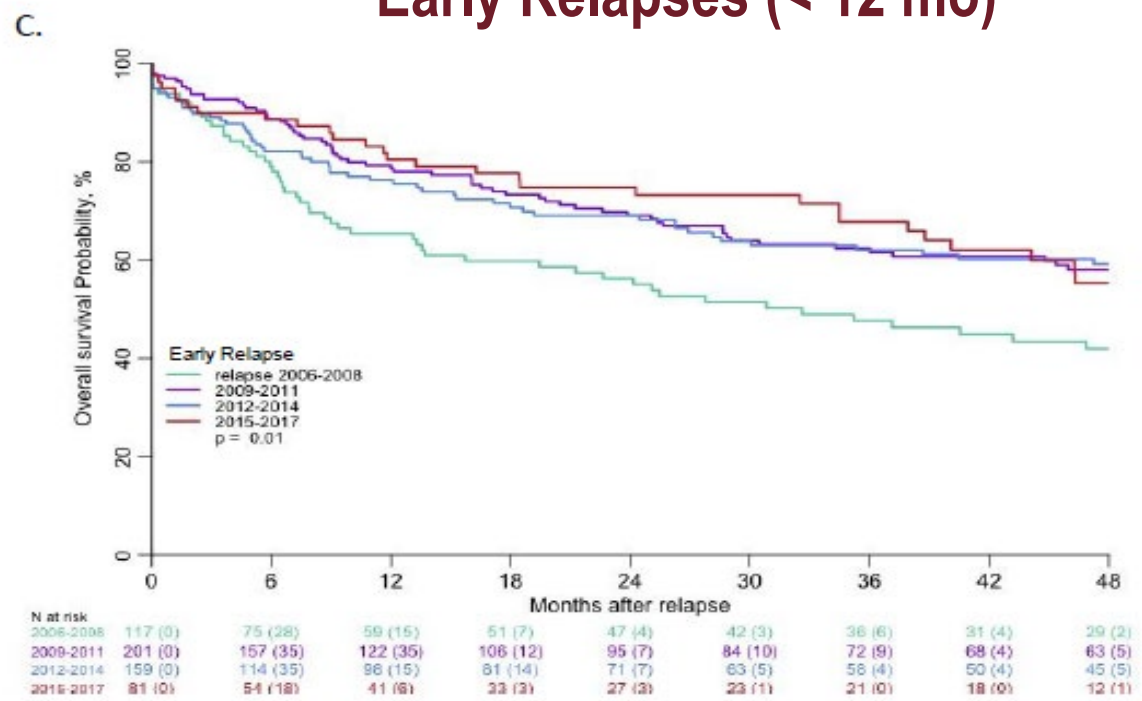
- Honoraria: Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead Kite, Sanofi, Roche, Alexion
- Consultancy: Takeda, BMS/Celgene, Novartis, Janssen, Gilead, Sanofi
- Speaker's Bureau: Takeda
- Research Support: Takeda, BMS/Celgene
- Non-profit organizations: Presidency of the EBMT

New Treatment Strategies Have Been Able to Improve OS After Auto-HCT

Global Population of Patients

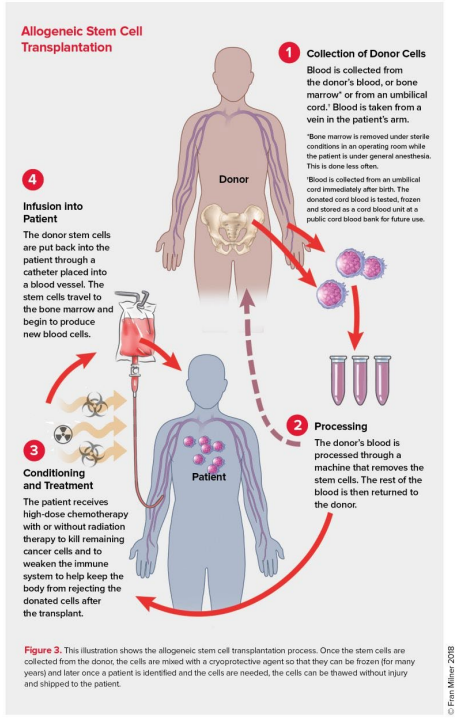


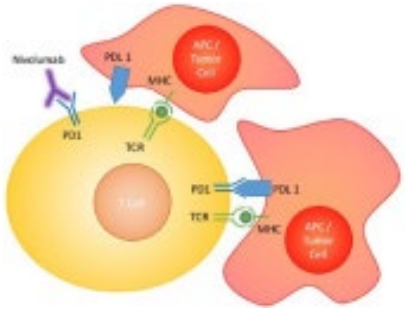
Early Relapses (< 12 mo)

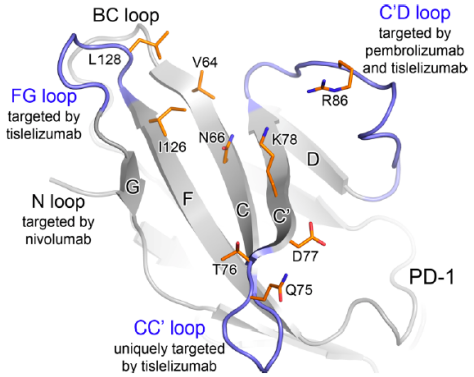


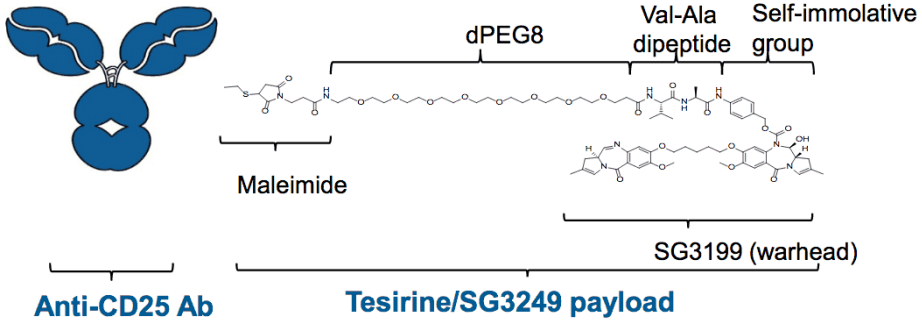
Bazarbachi Al et a, Leuk (in press)

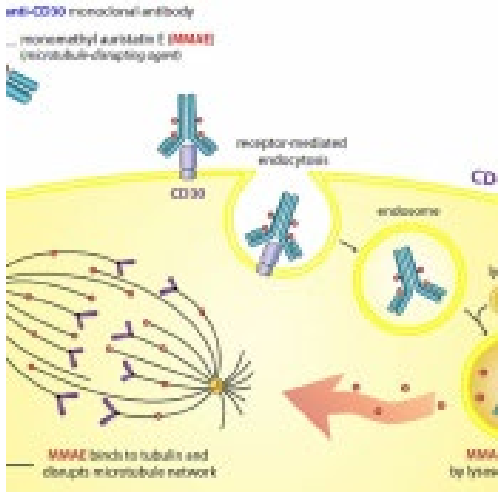
The Future is Bright for RR HL

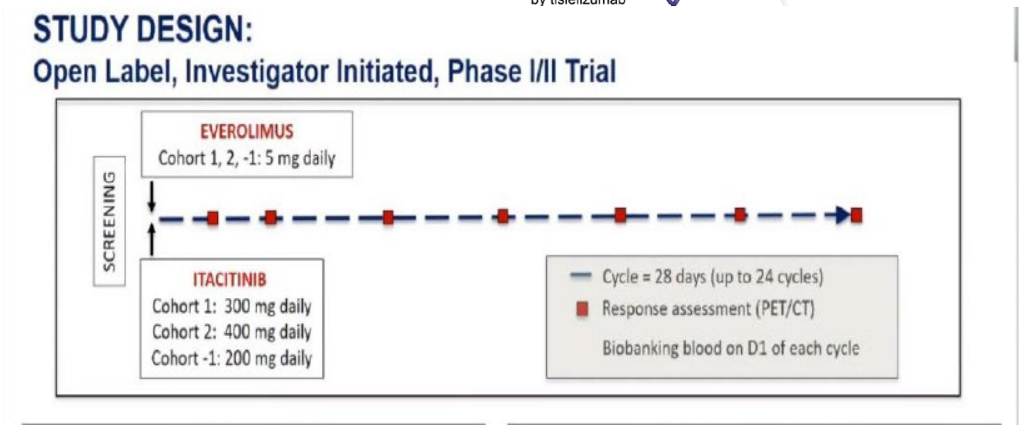


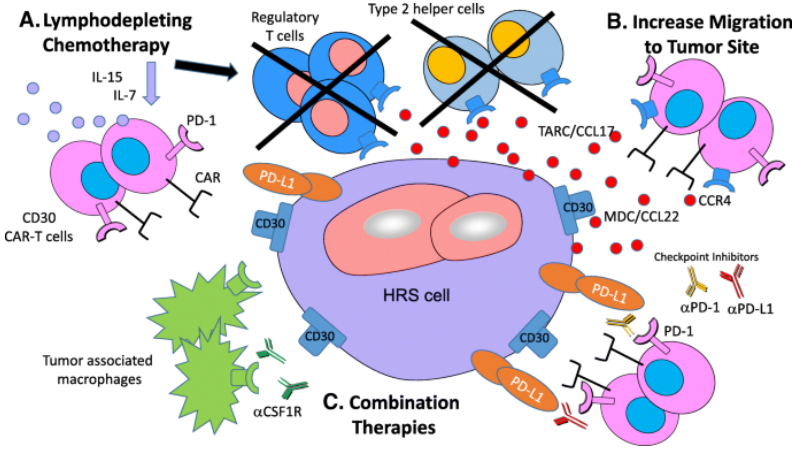












Treatment Strategies for Patients Failing Auto-HCT, BV and CPIs

- Allogeneic Stem Cell Transplantation
- CD30 CART Cells
- New checkpoint inhibitors
- AFM-13
- Camidanlumab Tesirine
- Small molecules

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Indications for HCT in cHL

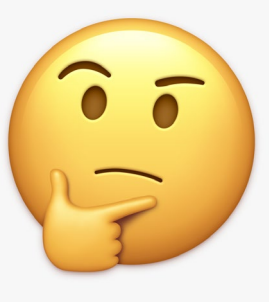
Disease Risk	MSD	MUD	Alternative Sources	Auto-HCT
CR1	GNR/III	GNR/III	GNR/III	GNR/I
CR1>1, prev auto NO	D/III	D/III	GNR/III	S/I
CR>1, prev auto YES	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

Duarte R et al, BMT 2019

Disease Risk	MSD	MUD	Alternative Sources	Auto-HCT
CR1	GNR/III	GNR/III	GNR/III	GNR/I
CR1>1, prev auto NO	D/III	D/III	GNR/III	S/I
CR>1, prev auto YES	S/II	S/II	CO/III	CO/III
Refractory	D/II	D/II	D/III	CO/III

Snowden J et al, submitted

Which Is the Best Sequence?



Brentuximab Vedotin

Check Point Inhibitor (NIVO, PEMBRO)

Allogeneic Stem Cell Transplantation

No Curative Potential

Better short-term toxicity profile

Results Less mature

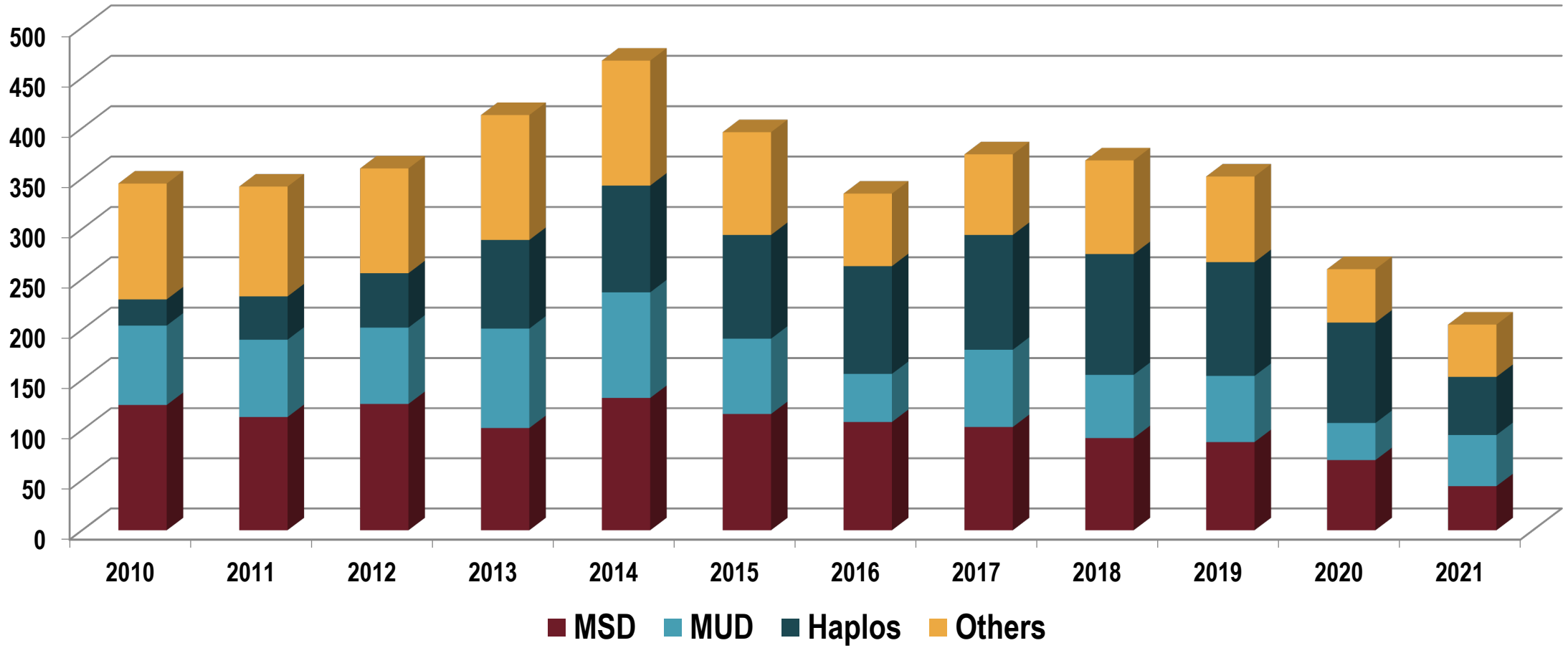
Known Curative Potential

Significant morbi-mortality

Long-term Follow Up

Well identified risk-adapted patient's profile

HCT in cHL. The EBMT Experience



EBMT Database, with permission

Allotransplants after CPIs

N = 209
- 87 Haplo/PtCy
- 25 non-Haplo/PtCy
- 91 non-Haplo/non-PtCy
- 6 PtCy + ATG

Median age: 31.5 yrs

Male patients - 60%

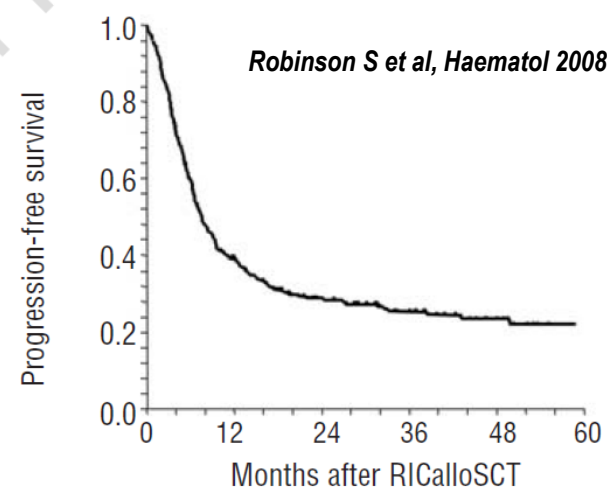
HCT-CI
- 0-2 - 129
- ≥ 3 – 66

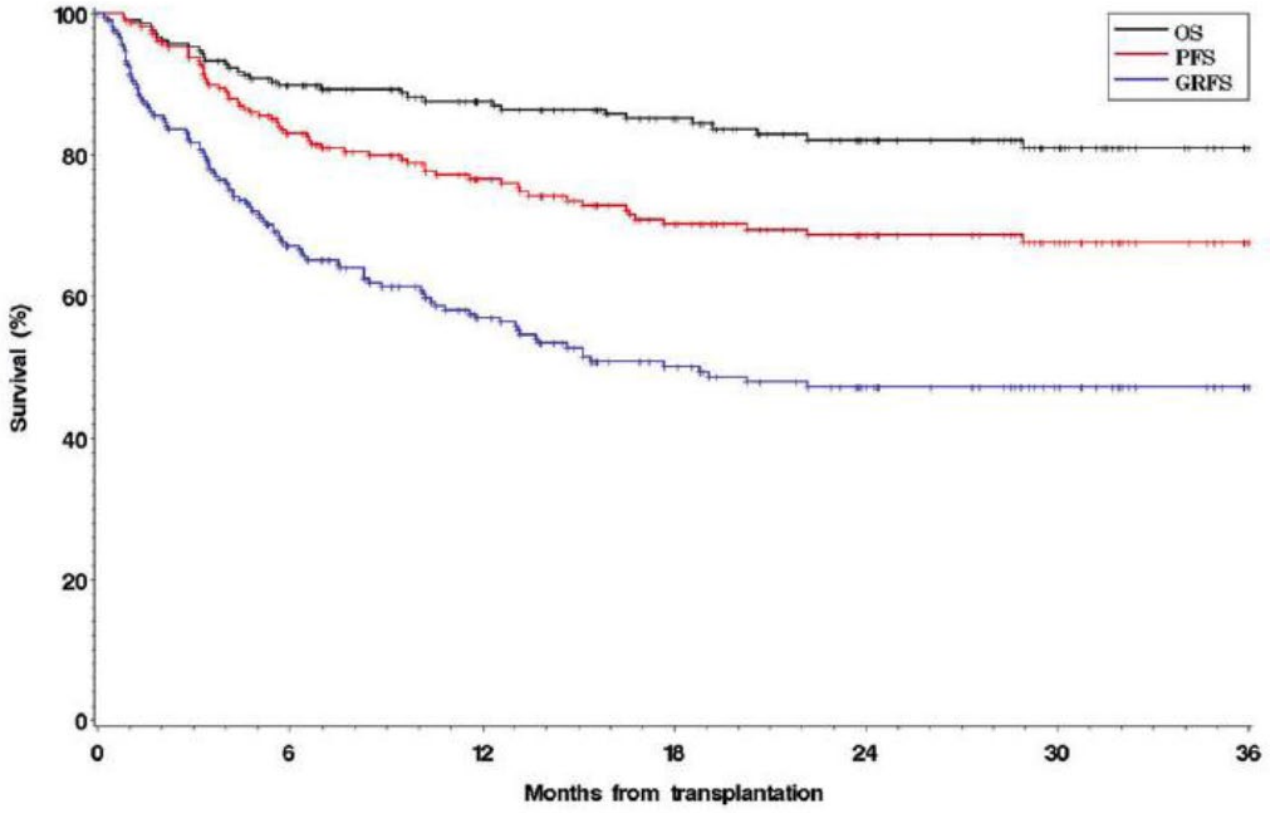
Median number of tx: 4 (2-11)

Best response to CPIs CR – 39%

Median time from last dose CPIs to Allo-HCT, 81 days

CR before allo-HCT – 58%





Merryman RW et al, Leuk 2021

Allotransplants after CPIs

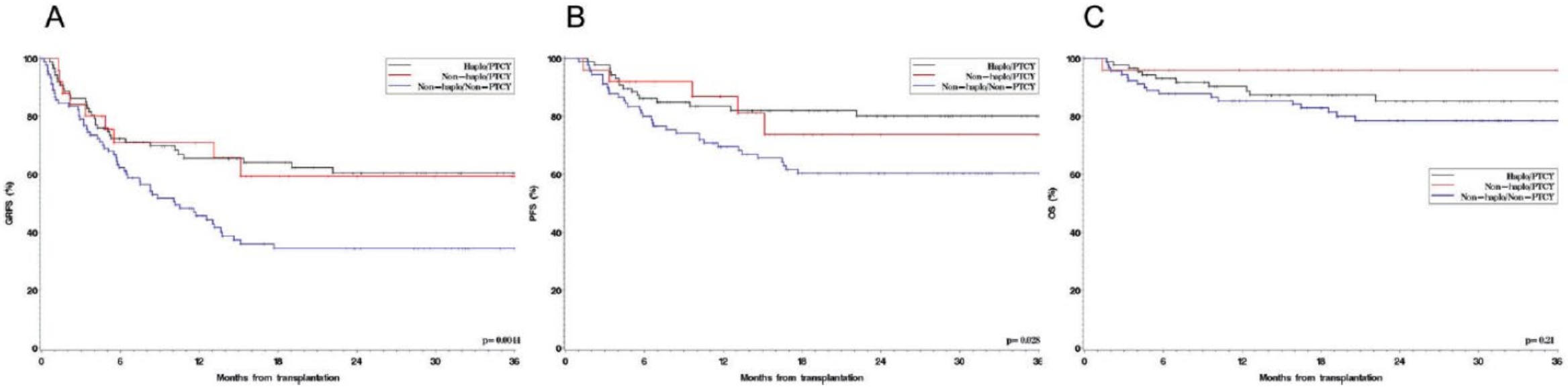
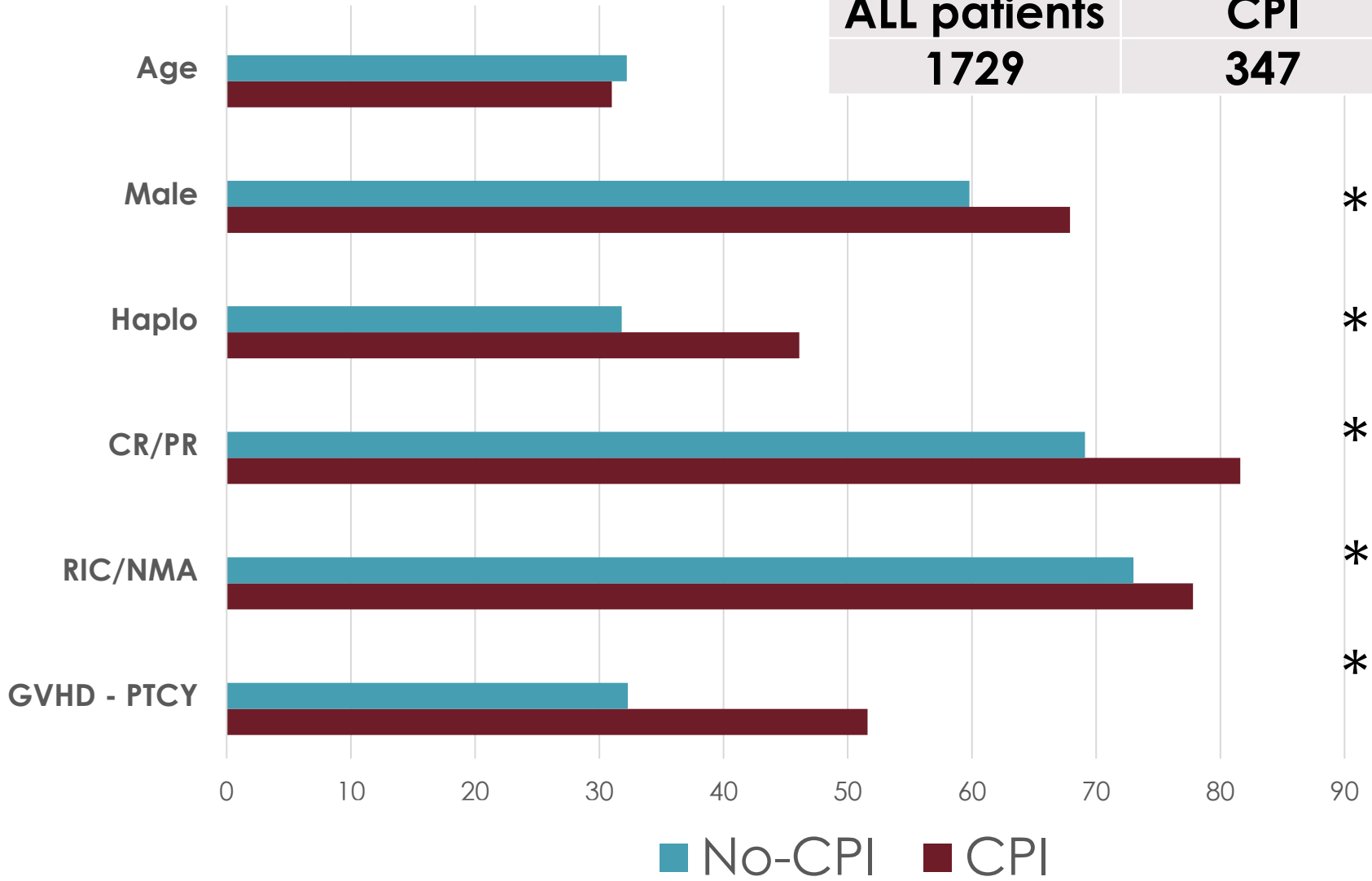


Fig. 2 Survival outcomes based on donor type and GVHD prophylaxis regimen. A GRFS, **B** PFS, **C** OS based on donor type and GVHD prophylaxis regimen. (Note: the six patients who received PTCy + ATG are not included in this figure).

Merryman RW et al, Leuk 2021

Impact of Prior CPI in Long-Term Outcome of Allo-HCT. Patient Characteristics

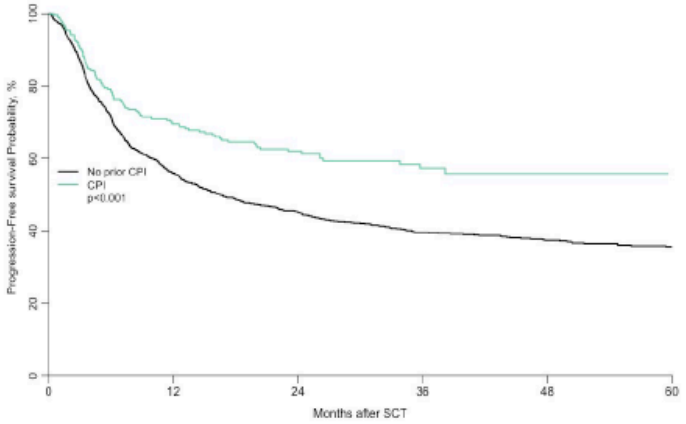
	ALL patients	CPI	No prior CPI
	1729	347	1382



Perales MA et al, EBMT 2022 (Presidential Symposium)

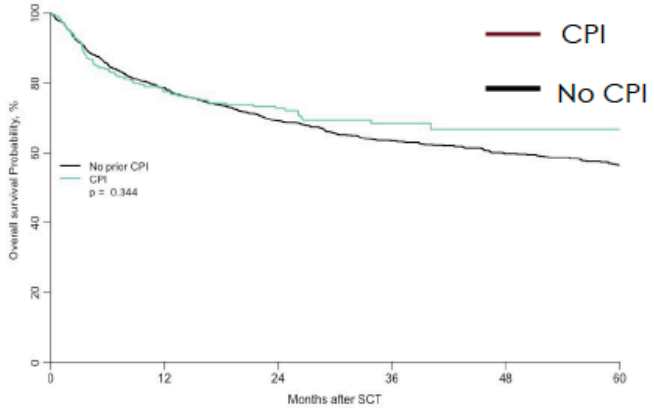
Prior CPI Improves PFS but Does Not Affect OS. Prior CPI is Associated with Lower Relapse and Similar NRM

Progression-Free Survival



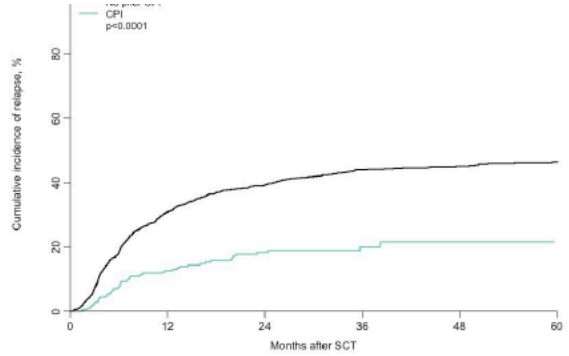
HR 0.75,0.59-0.95, p=0.0171

Overall Survival



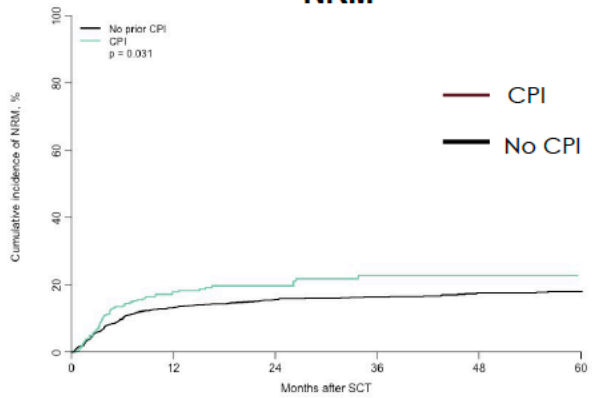
HR 0.96, 0.72-1.27; p=0.76949

Relapse



HR 0.53, 0.38-0.75, p=0.00023

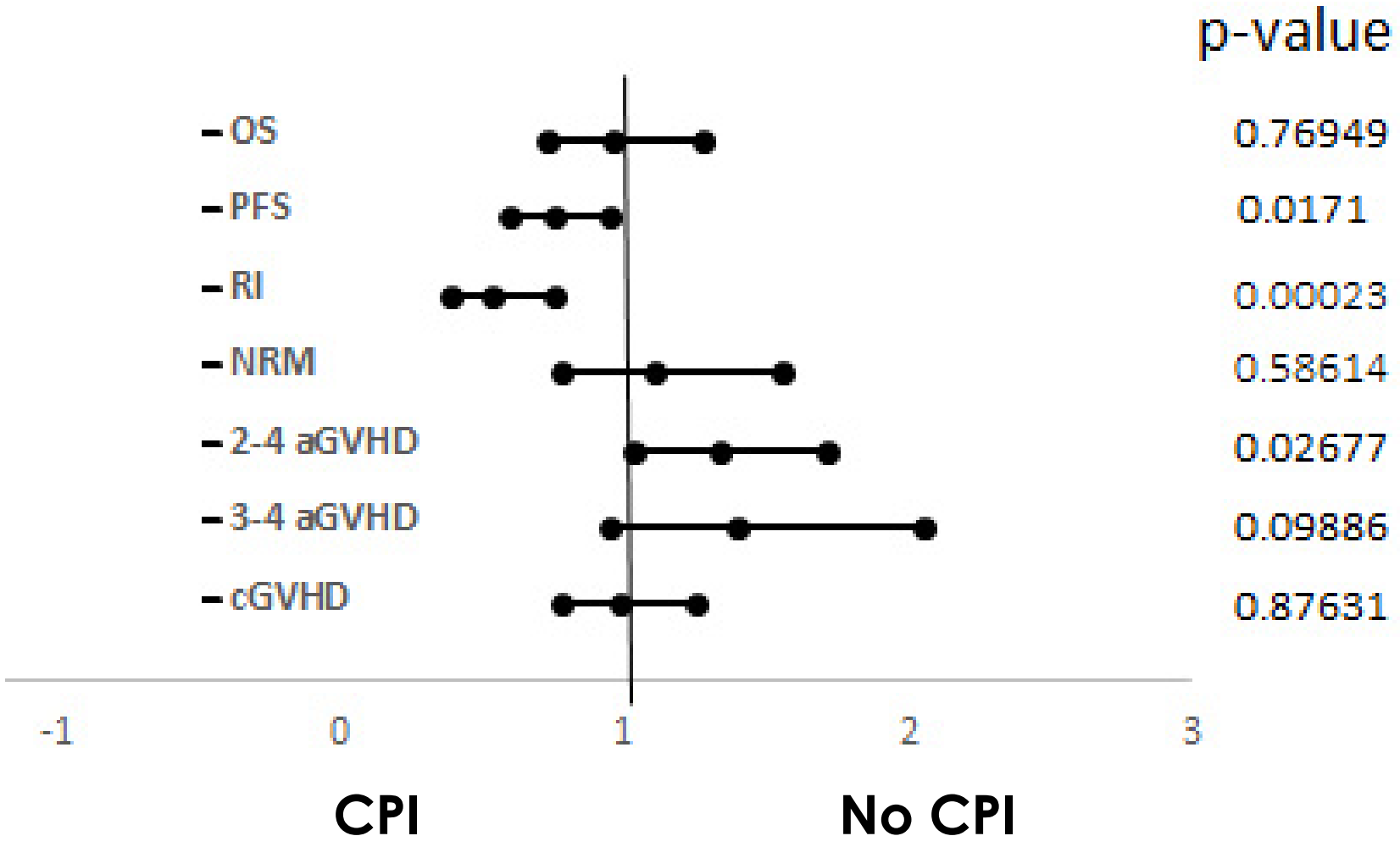
NRM



HR 1.1, 0.78-1.56; p=0.58614

Perales MA et al, EBMT 2022 (Presidential Symposium)

MVA Shows Significant Difference in PFS and Relapse Incidence, and Gr 2-4 aGVHD



Perales MA et al, EBMT 2022 (Presidential Symposium)

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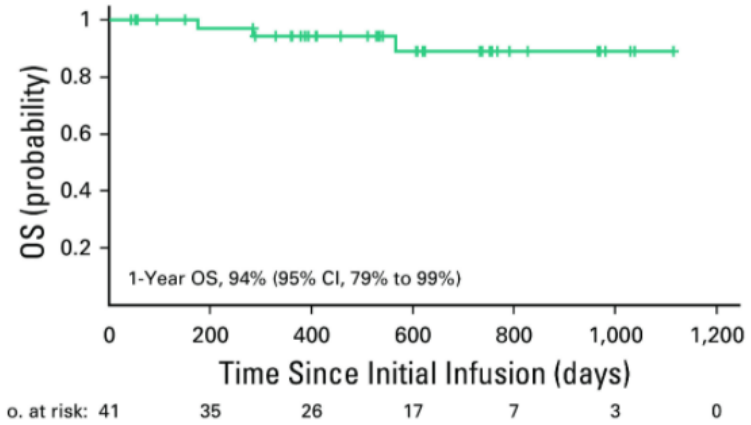
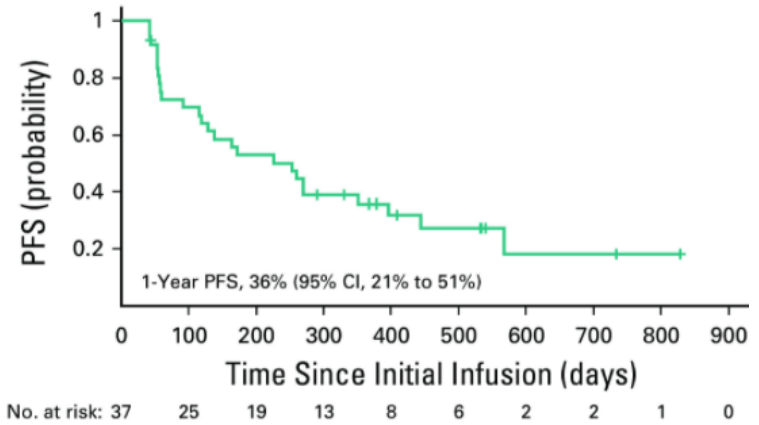
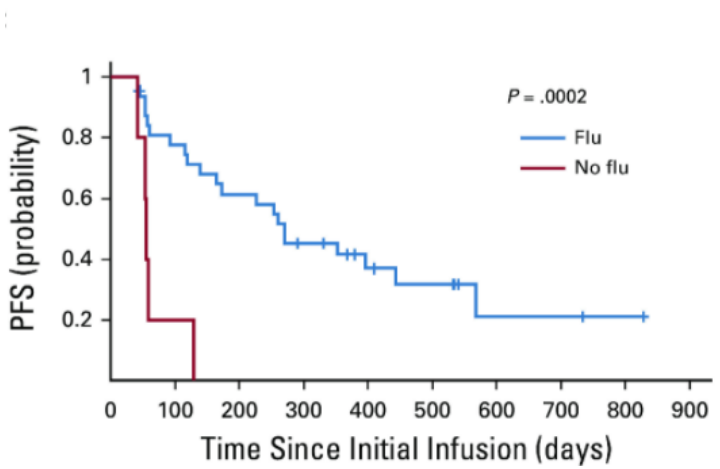
CD30 CART Cells in Patients with RR cHL







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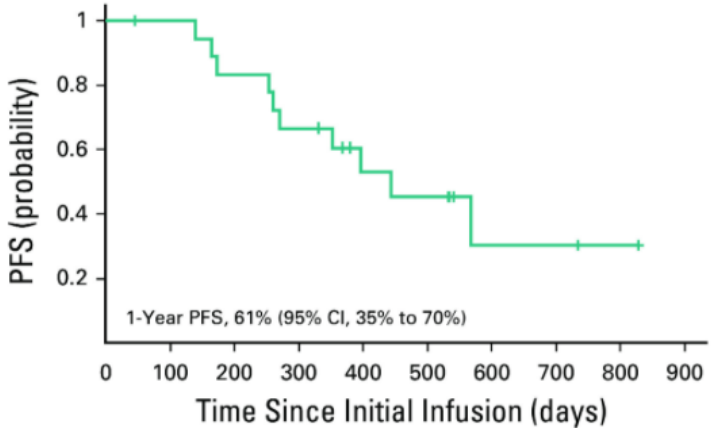
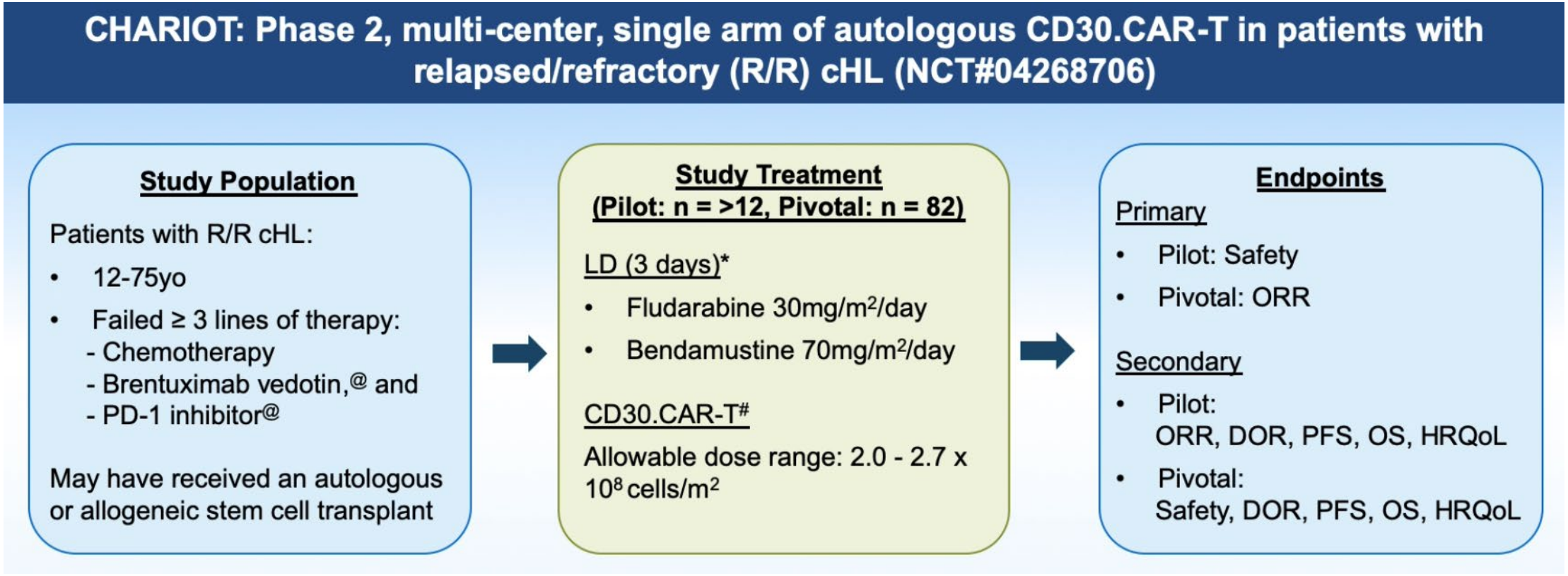


Ramos C et al, JCO 2020

CD30 CART Cells in Patients with RR cHL



Ahmed S et al, ASH2021

CD30 CART Cells in Patients with RR cHL

Patient Demographics

- Seventeen (17) R/R cHL patients were screened and 15 patients enrolled into the Pilot part of the trial, from 4 sites in the US.
  - Fourteen (14) heavily pre-treated patients were treated with Fludarabine/Bendamustine LD chemotherapy and a single infusion of CD30.CAR-T. One patient received additional dose of CD30.CAR-T following disease progression.
  - One enrolled patient is awaiting LD chemotherapy and CD30.CAR-T cells at data cut-off date.

Clinical Variables (n = 14)		No. of Patients (%)
Age (years)	Median (Range)	34 (21-57)
Sex	Male	10 (71.4)
	Female	4 (28.6)
Subtype of cHL	Nodular sclerosis	10 (71.4)
	Mixed cellularity	4 (28.6)
Lugano Classification Stage (At Study Entry)	Stage I-II	2 (14.3)
	Stage III-IV	12 (85.7)
Relapsed/ Refractory@	Relapsed	5 (35.7)
	Refractory	9 (64.3)
ECOG Performance Status	0	11 (78.6)
	1	3 (21.4)

@ To last line of prior therapy.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Clinical Variables (n = 14)		No. of Patients (%)
No. of Prior Systemic Therapy Regimens	Median (Range)	6 (3-18)
	Prior brentuximab vedotin	12 (85.7)
	Prior PD-1 inhibitor	13 (92.9)
	Prior autologous/ allogeneic stem cell transplant	12 (85.7)
Bridging Therapy & Types	Received bridging therapy, n	6 (40.0)*
	Brentuximab vedotin + steroids	1 (16.7)#
	Chemotherapy	2 (33.3)#
	Radiation	1 (16.7)#
	Immune checkpoint inhibitors	1 (16.7)#
	Steroids	1 (16.7)#

*Percentage was based on n = 15 enrolled patients.
#Percentages were based on n = 6 patients that received bridging therapies.
Abbreviation: PD-1, programmed cell death protein 1.

Ahmed S et al, ASH2021

CD30 CART Cells in Patients with RR cHL

Overall Safety Profile

- All 14 treated patients had at least 1 adverse event (AE).
- Grade 3-4 AEs were observed in 7 (50%) treated patients and most of the Grade 3-4 AEs were hematologic toxicities (anemia, neutropenia, and thrombocytopenia).
- Ten (71.4%) patients developed AEs related to CD30.CAR-T. The majority of these AEs were Grade 1-2, with Grade 3 AEs (anemia, neutropenia and thrombocytopenia) observed in 2 patients. Grade 2 ventricular tachycardia was reported in 1 (7.1%) patient.

Adverse Event Overview (N = 14)		No. of Patients N (%)
Post CD30.CAR-T Infusion	Patients with at least one AE	14 (100.0)
	Grade 3-4 AEs	7 (50.0)
	AE Related to Fludarabine/ Bendamustine	14 (100.0)
	AE Related to CD30.CAR-T Infusion	10 (71.4)
	SAEs	2 (14.3)
	AE Leading to Discontinuation	0 (0)
	Fatal AE	0 (0)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Adverse Events of Special Interest (AESI)

- One patient experienced a Grade 1 cytokine release syndrome reported as a serious adverse event (hospitalization for Grade 1 fever), which resolved within 5 days.
- No events of neurotoxicity were observed.
- Four (4) patients developed Grade 1-2 rash which were related to CD30.CAR-T. Three (3) rashes subsided with topical glucocorticoids and one was self-limited.

AESI (N = 14)	Total (%)	Grade 1 (%)	Grade 2 (%)	Grade 3-5 (%)
Cytokine Release Syndrome	1 (7.1)	1 (7.1)	0 (0)	0 (0)
ICANS (Neurotoxicity)	0 (0)	0 (0)	0 (0)	0 (0)
Rash (Including Macular and Maculo-papular)	4 (28.6)	3 (21.7)	1 (7.1)	0 (0)

Abbreviations: AESI, adverse events of special interest; ICANS, immune effector cell-associated neurotoxicity syndrome.

Ahmed S et al, ASH2021

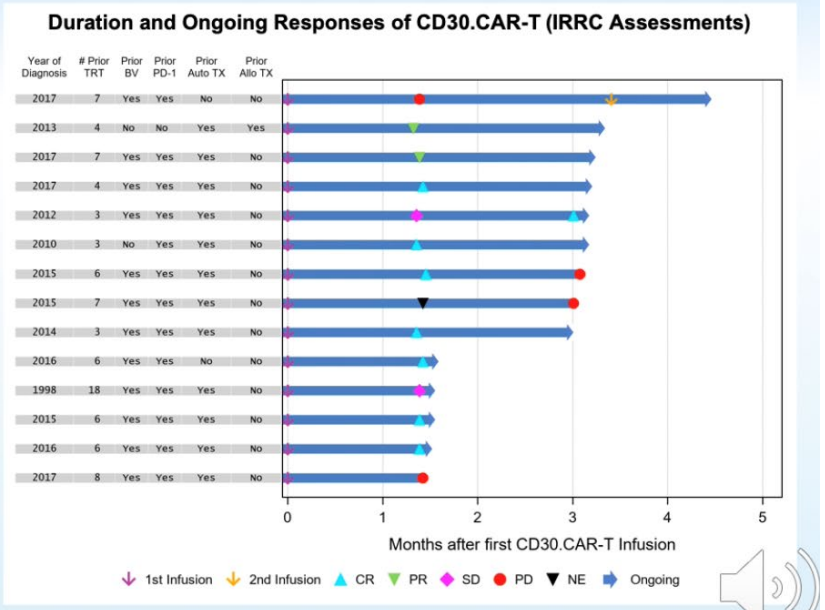
CD30 CART Cells in Patients with RR cHL

Anti-Tumor Efficacy

- Promising anti-tumor response of CD30.CAR-T was observed, with ORR of 71.4% and CR of 57.1% by IRRC assessments per Lugano Classification (Cheson, 2014).[8]
- Follow-up for duration of response is ongoing.

Response Assessments (N = 14)		By IRRC N (%)	By Investigators N (%)
ORR (CR + PR)		10 (71.4)	13 (92.9)
Best Overall Response	CR	8 (57.1)	6 (42.9)
	PR	2 (14.3)	7 (50.0)
	SD	1 (7.1)	1 (7.1)
	PD	3 (21.4)	0 (0)

Abbreviations: CR, complete response; IRRC, Independent Radiologist Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.



Ahmed S et al, ASH2021

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Checkpoint Inhibitors. Clinical Trial results

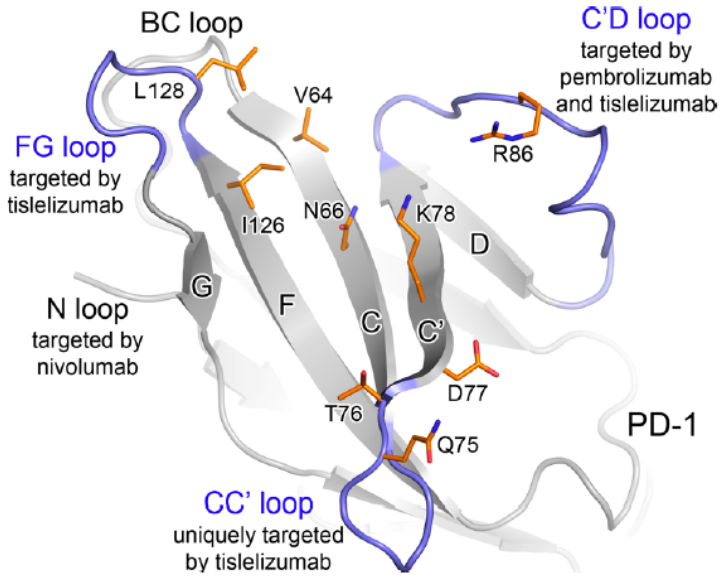
Table 1. Checkpoint inhibitors in relapsed refractory classic Hodgkin Lymphoma.

Agent	Nivolumab [13]	Pembrolizumab [14]	Sintilimab [15]	Tislelizumab [16]	Camrelizumab [17]	Avelumab [18]
Level of evidence	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2	Phase 1
Prior therapy	Progressive after ASCT, BV-naïve or BV-received	progressive after ASCT, 20% prior BV, 20% prior PD-1 blocker	ASCT-ineligible or progressive after ASCT, 6% had prior BV	ASCT ineligible or progressive after ASCT, 6% had prior BV	ASCT ineligible or progressive after ASCT, 8% had BV	SCT ineligible or progressive after SCT, 27% had prior allo-SCT
Regimen	3 mg/kg Q2weeks	200 mg Q3week	200 mg Q3week	200 mg Q3week	200 mg Q3week	Dose escalation upto 10 mg/kg Q3week
Response rate	ORR: 69% CR:16%	ORR: 71.9% CR: 27.6%	ORR:80.4% CR: 34%	ORR: 87.1% CR: 62.9%	ORR: 78.3% CR: 37.3	ORR: 54.8% CR: 6.5%
Survival	Median PFS: 14.7 months	Median PFS 13.7 months	77% alive and progression-free at 6 months	84.1% alive and progression-free at 6 months	81.1% were alive and progression-free at 6 months	NA
AE	12% serious drug related AE.	72.9%, 12% ≥grade 3	any grade 100%, ≥grade 3 25%	Any grade 92.9%, ≥grade 3 21.4%	Any grade: 100% ≥grade 3 32%	≥grade 3: 36.7%
Common AE:	Fatigue (23%), diarrhea (15%), and IRR (14%);	Hypothyroidism (14.3%) Fever (11.4%) Rash (11%) Fatigue (11%) Diarrhea (8.6%) Neutropenia (5.2%)	Pyrexia (43%), hypothyroidism (22%), transaminitis (10%), pneumonitis (13%), rash (10%)	Rash (10%), transaminitis (12%), URTI (10%) diarrhea (10%), cytopenias (10–15%)	RCEP (97%) Transaminitis (25%) Cytopenia (13–14%) Hypothyroidism (26%)	IRR (26.7%), nausea (20.0%), rash (20.0%), fatigue (13. 3%
Grade 3 Pneumonia/ pneumonitis	2%	4.8%	1%	5.7%	4.0%	NA
irAE	40%	33.8%	54%	39%	14.7%	NA
IRR	14%	5.2%	9%	38.6%	14%	26.7%

ASCT: autologous stem cell transplant (ASCT); BV: brentuximab vedotin; PD-1: programmed cell death-1; SCT: stem cell transplant (autologous and allogeneic); allo-SCT: allogeneic stem cell transplant; Q: every; ORR: overall response rates; CR: complete response; PFS: progression free survival; NA: not available; AE: adverse event; RCEP: reactive capillary endothelial proliferation; IRR: infusion related reactions; irAE: immune related adverse events; URTI: upper respiratory tract infection.

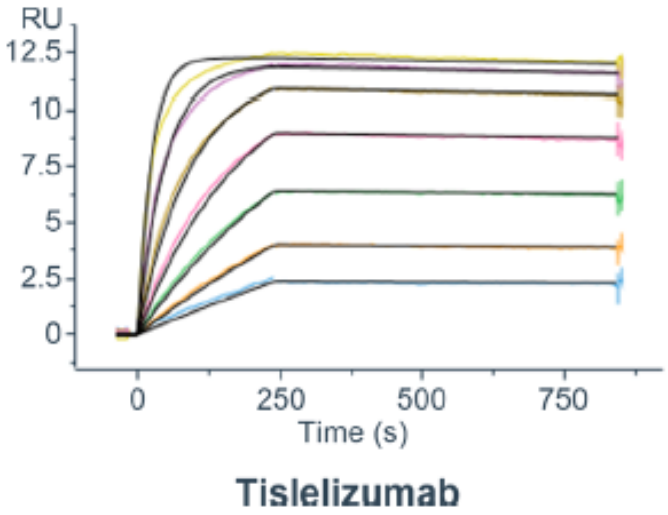
Desai & Ansell. Leukemia and Lymphoma, 2021

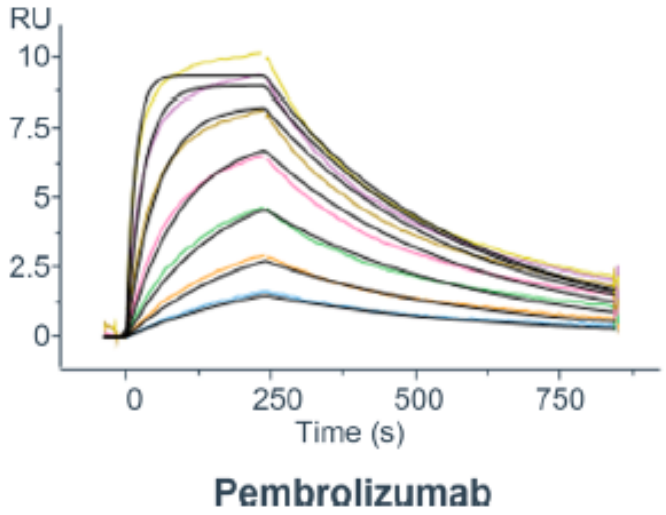
Newer PD1 inhibitors

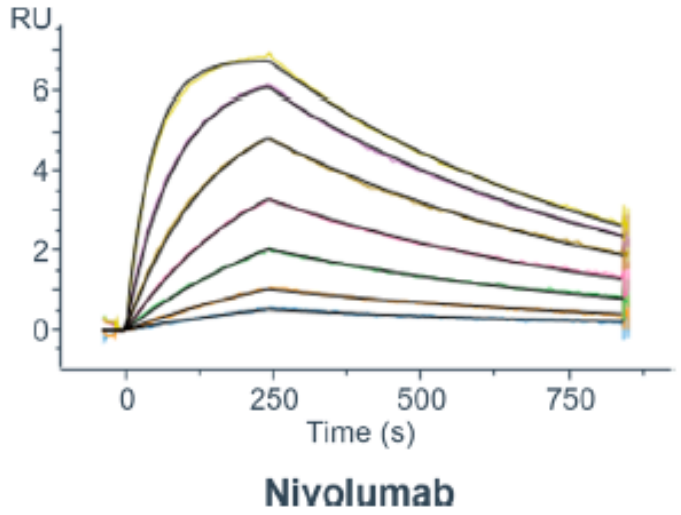


Hong et al (2021) FEBS Open Bio

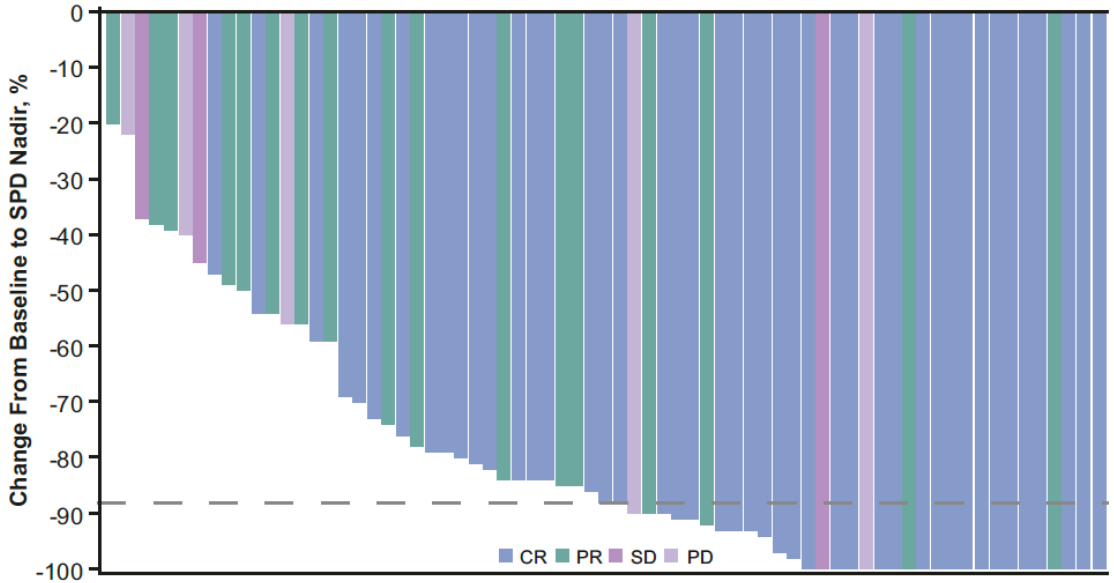
- Crystal structural studies of PD1-drug binding reveal some unique epitopes (note the CC' loop)
- Translates into different binding kinetics
- Tislelizumab has markedly prolonged dissociation rate

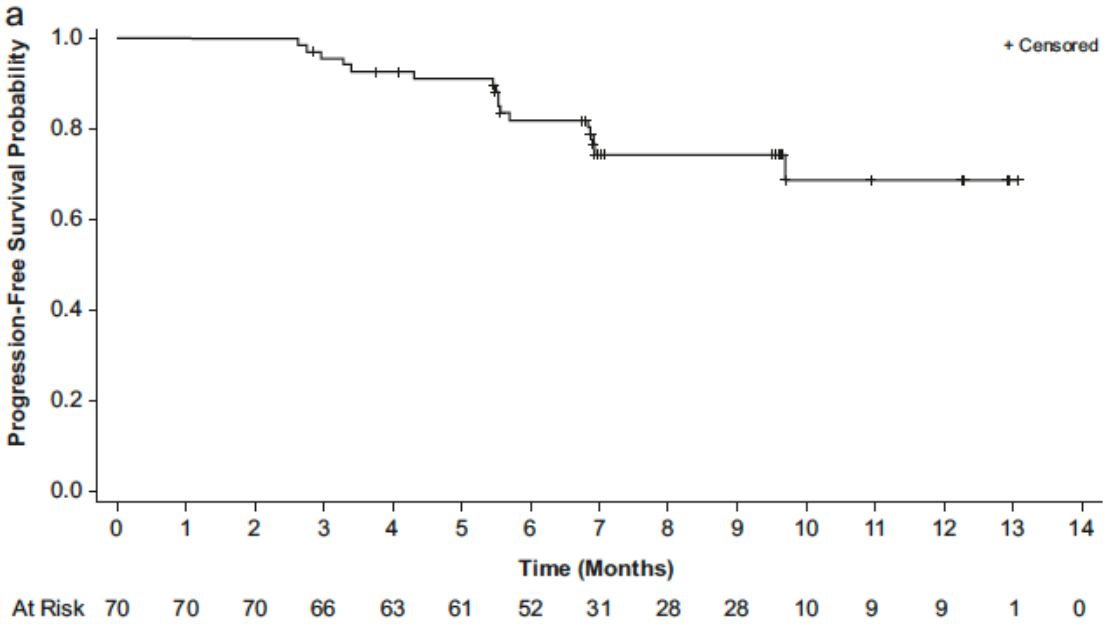






Tislelizumab Clinical Data





Song et al (2020) Leukemia

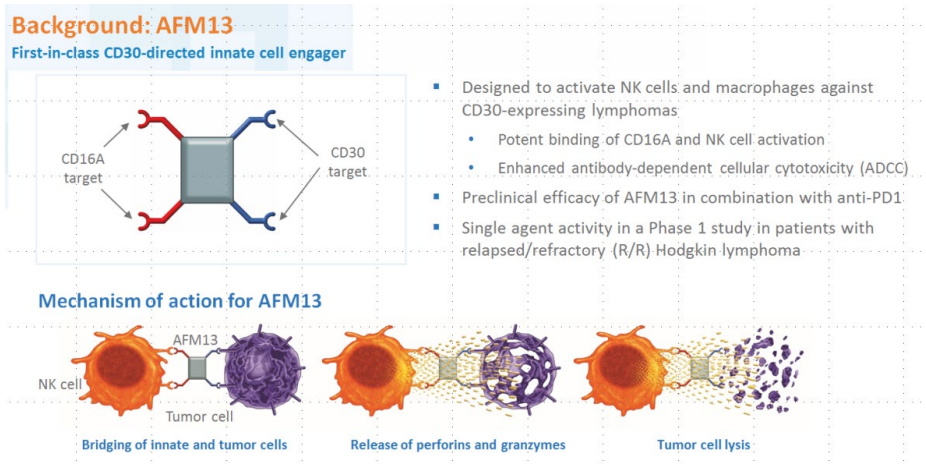
- 70 pts, median age 33y, median prior lines 3, mostly BV naïve, 52% refractory, 82% not suitable ASCT
- Median FU 9.8mo; 24% discontinued Rx
- ORR: 87%; CRR: 63% (52% CRR in primary refractory)
- Infusion reactions 36% (1 G3); 4 pts discontinued due to irAE (3 pneumonitis; 1 renal injury)

Treatment Strategies for Patients Failing Auto-HCT, BV and CPIs

- Allogeneic Stem Cell Transplantation
- CD30 CART Cells
- New checkpoint inhibitors
- AFM-13
- Camidanlumab Tesirine
- Small molecules

A phase 1b study of AFM13 in combination with pembrolizumab in patients with relapsed or refractory Hodgkin lymphoma

Nancy L. Bartlett,[1] Alex F. Herrera,[2] Eva Domingo-Domenech,[3] Amitkumar Mehta,[4] Andres Forero-Torres,[4] Ramon Garcia-Sanz,[5] Philippe Armand,[6] Sumana Devata,[7] Antonia Rodriguez Izquierdo,[8] Izidore S. Lossos,[9] Craig Reeder,[10] Taimur Sher,[11] Robert Chen,[2] Sylvia E. Schwarz,[12] Leila Alland,[13] Andras Strassz,[12] Kim Prier,[12] Cassandra Choe-Juliak,[13] and Stephen M. Ansell[14]



	Part 1			Part 2		
	Cohort 1 (0.1 × 3)/0.5 mg/kg (n = 3)	Cohort 2 (0.5 × 3)/1.5 mg/kg (n = 3)	Cohort 3 (3.0 × 3)/7.0 mg/kg (n = 6)	(3.0 × 3)/ 7.0 mg/kg (n = 18)	MAD* (3.0 × 3)/ 7.0 mg/kg (n = 24)	All patients (N = 30)
Median age, y (min, max)	29.0 (25, 73)	34.0 (33, 53)	36.0 (26, 49)	27.5 (18, 52)	32.0 (18, 52)	33.5 (18, 73)
Sex						
Male	2 (66.7)	2 (66.7)	5 (83.3)	11 (61.1)	16 (66.7)	20 (66.7)
Female	1 (33.3)	1 (33.3)	1 (16.7)	7 (38.9)	8 (33.3)	10 (33.3)
Prior therapies, no. (%)						
3	0	0	0	14 (77.8)	14 (58.3)	14 (46.7)
4	1 (33.3)	1 (33.3)	3 (50.0)	2 (11.1)	5 (20.8)	7 (23.3)
5	0	1 (33.3)	2 (33.3)	0	2 (8.3)	3 (10.0)
6	1 (33.3)	1 (33.3)	1 (16.7)	1 (5.6)	2 (8.3)	4 (13.3)
7	1 (33.3)	0	0	1 (5.6)	1 (4.2)	2 (6.7)
Prior autologous stem cell transplant	2 (66.7)	3 (100.0)	4 (66.7)	3 (16.7)	7 (29.2)	12 (40.0)

Bartlett N et al, Blood 2020

AFM-13 in Combination with Pembrolizumab for RR cHL

	AFM13		AFM13 + pembrolizumab	
	All grades, ≥10% (n = 30), n (%)	≥Grade 3 (n = 30), n (%)	All grades, ≥10%, n (%)	≥Grade 3 (n = 30), n (%)
Any AE	29 (97)	7 (23)	22 (73)	2 (7)
IRR	27 (90)	4 (13)	8 (27)	1 (3)
Rash	9 (30)	—	6 (20)	—
Nausea	7 (23)	1 (3)	7 (23)	1 (3)
Pyrexia	7 (23)	—	4 (13)	—
Fatigue	5 (17)	—	5 (17)	—
Diarrhea	6 (20)	—	5 (17)	—
Headache	5 (17)	—	3 (10)	—
Elevated ALT	4 (13)	—	3 (10)	—
Elevated AST	4 (13)	1 (3)	2 (7)	—
Neutropenia	2 (7)	1 (3)	2 (7)	—
Gastritis	1 (3)	1 (3)	1 (3)	1 (3)
Vomiting	2 (7)	1 (3)	1 (3)	1 (3)
Hypotension	1 (3)	1 (3)	—	—
Thrombocytopenia	2 (7)	—	2 (7)	—
URTI	2 (7)	—	2 (7)	—

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AFM-13 in Combination with Pembrolizumab for RR cHL

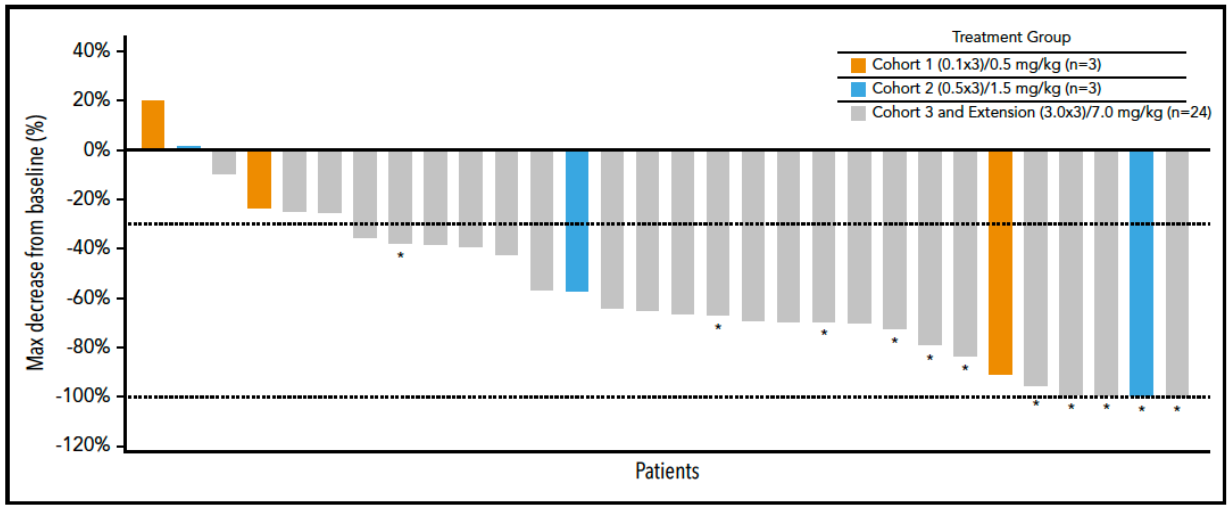

Figure 1. Best response according to tumor volume. The dashed line (−30%) represents clinically meaningful responses (30% reduction from baseline). *All assessments are based on CT scan, CRs are based on PET scans (metabolic assessment) and appear opaque on CT scans. NE, not evaluable; PR, partial response; SD, stable disease.

	CMR, n (%)	PMR, n (%)	NMR, n (%)	PD, n (%)	ORR, n (%)
Investigator assessment					
Cohorts 1 and 2 (n = 6)	1 (17%)	3 (50%)	0 (0%)	2 (33%)	4 (67%)
Cohort 3 and extension (n = 24)	10 (42%)	11 (46%)	2 (8%)	1 (4%)	21 (88%)
Safety analysis set (n = 30)	11 (37%)	14 (47%)	2 (7%)	3 (10%)	25 (83%)
Investigator assessment					
Cohorts 1 and 2 (n = 5)	1 (20%)	2 (40%)	2 (40%)	0 (0%)	3 (60%)
Cohort 3 and extension (n = 24)	11 (46%)	10 (42%)	0 (0%)	3 (13%)	21 (88%)
Safety analysis set (n = 29)	12 (42%)	12 (42%)	2 (7%)	3 (10%)	24 (83%)

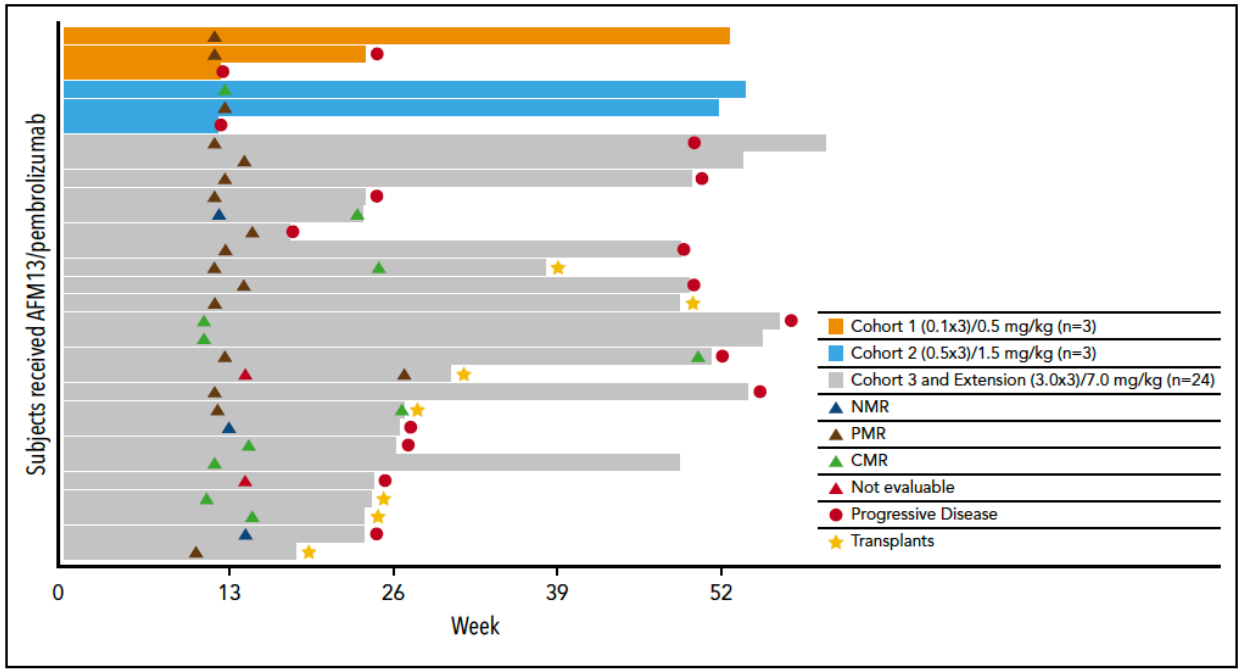

Figure 2. Duration and deepening of responses.

Bartlett N et al, Blood 2020

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Camidanlumab tesirine in patients with relapsed or refractory lymphoma: a phase 1, open-label, multicentre, dose-escalation, dose-expansion study

Mehdi Hamadani, Graham P Collins, Paolo F Caimi, Felipe Samaniego, Alexander Spira, Andrew Davies, John Radford, Tobias Menne, Anand Karnad, Jasmine M Zain, Paul Fields, Karin Havenith, Hans G Cruz, Shui He, Joseph Boni, Jay Feingold, Jens Wuerthner, Steven Horwitz

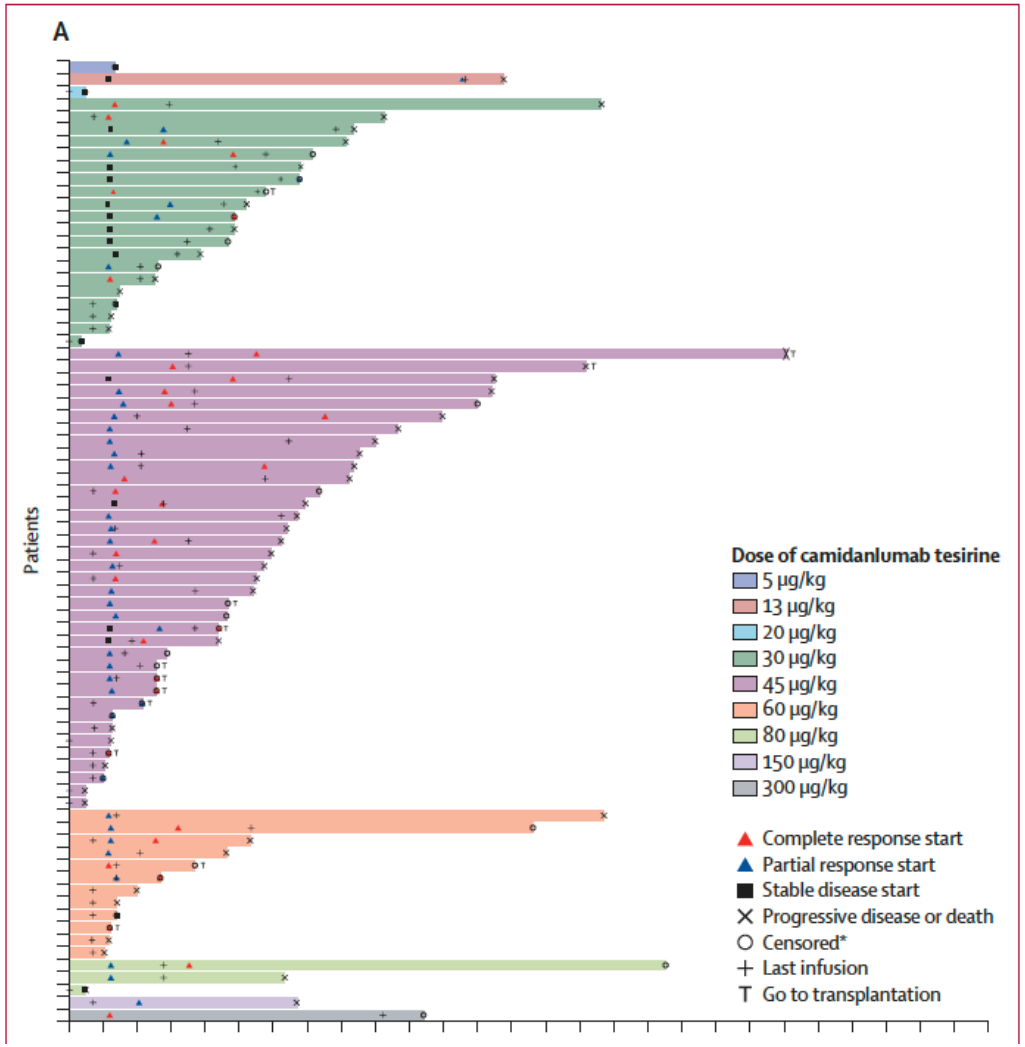
More significant side effects:

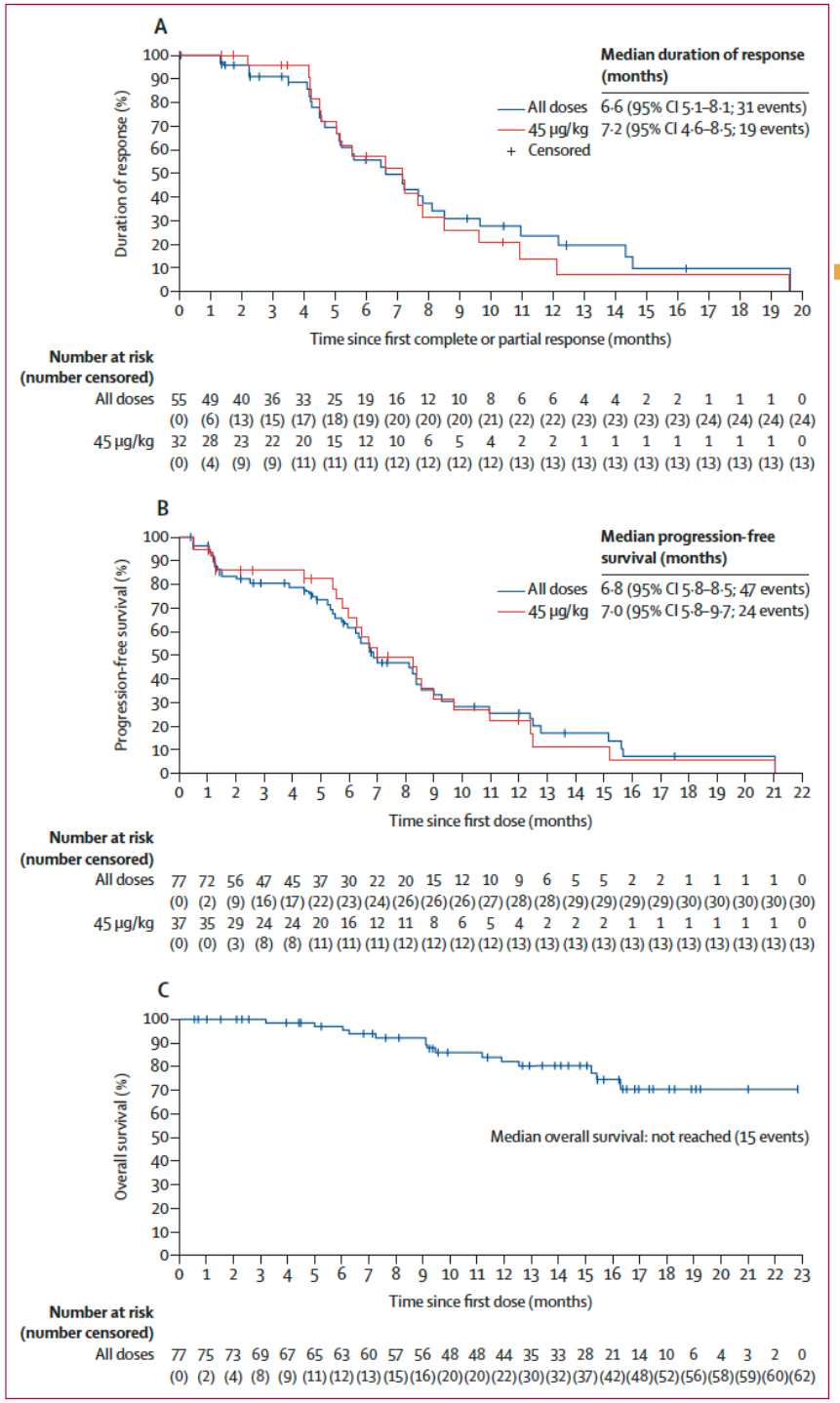
- Autoimmune toxicities:
  - Peripheral sensory neuropathy: 9 (7%)
  - Hypothyroidism: 8 (6%)
- Guillain-Barré syndrome: 5 (4%)

Characteristic	N = 77
Sex Male / Female	 33 (43%) / 44 (57%)
Age (years)	38 (31-53)
ECOG PS 0/1/2	 31 (40%) / 42 (55%) / 4 (5%)
Disease stage at inclusion 1-2 3 /4	 25 (32%) 16 (21%) / 36 (47%)
Previous systemic therapies [median (range)]	5 (4 – 7)
Previous BV	75 (97%)
Previous CPIs	57 (74%)
Previous BV + CPIs	57 (74%)
Previous HCT auto-HCT allo-HCT Both	47 (61%) 37 (48%) 3 (4%) 7 (9%)
Response to initial therapy Relapsed / Refractory	 50 (65%) / 25 (32%)
Response to last therapy Relapsed / Refractory / other	 24 (31%) / 49 (64%) / 4 (5%)

Hamadani M et al, Lancet Hermatol 2021

Cami-T in Patients with RR cHL





Hamadani M et al, Lancet Hematol 2021

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Small Molecules in the Tx of RR cHL

- The combination of ruxolitinib (20 mg BID daily) + nivolumab 480 mg IV monthly in patients that have failed CPIs (Bachanova V et al, ASH 2021)
  - Well tolerated (27% immune mediated adverse reactions)
  - High remission frates (24% CR) and durable responses (median DOR 12.5 mo)
- The combination of vorinostat (100-200 mg BID D1-5, 8-12) + pembrolizumab (200 mg D1)
  - Well tolerated
  - ORR 75%, CR 34%
  - 1-yr DoR 67%
  - 1-yr PFS 47% / 1-yr OS 93%

Hamadani M et al, Lancet Hermatol 2021

Conclusions

- The landscape of “triple refractory” cHL has significantly changed
- Allo-HCT still represents the only curative strategy for these patients
  - Importance of modulating toxicities after transplant related to CPI
- Many promising immunotherapy strategies in the setting of prospective clinical trials
- Other new molecules are coming

Thanks for Your Attention!!

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