Lymphoma Update 2022:

Big Phase III Trials, the *Most* Rapid Progress in Oncology

Hodgkin: new 1st line rx

Non-Hodgkin: CAR-T Cellular Therapy and Beyond

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Disclosure of Conflicts of Interest

Joshua Brody MD, has the following financial relationships to disclose:

Research Funding:

Astrazeneca, Genentech/Roche, Kite/Gilead, Merck

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ADC Therapeutics, Asgard Therapeutics AB, Conjupro Biotherapeutics, Epizyme, Genentech/Roche, Kite/Gilead, Seattle Genetics

Hodgkin Lymphoma Update 2022

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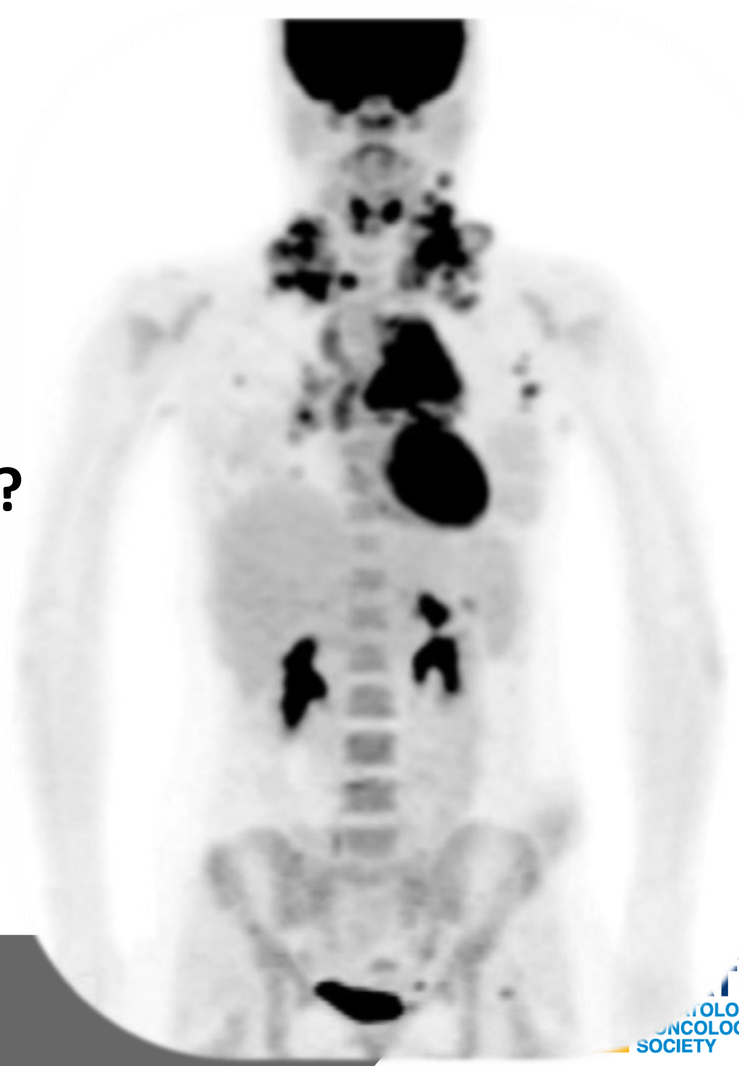
Case Study

21 year old healthy woman in final semester of college, develops cervical adenopathy.

- FNA: non-diagnostic
- rx with abx with persistent progression of LNs
- excisional bx: nodular sclerosing Hodgkin lymphoma.
- PET: FDG-avid adenopathy above/below diaphragm
- Dx: stage IIIA



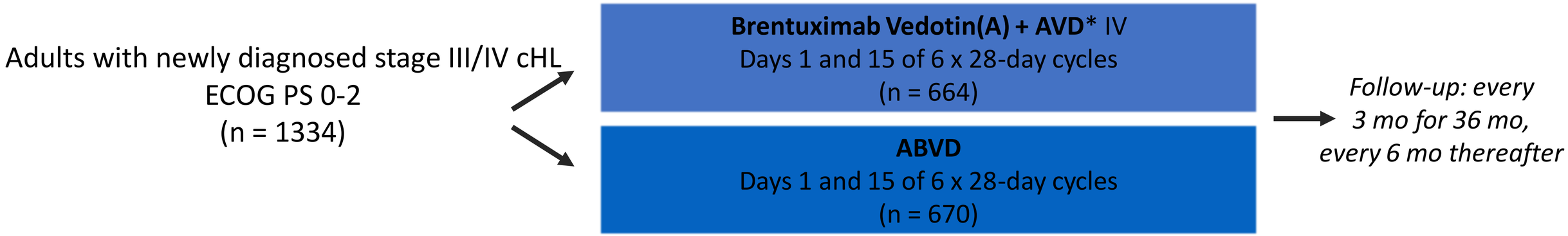
Which is true for patients with advanced stage Hodgkin lymphoma?

A. AAVD has superior overall survival (OS) versus ABVD
B. AAVD has superior PFS versus ABVD but no difference in OS
C. AAVD has inferior PFS versus ABVD
D. AAVD has inferior overall survival versus ABVD

1st line: AAVD vs ABVD – ECHELON-1

ECHELON-1 Update: Background

- Updated analysis of international, open-label phase III trial (median follow-up: 73 mo)



Primary endpoint: modified PFS per independent review

2-yr PFS rate with BV + AVD vs ABVD: 82.1% vs 77.2% (HR: 0.77; *P* = .04)

Update:

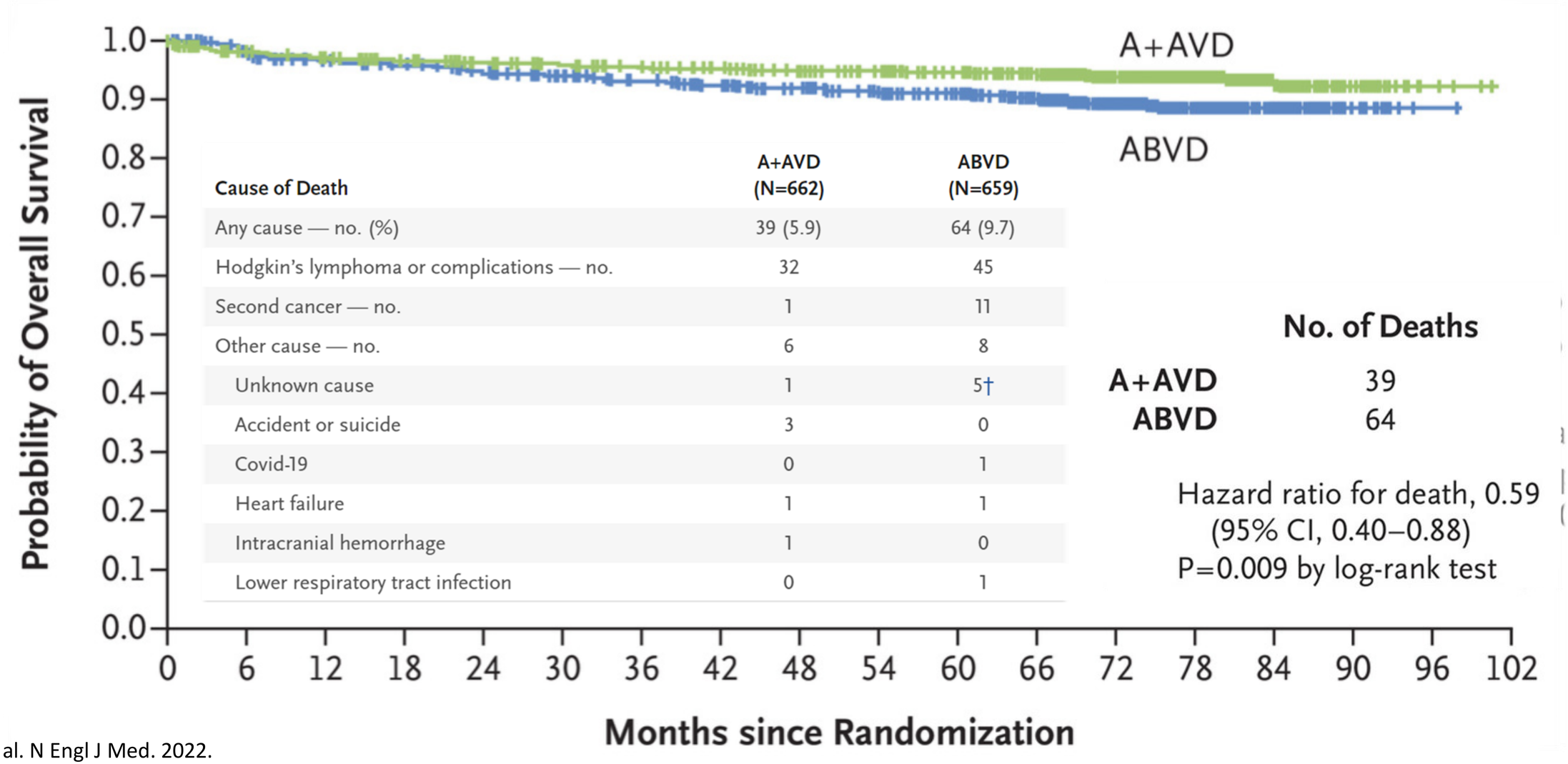
Key secondary endpoint: α-controlled, event-driven OS analysis

LTFU assessments: OS for PET2+ vs PET2- patients; investigator-assessed PFS; subsequent tx; safety

Connors. NEJM. 2018;378:331. NCT01712490.

1st line: AAVD vs ABVD – ECHELON-1

ECHELON-1 Update: PFS and Overall Survival

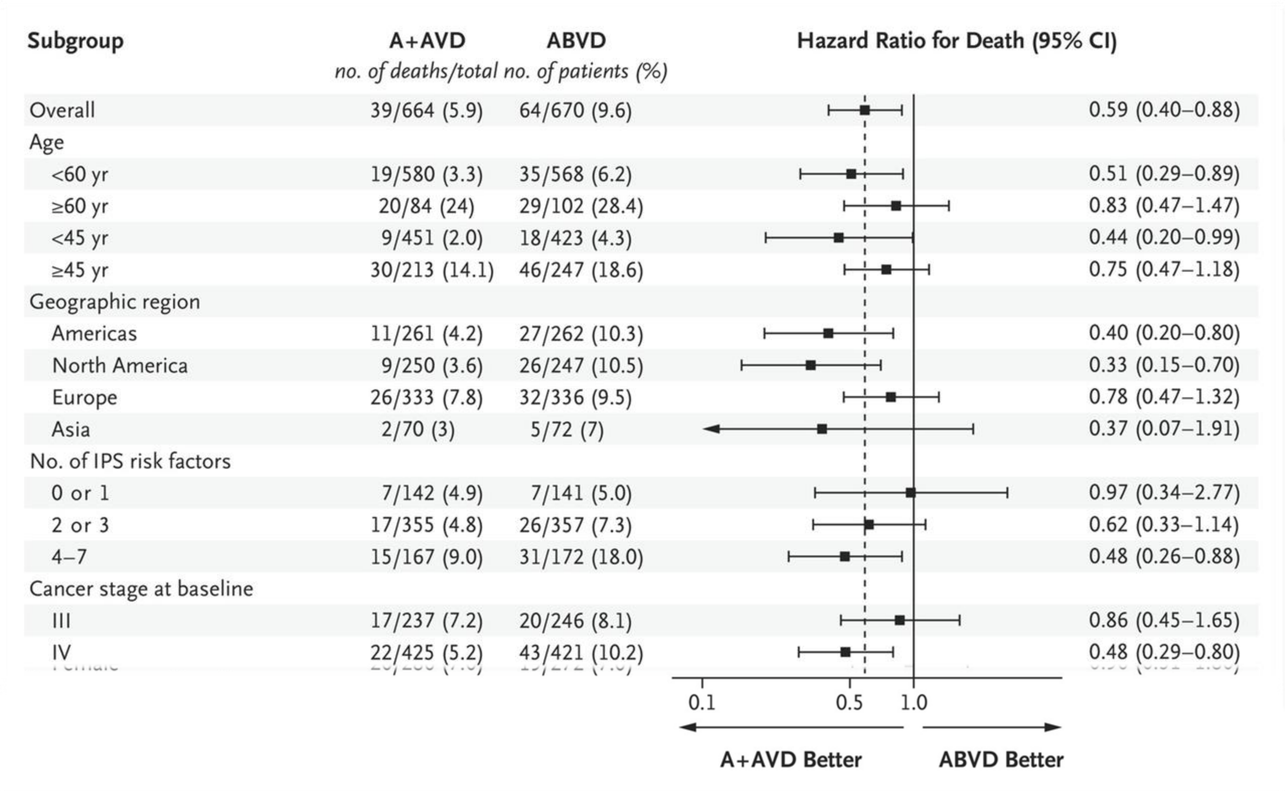


Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

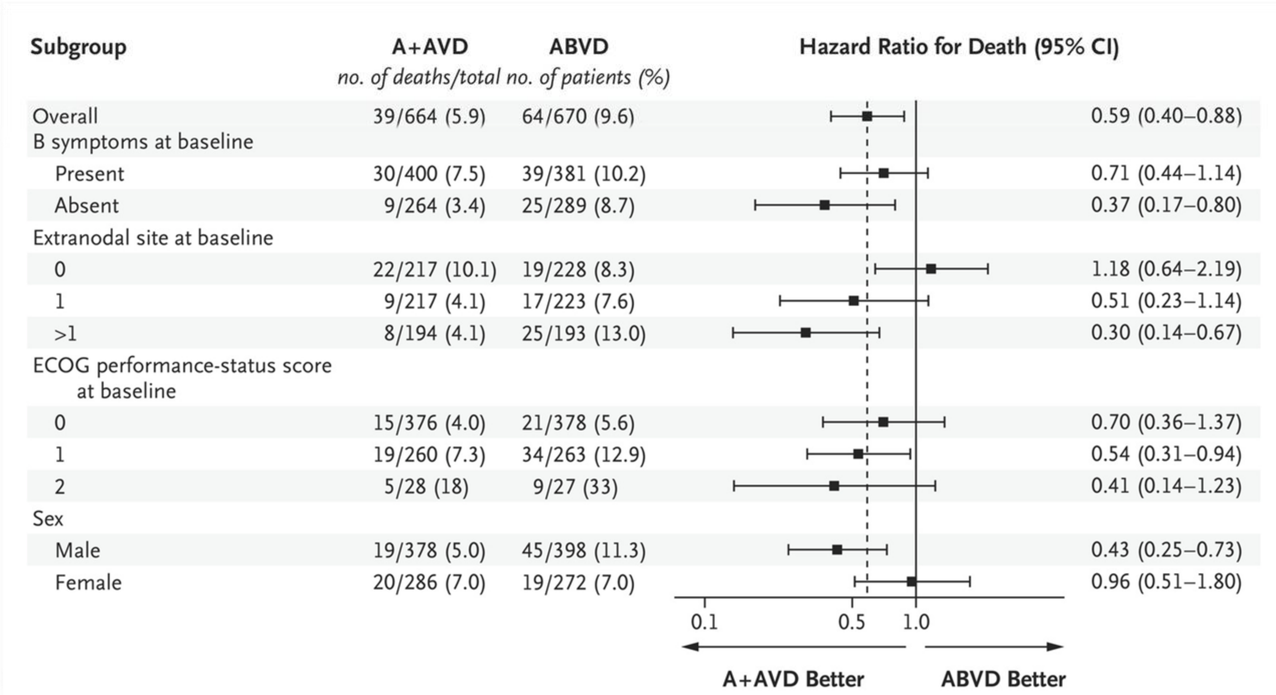
Ansell SM, et al. N Engl J Med. 2022.

1st line: AAVD vs ABVD – ECHELON-1

ECHELON-1 Update: PFS and Overall Survival



Subgroup	A+AVD	ABVD	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40–0.88)
Age			
<60 yr	19/580 (3.3)	35/568 (6.2)	0.51 (0.29–0.89)
≥60 yr	20/84 (24)	29/102 (28.4)	0.83 (0.47–1.47)
<45 yr	9/451 (2.0)	18/423 (4.3)	0.44 (0.20–0.99)
≥45 yr	30/213 (14.1)	46/247 (18.6)	0.75 (0.47–1.18)
Geographic region			
Americas	11/261 (4.2)	27/262 (10.3)	0.40 (0.20–0.80)
North America	9/250 (3.6)	26/247 (10.5)	0.33 (0.15–0.70)
Europe	26/333 (7.8)	32/336 (9.5)	0.78 (0.47–1.32)
Asia	2/70 (3)	5/72 (7)	0.37 (0.07–1.91)
No. of IPS risk factors			
0 or 1	7/142 (4.9)	7/141 (5.0)	0.97 (0.34–2.77)
2 or 3	17/355 (4.8)	26/357 (7.3)	0.62 (0.33–1.14)
4–7	15/167 (9.0)	31/172 (18.0)	0.48 (0.26–0.88)
Cancer stage at baseline			
III	17/237 (7.2)	20/246 (8.1)	0.86 (0.45–1.65)
IV	22/425 (5.2)	43/421 (10.2)	0.48 (0.29–0.80)



Subgroup	A+AVD	ABVD	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	39/664 (5.9)	64/670 (9.6)	0.59 (0.40–0.88)
B symptoms at baseline			
Present	30/400 (7.5)	39/381 (10.2)	0.71 (0.44–1.14)
Absent	9/264 (3.4)	25/289 (8.7)	0.37 (0.17–0.80)
Extranodal site at baseline			
0	22/217 (10.1)	19/228 (8.3)	1.18 (0.64–2.19)
1	9/217 (4.1)	17/223 (7.6)	0.51 (0.23–1.14)
>1	8/194 (4.1)	25/193 (13.0)	0.30 (0.14–0.67)
ECOG performance-status score at baseline			
0	15/376 (4.0)	21/378 (5.6)	0.70 (0.36–1.37)
1	19/260 (7.3)	34/263 (12.9)	0.54 (0.31–0.94)
2	5/28 (18)	9/27 (33)	0.41 (0.14–1.23)
Sex			
Male	19/378 (5.0)	45/398 (11.3)	0.43 (0.25–0.73)
Female	20/286 (7.0)	19/272 (7.0)	0.96 (0.51–1.80)

Ansell SM, et al. N Engl J Med. 2022.

Ansell. ASCO 2022. Abstr 7503.

1st line: AAVD vs ABVD – ECHELON-1

ECHELON-1 Update: late effects, good and bad

Pregnancies	A+AVD (n=662)	ABVD (n=659)
Partners of male patients pregnant — n*	33	33
Total pregnancies – n*	44	46
Live birth‡	40	36
Pregnancy ongoing	1	6
Early termination	3	4
Stillbirth	0	0

Peripheral Neuropathy	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing PN events at last follow-up — n (%)	125 (18.9)	59 (9.0)
Grade 1	71 (10.7)	39 (5.9)
Grade 2	38 (5.7)	16 (2.4)
Grade 3‡	15 (2.3)	4 (0.6)
Grade 4‡	1 (0.2)	0

Second malignancies:

- AAVD, n = 23 (9 heme ; 14 solid) (2 s/p BMT)
- ABVD, n = 32 (17 heme ; 14 solid) (2 s/p BMT)

Ansell SM, et al. N Engl J Med. 2022.

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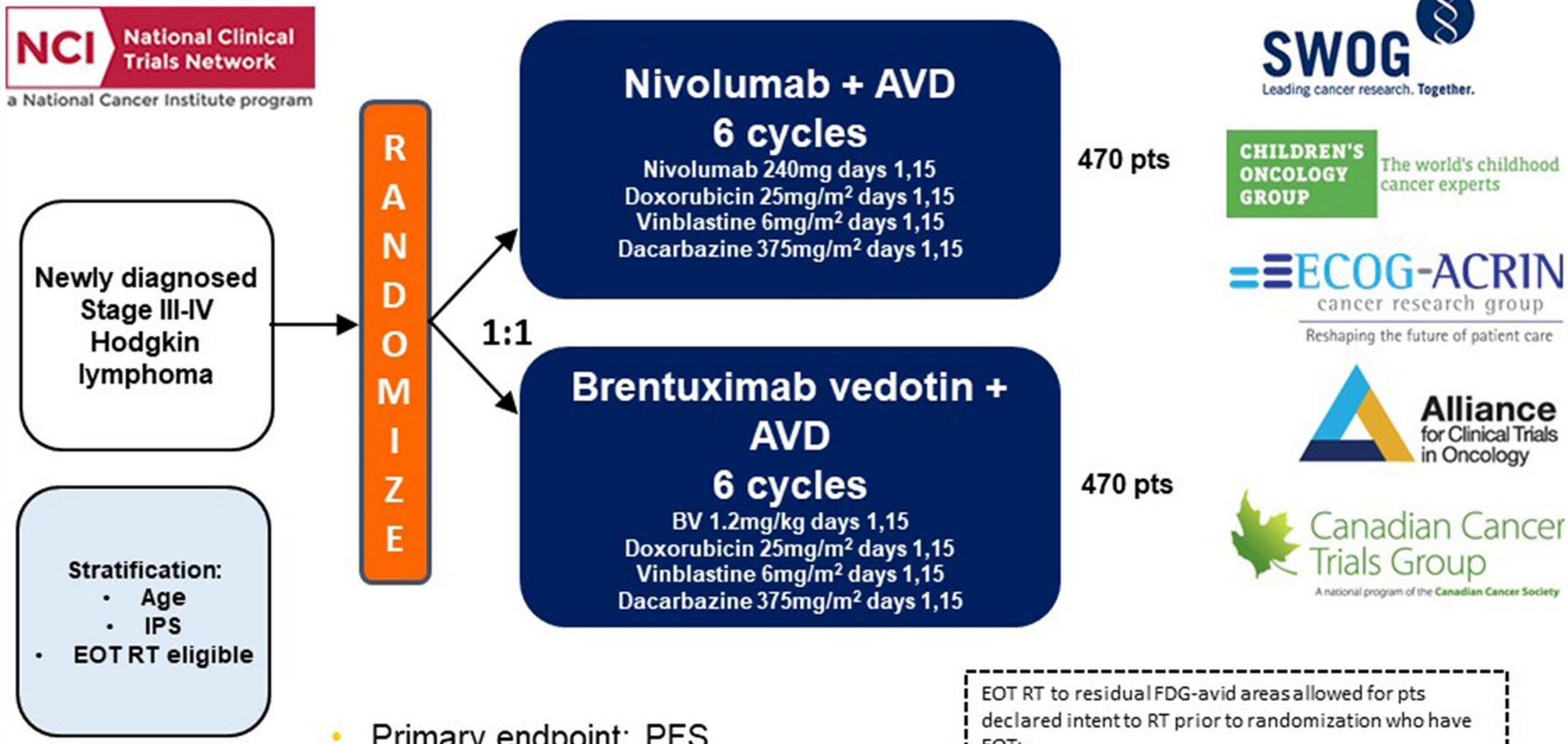
1st line: AAVD vs Nivo-AVD – SWOG 1826 (ongoing)



- Primary endpoint: PFS
- Secondary endpoints: EFS, OS, CR

EOT RT to residual FDG-avid areas allowed for pts declared intent to RT prior to randomization who have EOT:

- DS 4-5
- ≥ 30% reduction in max transverse diameter

AND

- Residual LN ≥ 2.5cm

OR

- Residual extranodal lesion > 1cm

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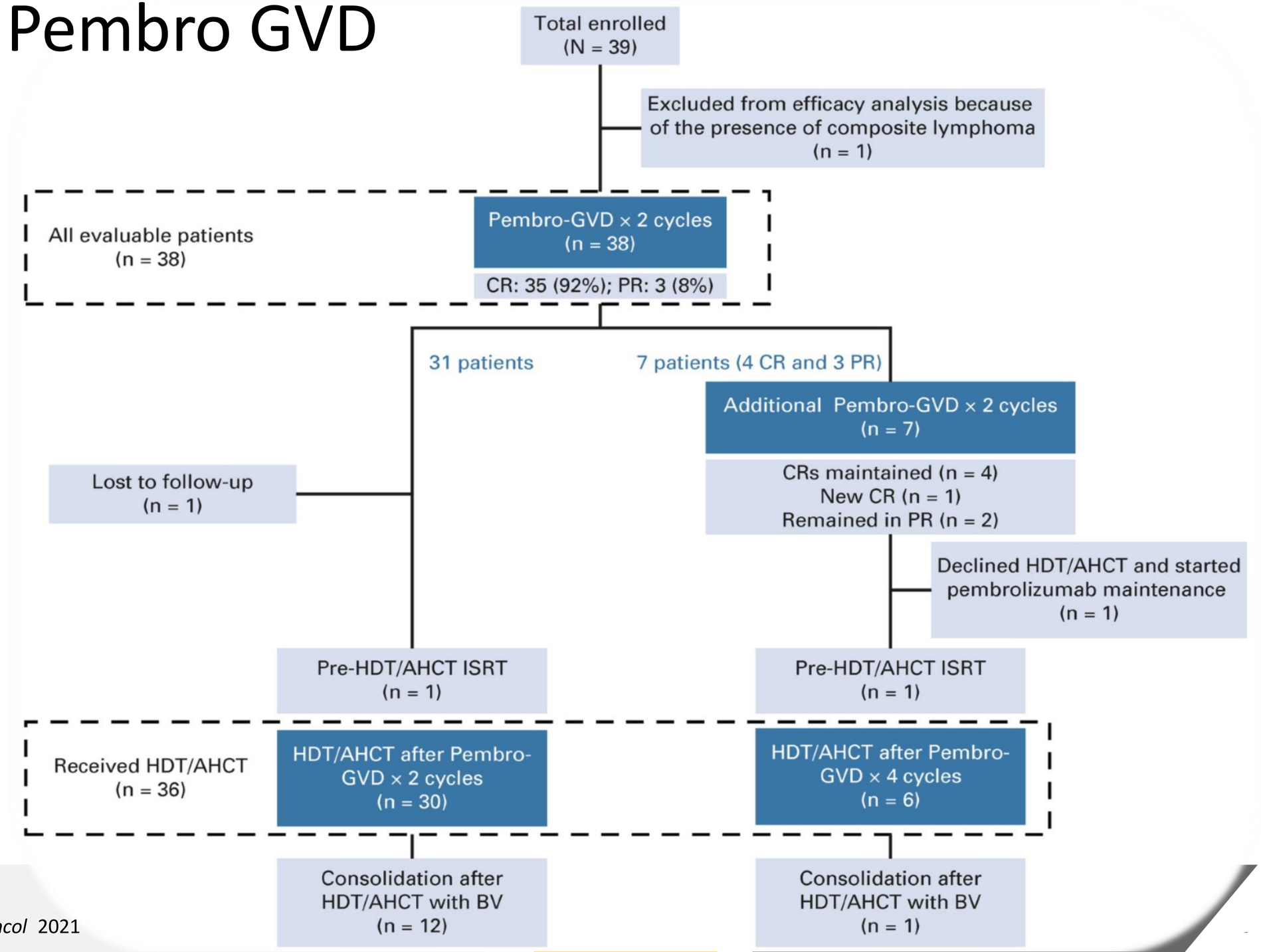
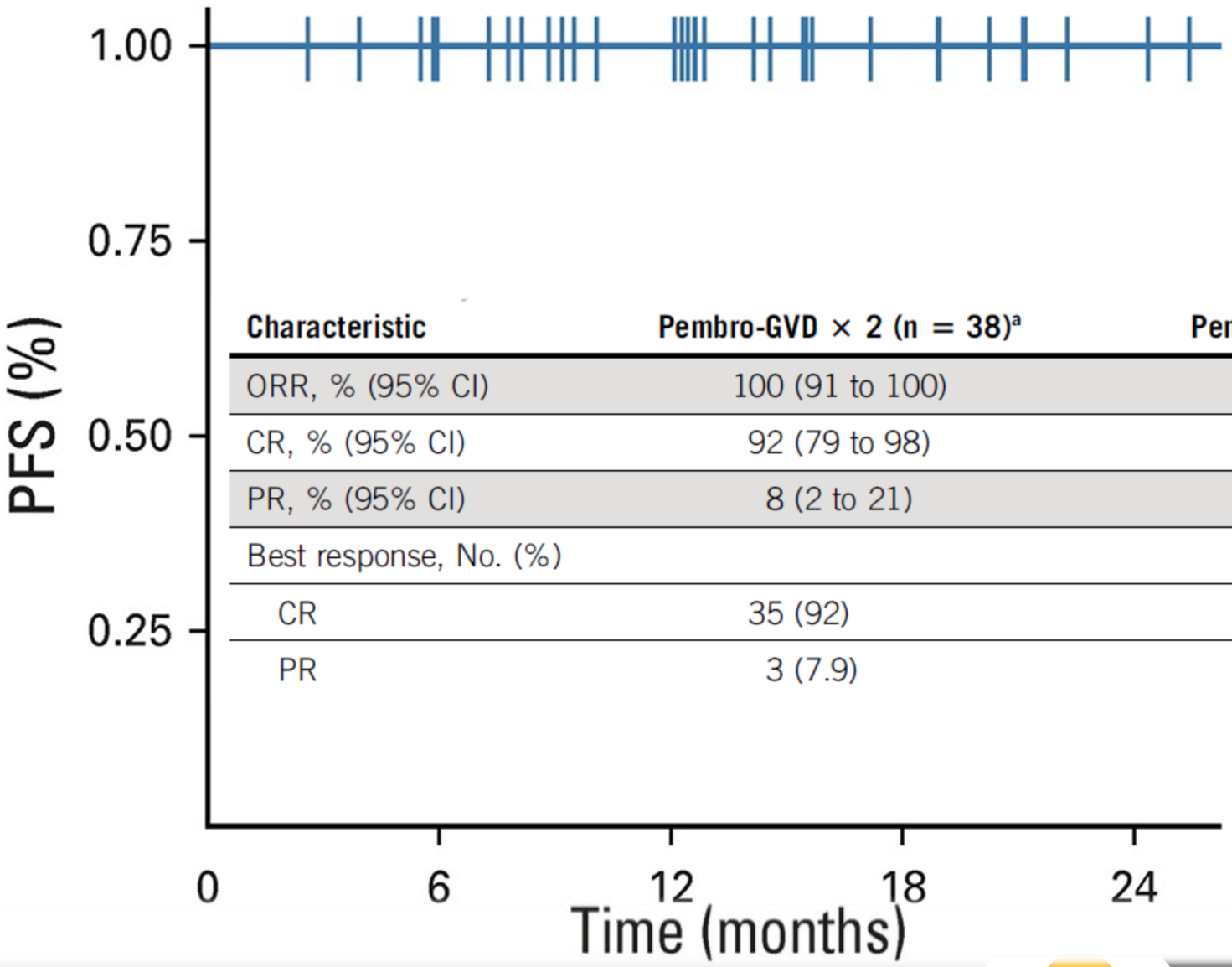
2nd line: Pembro GVD



Moskowitz AJ et al., *J Clin Oncol* 2021

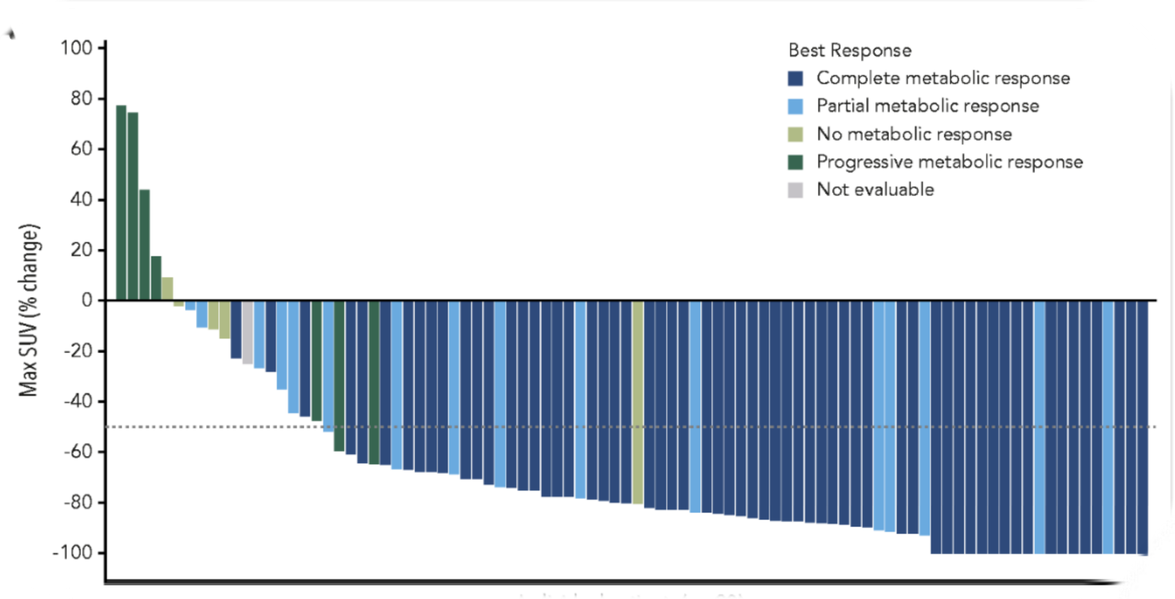
2nd line: Pembro GVD



Characteristic	Pembro-GVD × 2 (n = 38)[a]	Pembro-GVD × 4 (n = 7)	Pembro-GVD Overall (n = 38)
ORR, % (95% CI)	100 (91 to 100)	100 (59 to 100)	100 (91 to 100)
CR, % (95% CI)	92 (79 to 98)	71 (29 to 96)	95 (82 to 99)
PR, % (95% CI)	8 (2 to 21)	29 (4 to 71)	5 (1 to 18)
Best response, No. (%)			
CR	35 (92)	5 (71)	36 (95)
PR	3 (7.9)	2 (29)	2 (5.3)

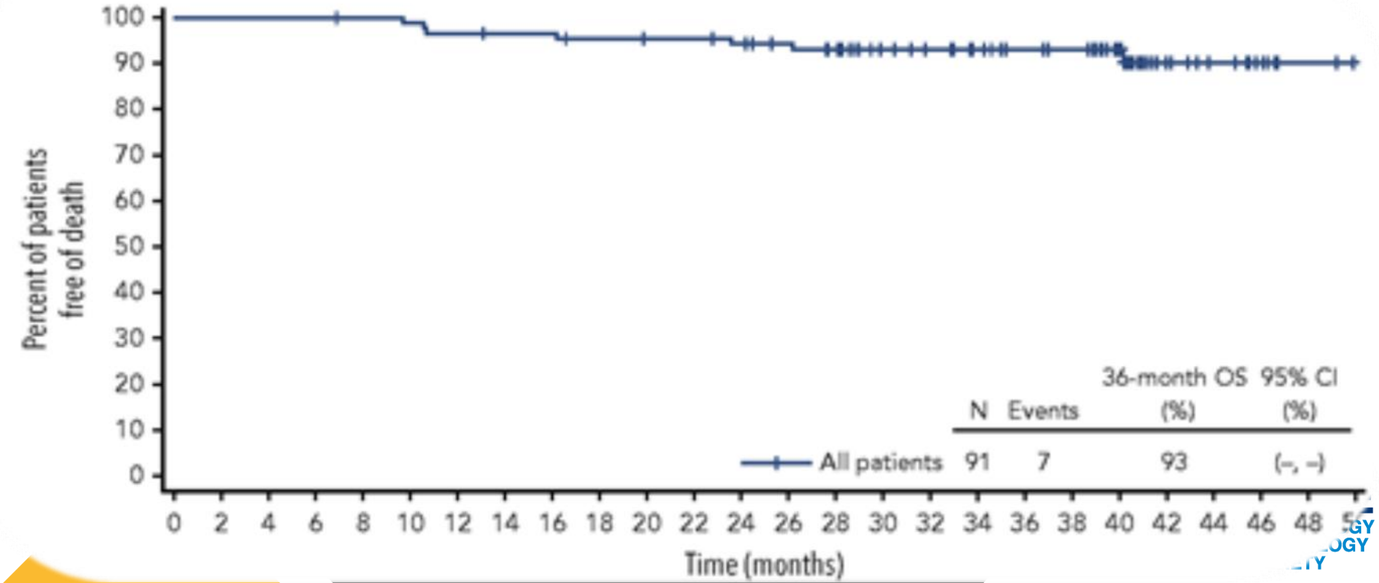
Moskowitz AJ et al., *J Clin Oncol* 2021

2nd line: Nivolumab + Brentuximab Vedotin



OR rate 85%

CR rate 67%

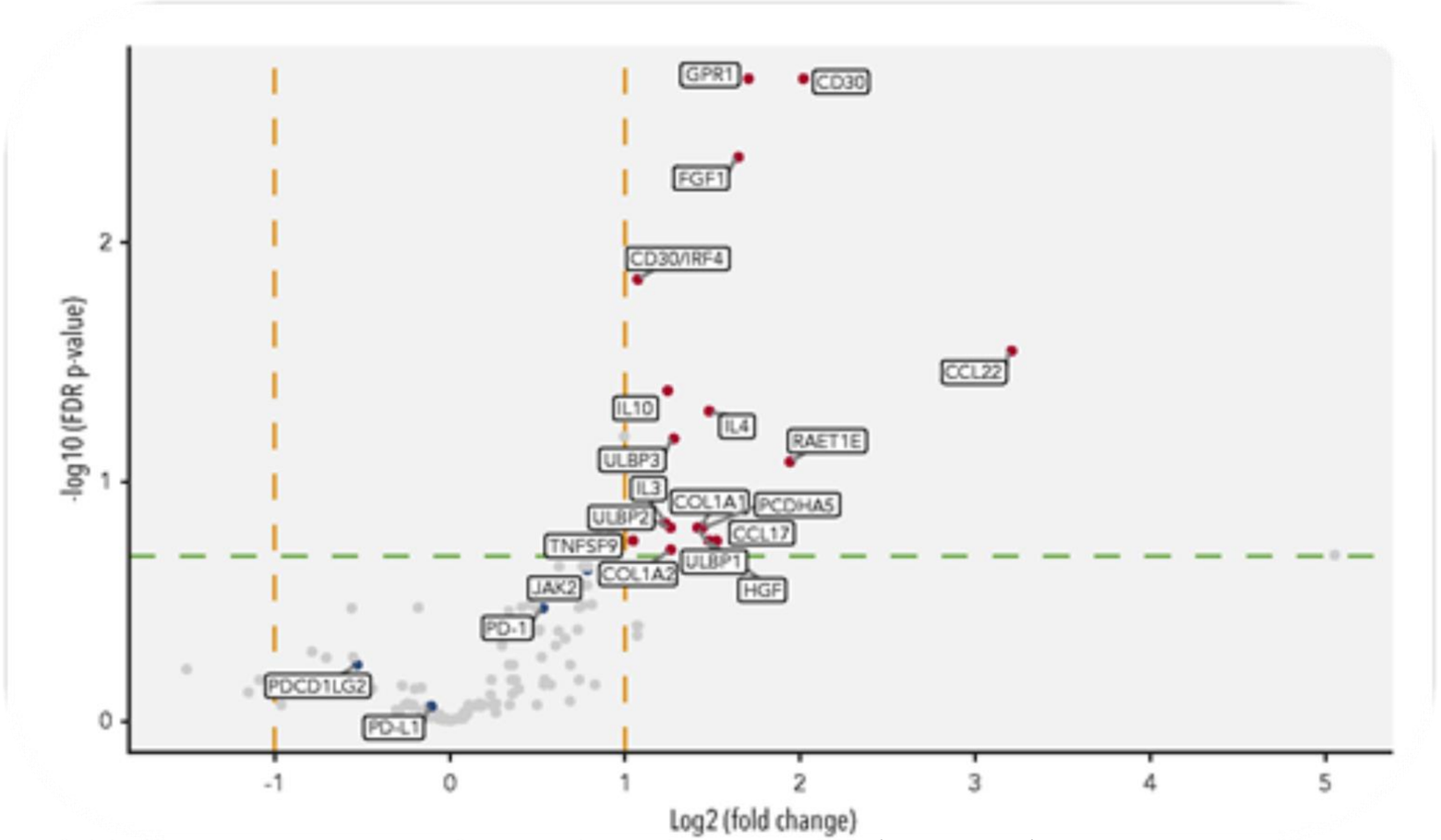


Advani RH et al., Blood . 2021 Aug 12;138(6):427-438

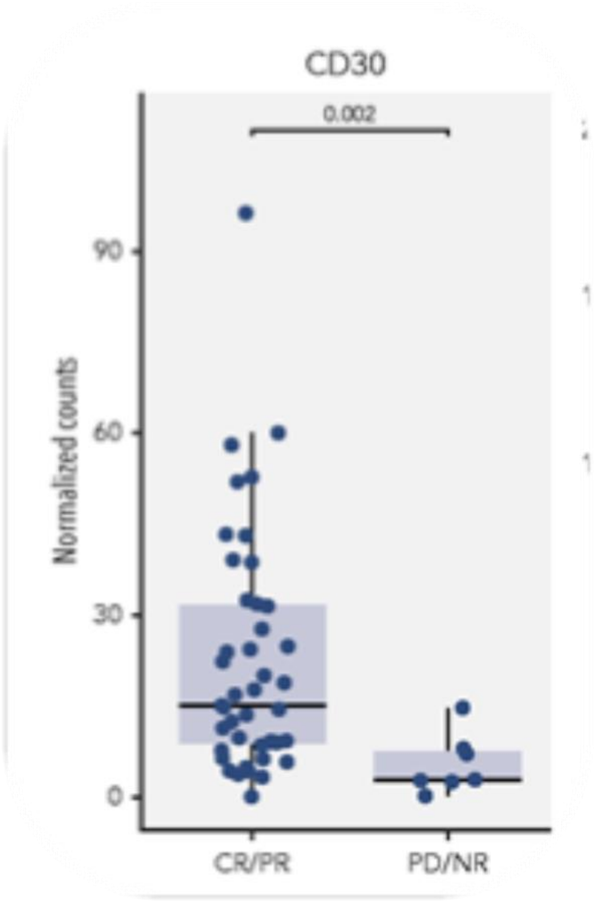
Herrera AF et al., Blood. 2018;131(11):1183-1194

2nd line: Nivolumab + Brentuximab Vedotin

Correlates of efficacy



fold change expression of 132 selected genes in CR/PR vs PD/NR patients.
red dots : differentially expressed genes



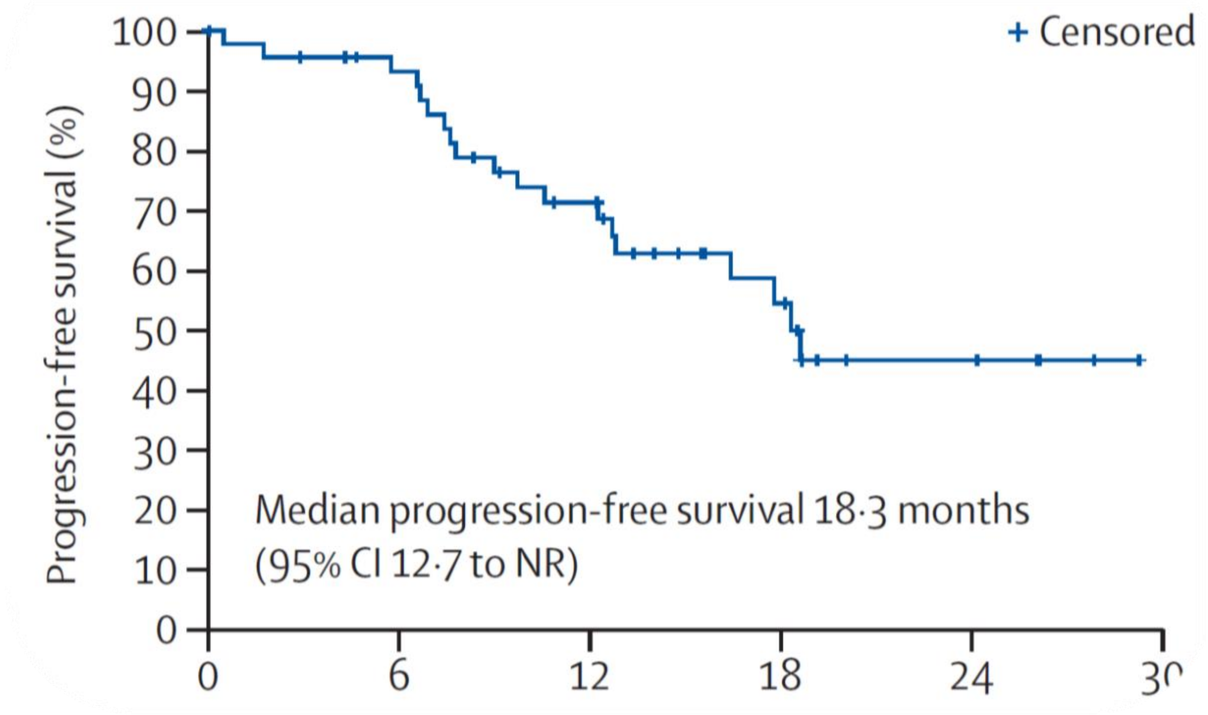
Baseline expression of CD30

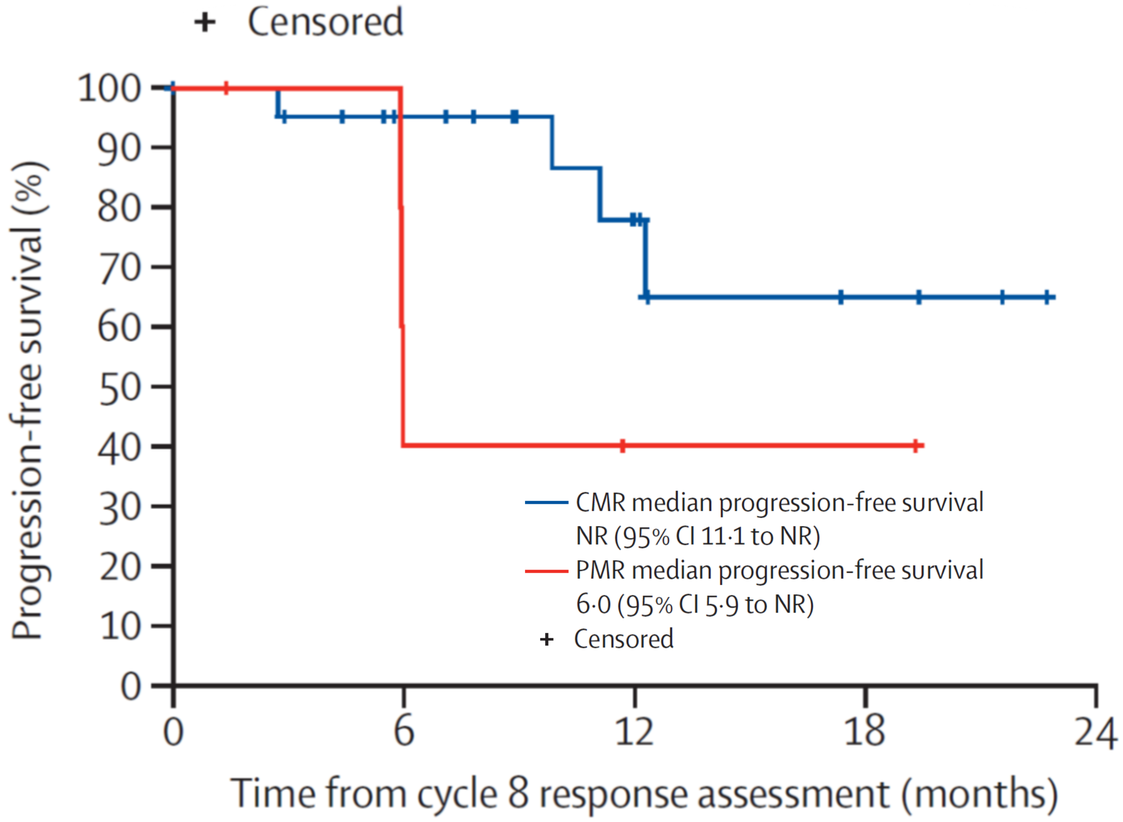
Advani RH et al., Blood . 2021 Aug 12;138(6):427-438

1st line (elderly): Nivolumab + Brentuximab Vedotin

OR rate – 61%
CR rate – 48%

At 46 patients, interim analysis failed to meet the predefined criteria.





Cheson BD et al., Lancet Haematol . 2020 Nov;7(11):e808-e815.

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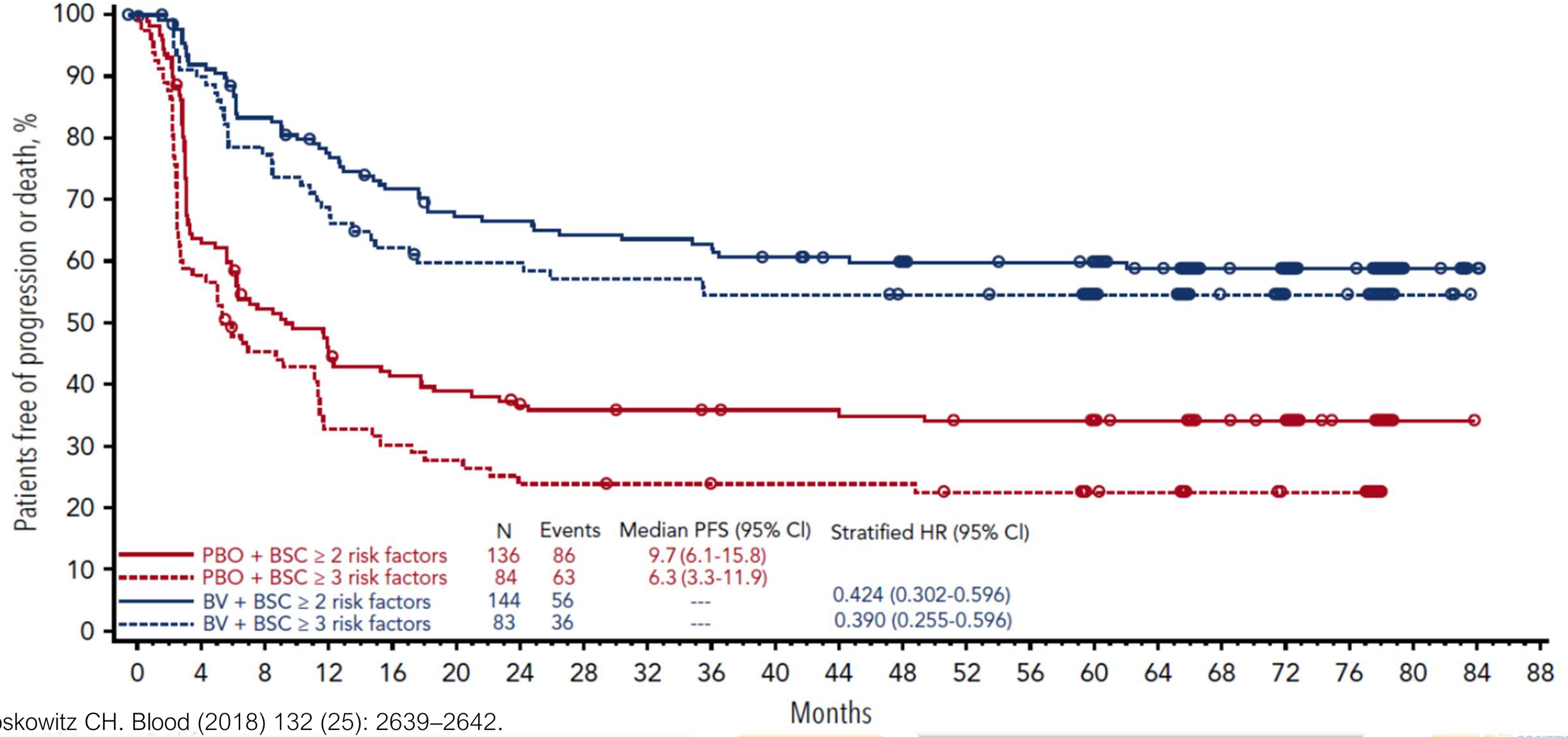
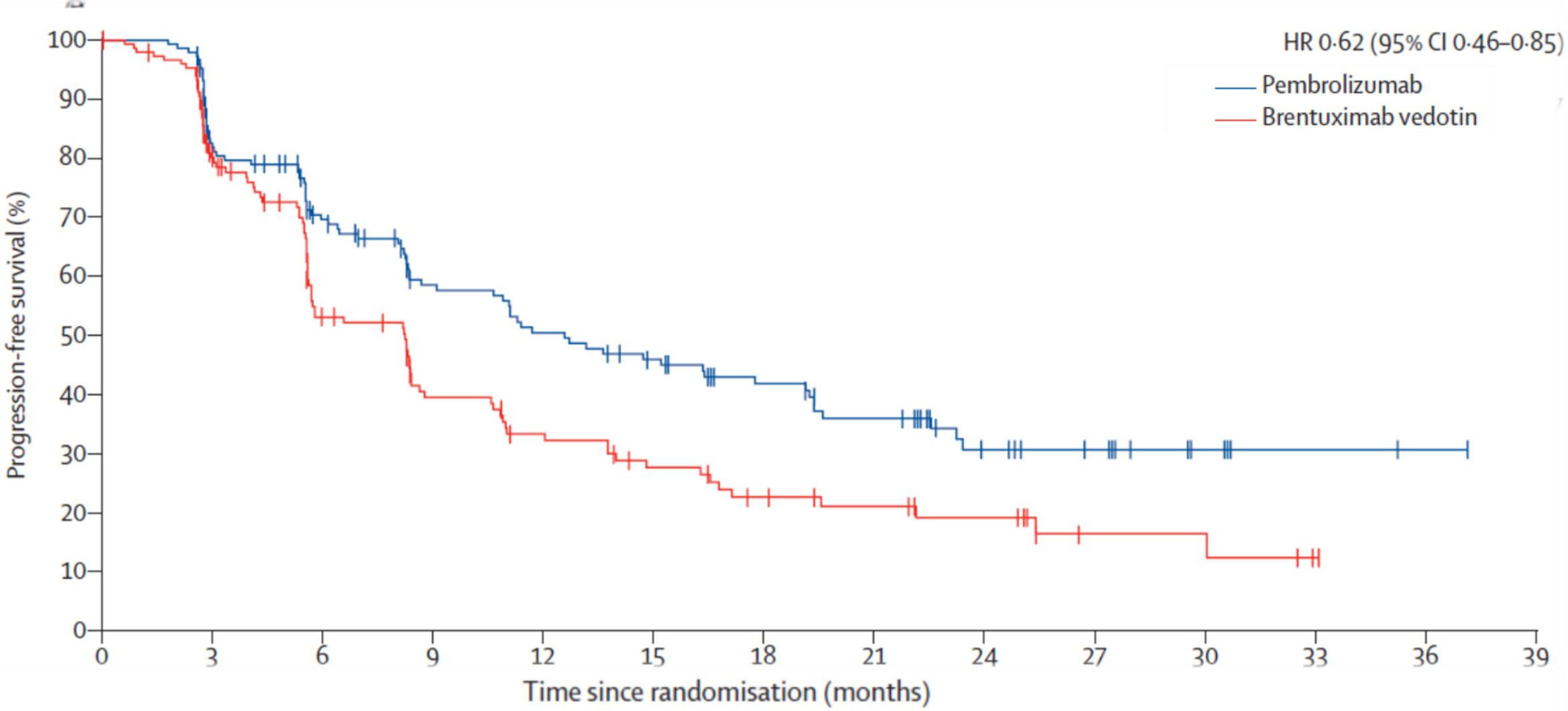
2.5th line: BV consolidation post-BMT - AETHERA



Moskowitz CH. Blood (2018) 132 (25): 2639–2642.

3rd line: Pembrolizumab vs Brentuximab Vedotin



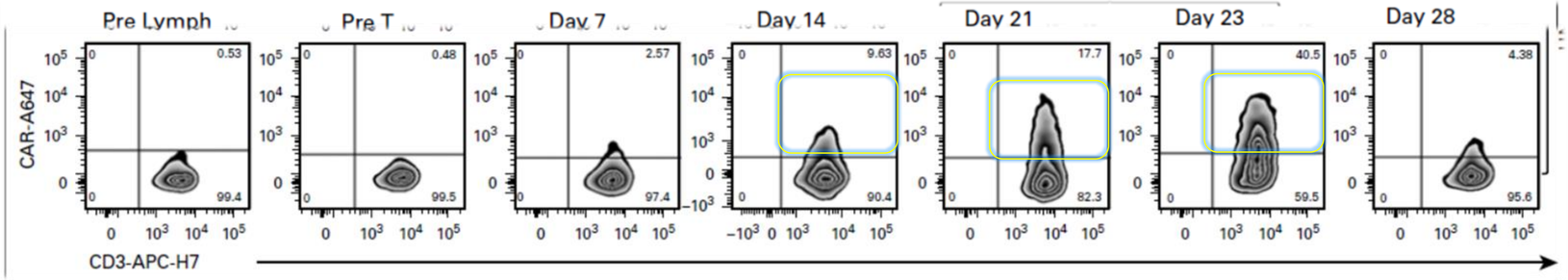
Kuruvilla J, et al., *Lancet Oncol.* 2021

> 3rd line: CD30 CAR-T (autologous)

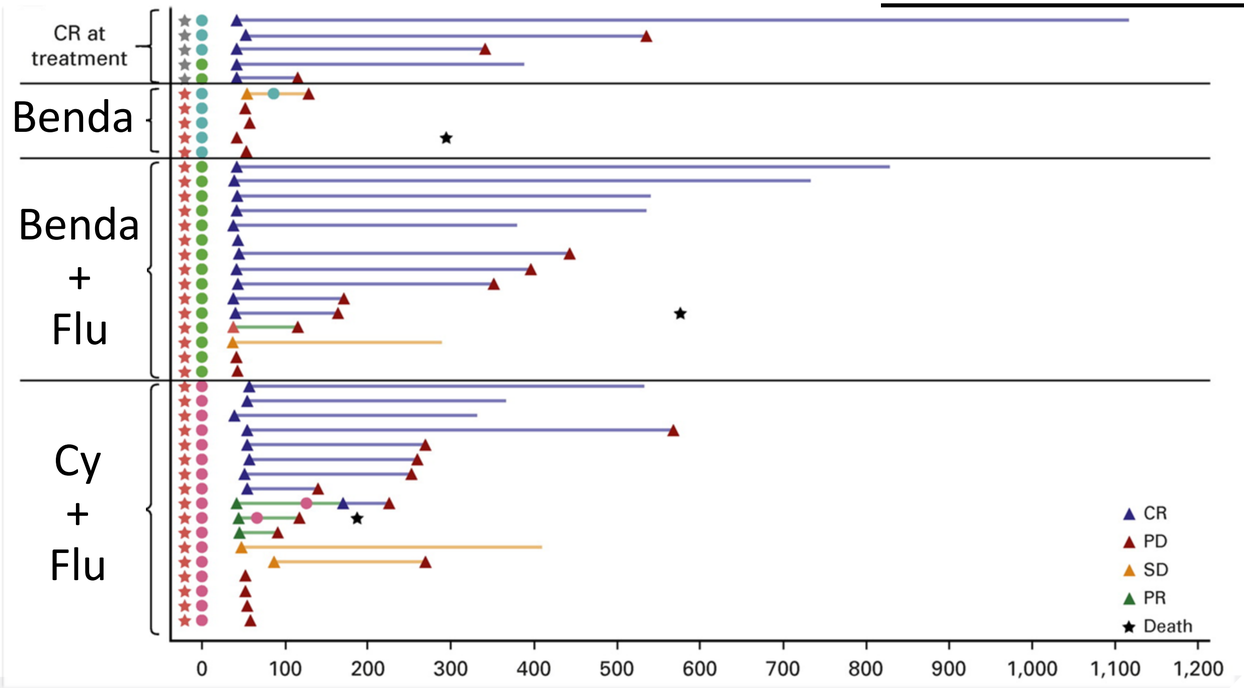
59% CR post-Flu

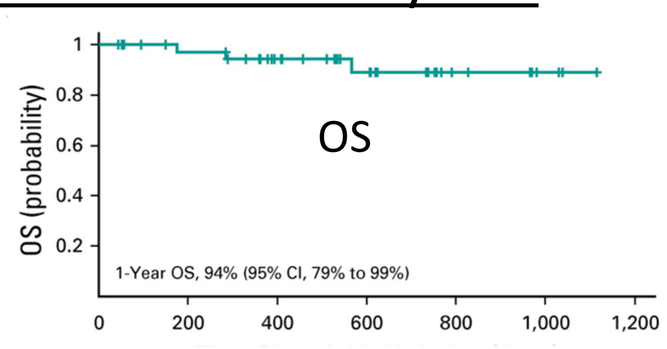
Response	All Patients (N = 37)	Benda (n = 5)	Benda-Flu (n = 15)	Cy-Flu (n = 17)
CR	19 (51)	0 (0)	11 (73)	8 (47)
PR	4 (11)	0 (0)	1 (7)	3 (18)
SD	4 (11)	1 (20)	1 (7)	2 (11)
PD	10 (27)	4 (80)	2 (13)	4 (24)

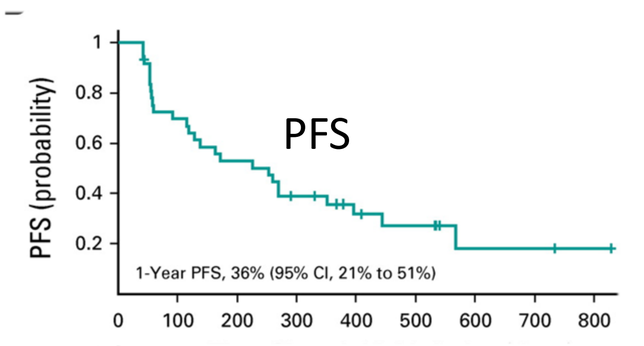
some CAR-T persistence x weeks

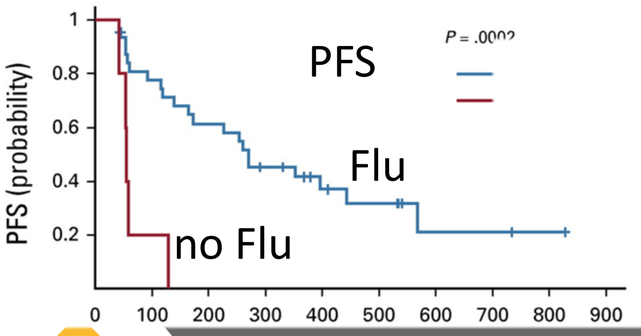


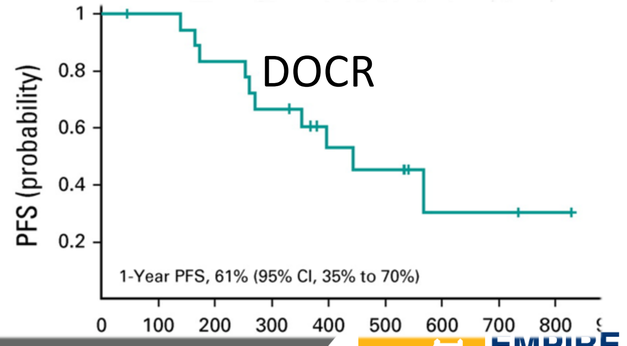
some durable remissions > 2 years





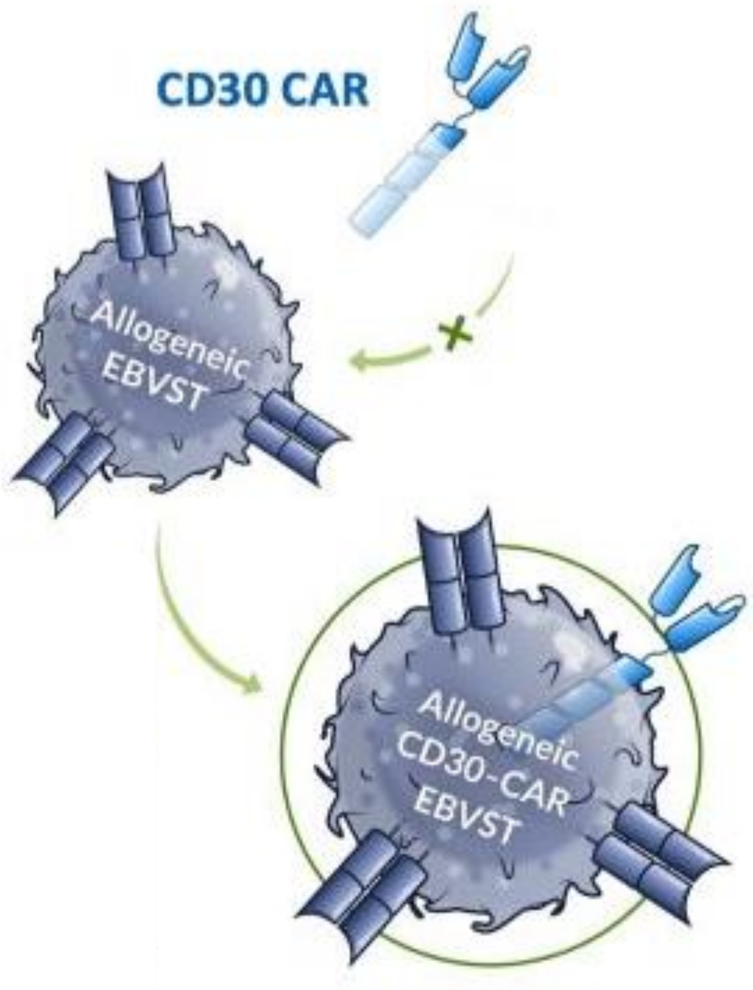


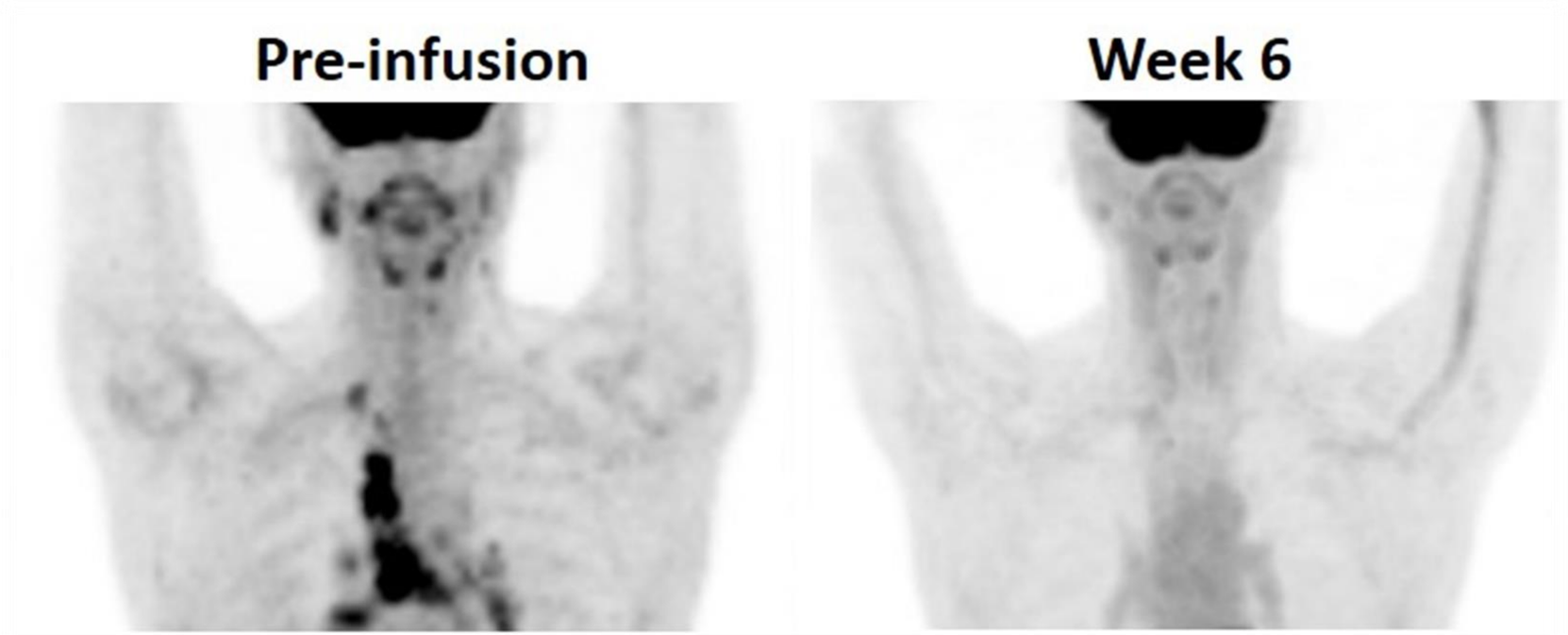




Ramos CA, et al., *J Clin Oncol*. 2020

> 3rd line: CD30 CAR-T (Allogeneic)





Pt with relapsed Hodgkin's lymphoma s/p 3 lines of rx → rx with CD30.CAR EBVSTS (dose level 2) → CR at 6 wks.

7 evaluable pts → 2 CR + 3 PR + 2 PD

Quach DH et al., ASH Annual Meeting 2021

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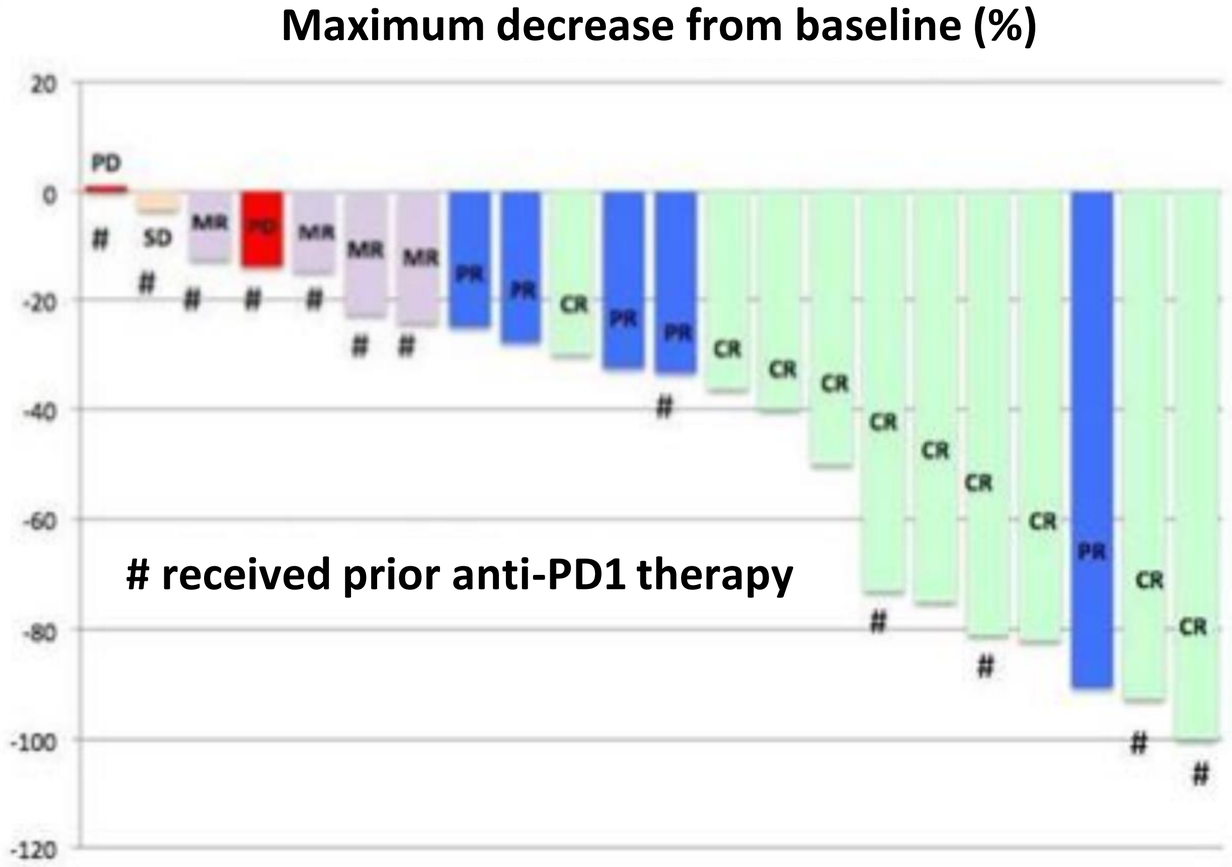
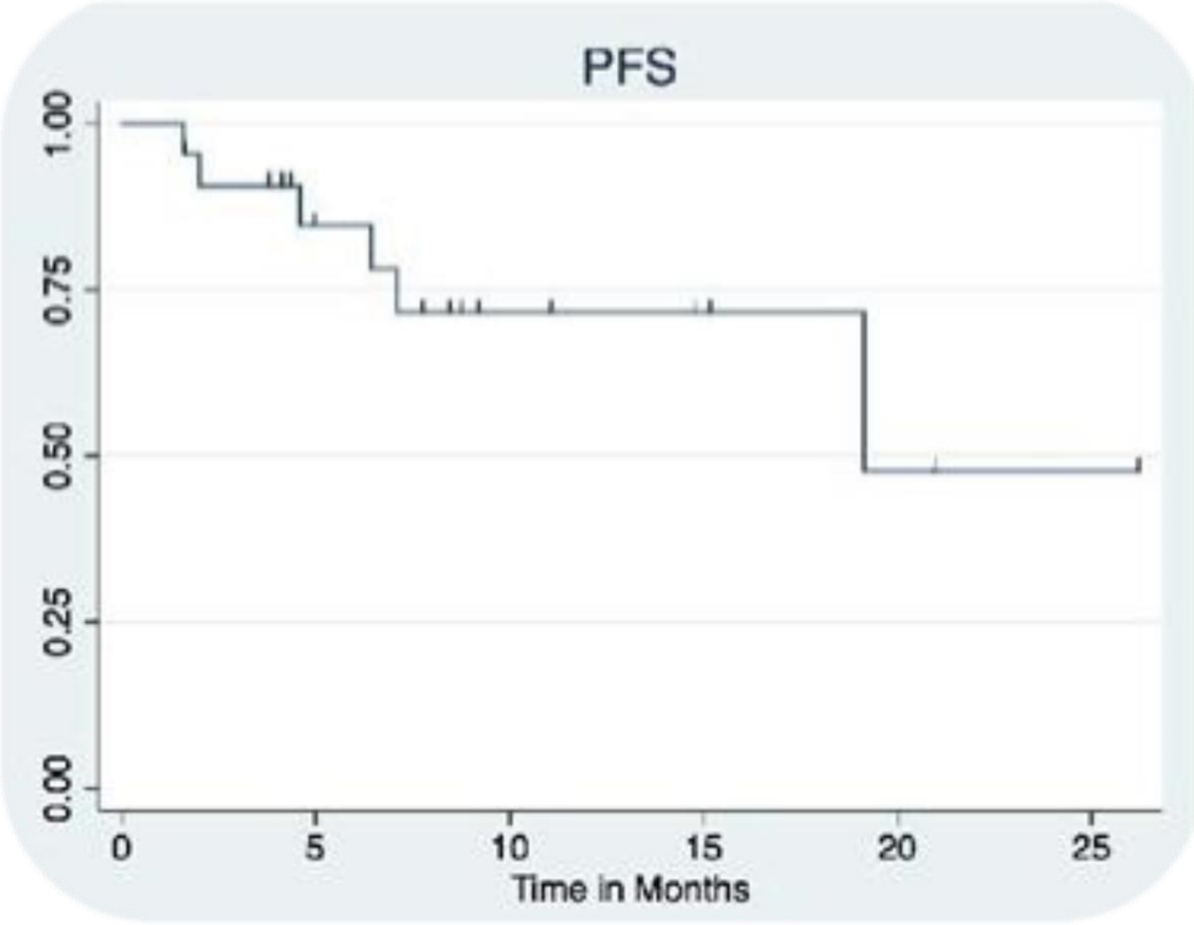
> 3rd line: Pembrolizumab and Entinostat (HDAC-i)





Sermer DJ et al., ASH Annual Meeting 2021

Non-Hodgkin Lymphoma Update 2022
Focus on DLBCL ≥ 2nd line: CAR-T and beyond

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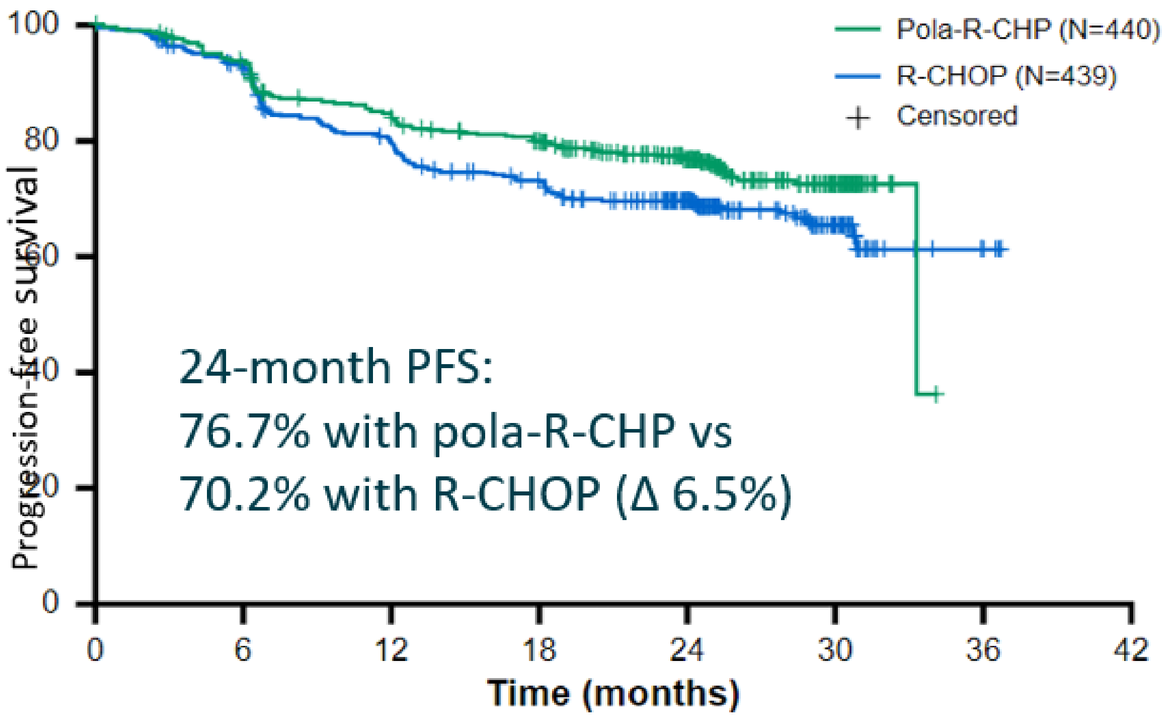
DLBCL 1st Line: POLARIX (RCHOP vs Pola-RCHP)

HR, 0.73 (95% CI, 0.57-0.95) (*P* < .02)



Most Common Adverse Events	Pola-R-CHP N = 435		R-CHOP N = 438	
	Any Grade %	Grade 3 or 4, %	Any Grade %	Grade 3 or 4, %
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12	26	8.4
Constipation	28.7	1.1	29	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	24.4	0	24	0.2
Decreased appetite	16.3	1.1	14.2	0.7
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8	8
Headache	12.9	0.2	13	0.9
Cough	12.9	0	12.1	0
Decreased weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13	0

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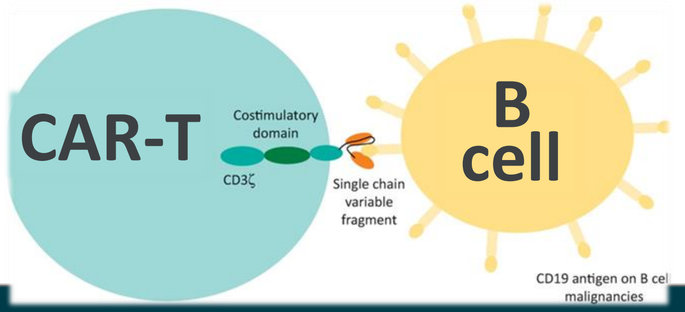
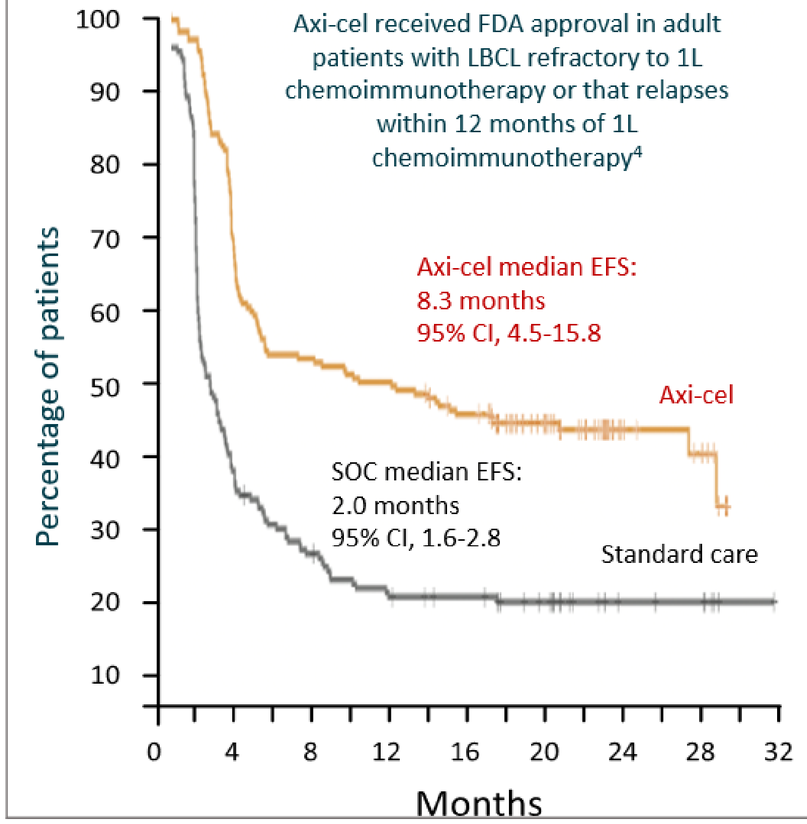
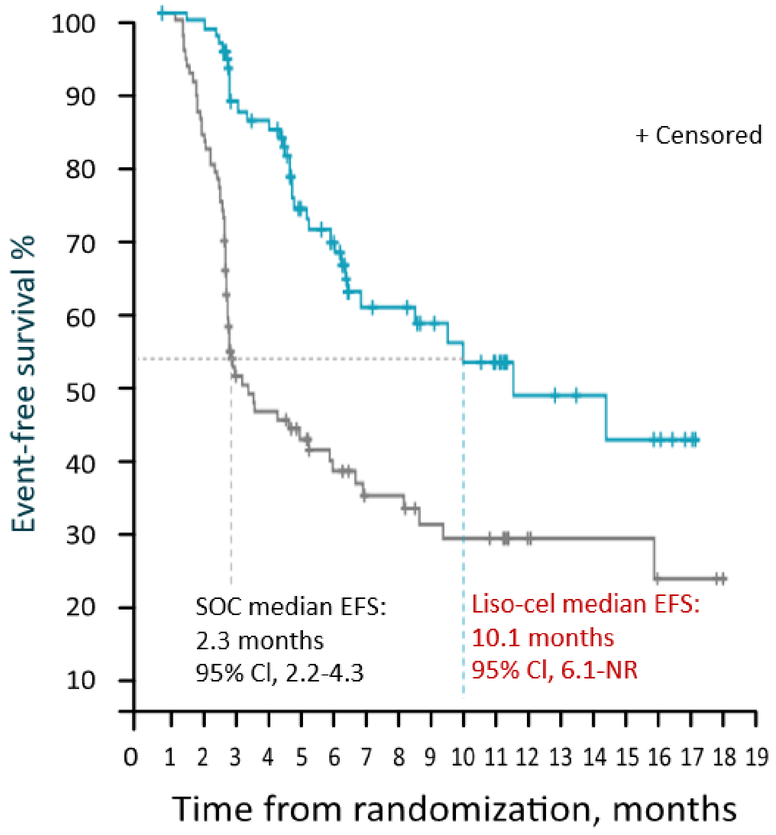
DLBCL 2nd Line: anti-CD19 CAR-T



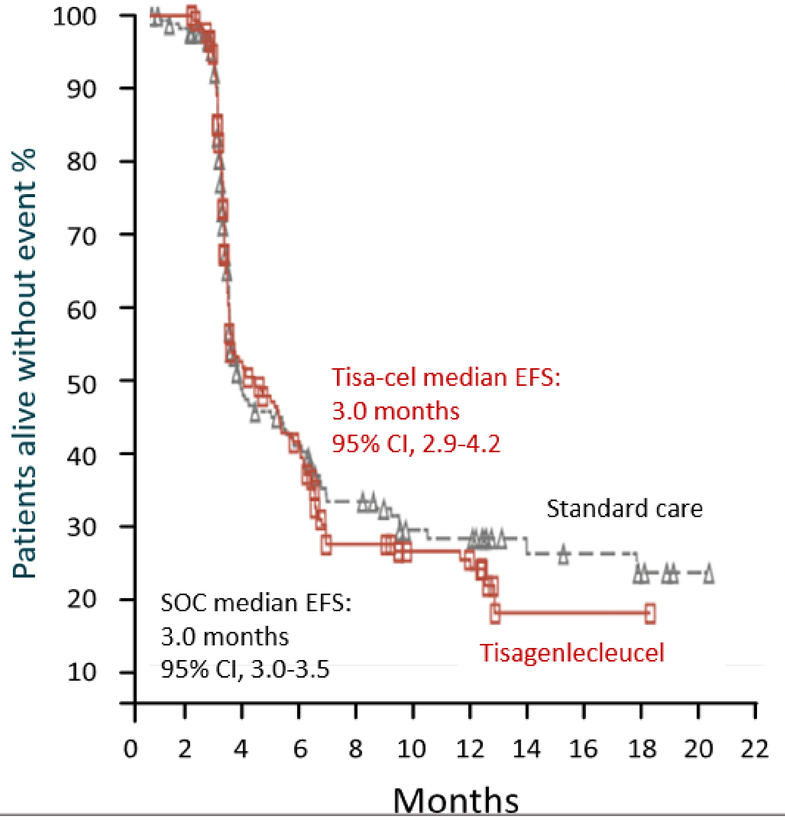
ZUMA-7[1]



TRANSFORM[2]



BELINDA[3]



1. Locke F, et al. N Engl J Med. 2022. 2. Kamdar M, et al. Lancet . 2022 3. Bishop M, et al. N Engl J Med. 2022.

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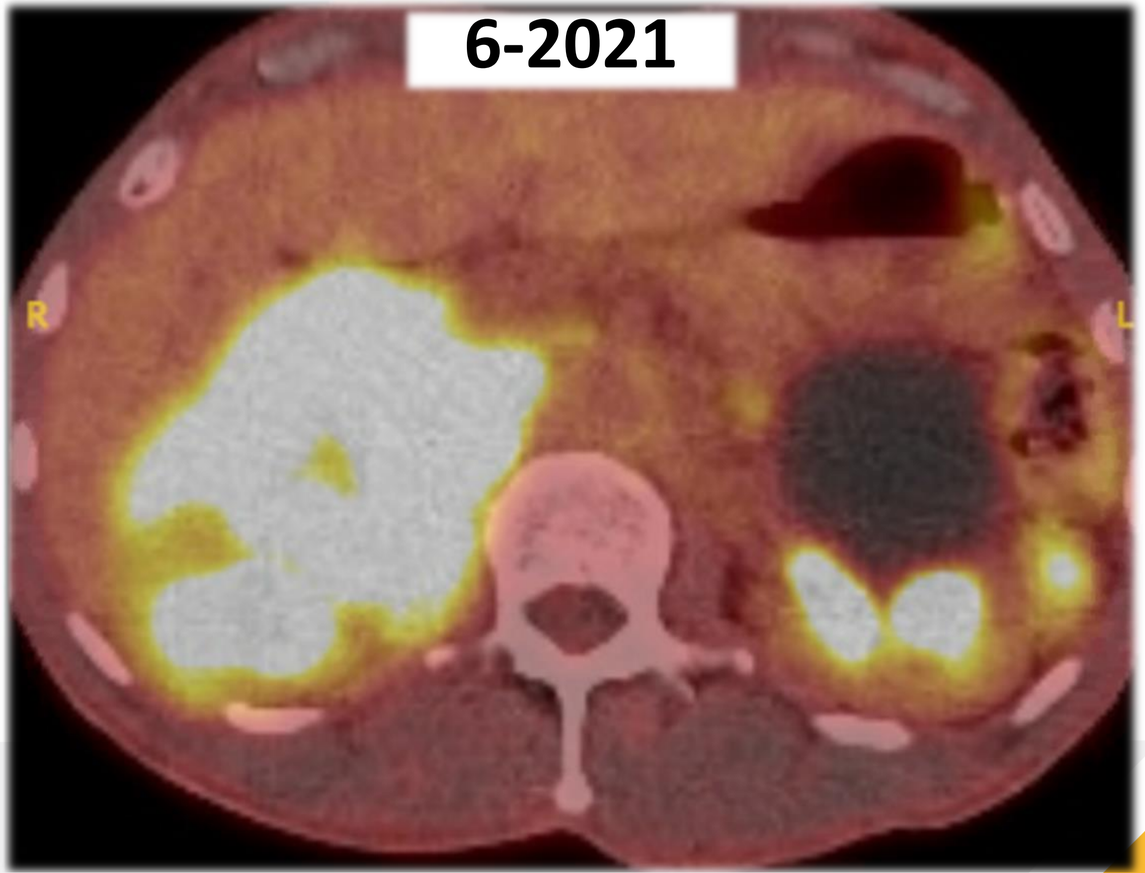
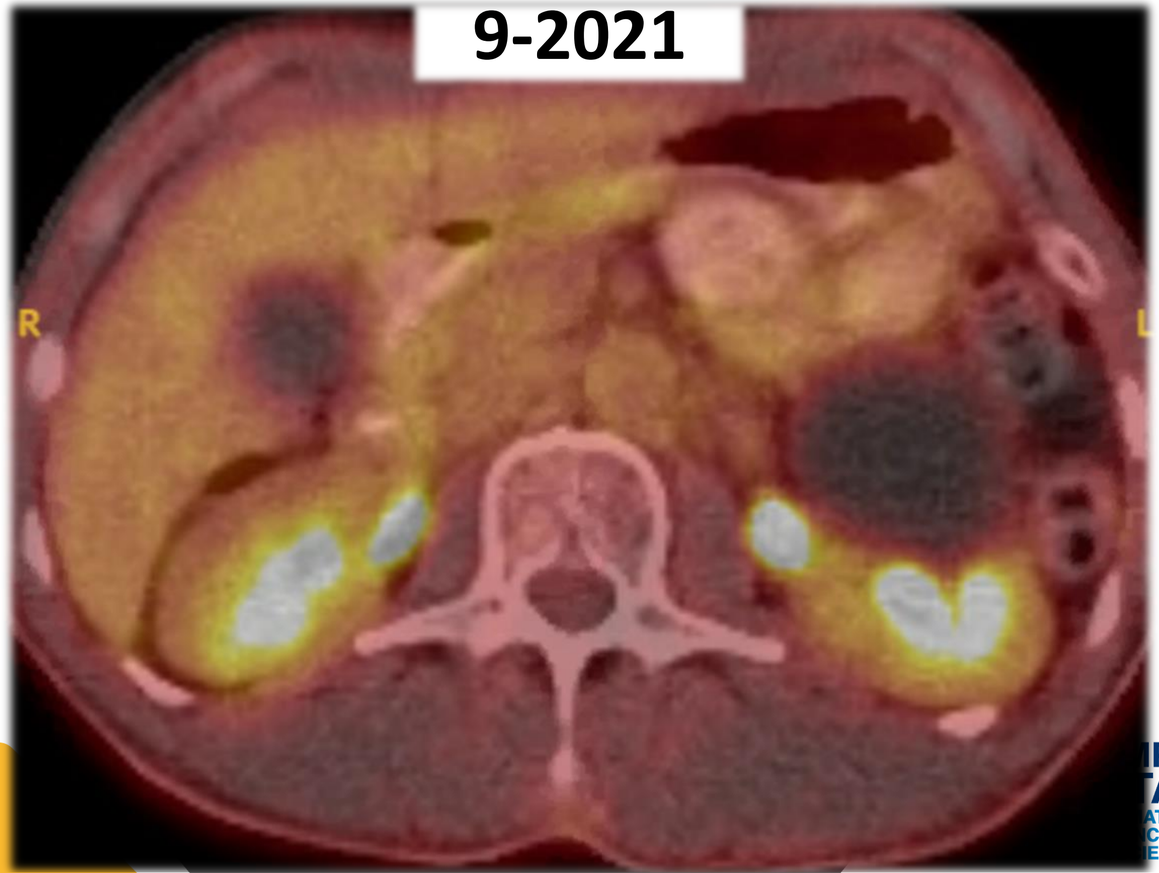
DLBCL 2nd Line: Case Study

70 yo man with DM2, HTN, double expressor GC-DLBCL, stage IIIA, dx 2020

- **RCHOP** x 6 complicated by febrile neutropenia x 1 → CMR
- 13 months s/p chemo, p/w progressive R abd pain → PET → bx = GC-DLBCL, ECOG PS 2
- seen by **BMT/CAR-T** team for discussion of treatment options
- enrolled on **Glofitamab** monotherapy expansion cohort





CAR-T versus other r/r DLBCL Therapies

-Polatuzumab Vedotin (CD79 ADC) + RTX + Benda
-Tafasitamab (CD79 mAb) + Lenalidomide
-Loncasituximab (CD19 ADC)
-Novel Agents: CD3xCD20 Bispecifics (Glofitamab, Epcoritamab…)

- Which is more effective?
- Which is safer?
- What is the optimal sequence?
- Will answers change in 5 years?

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CAR-T versus other r/r DLBCL Therapies

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-Novel Agents: CD3xCD20 Bispecifics (Glofitamab, Epcoritamab…)

Ideally: do not **compare** apple and oranges phase II non-randomized trials.

Ideally: **if** comparing trials, thoroughly **review differences in cohort** demographics.

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CAR-T versus other r/r DLBCL Therapies

-Polatuzumab Vedotin (CD79 ADC) + RTX + Benda
-Tafasitamab (CD19 mAb) + Lenalidomide
-Loncasituximab (CD19 ADC)
-Novel Agents: CD3xCD20 Bispecifics (Glofitamab, Epcoritamab…)

Today, we will: **compare** apple and oranges phase II non-randomized trials.

Today, **insufficient time** to thoroughly **review differences in cohort** demographics.

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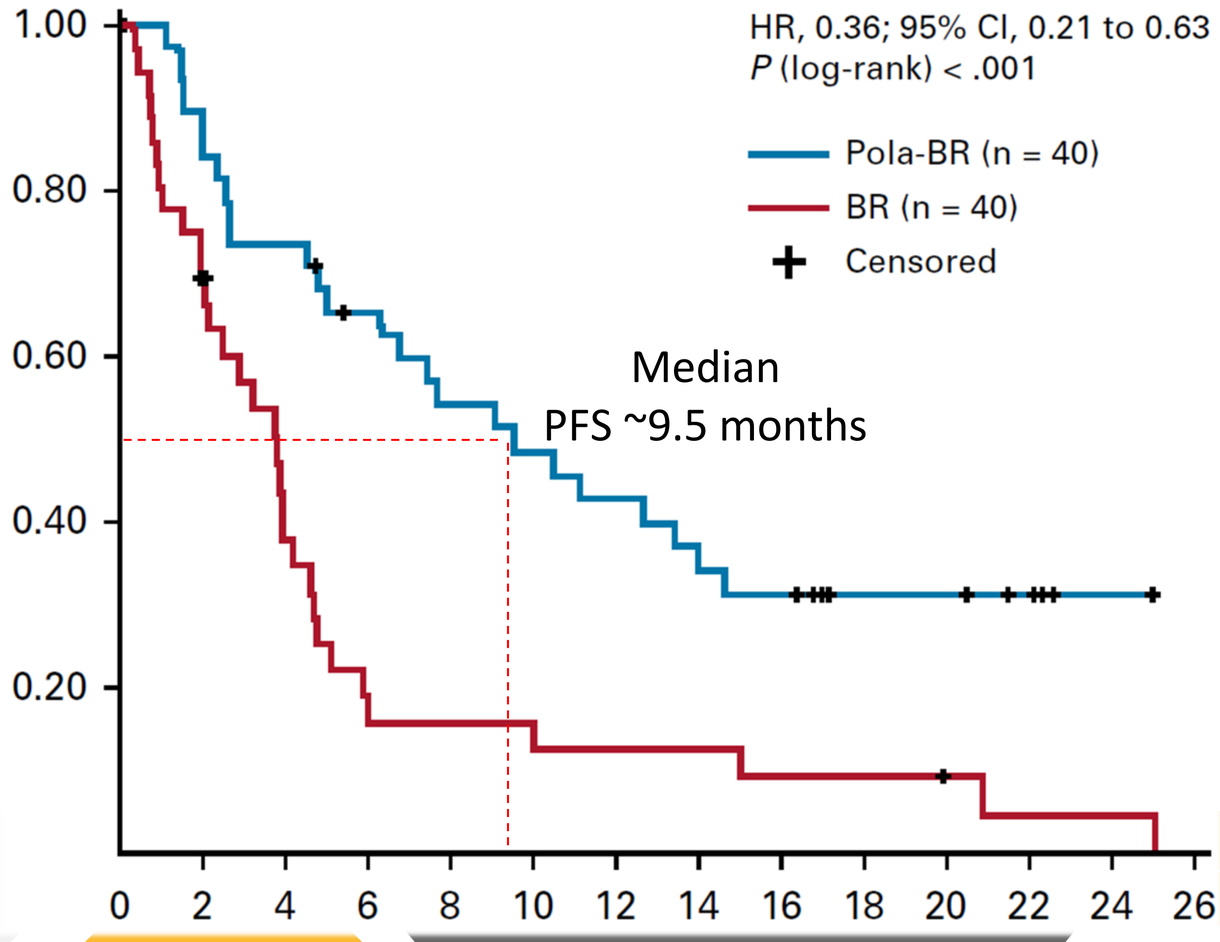
Polatuzuamb + RTX + Benda

Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Laurie H. Sehn, MD, MPH[1]; Alex F. Herrera, MD[2]; Christopher R. Flowers, MD, MSc[3]; Manali K. Kamdar, MD, MBBS[4]; Andrew McMillan, PhD[5]; Mark Hertzberg, MBBS, PhD[6]; Sarit Assouline, MDCM, MSc[7]; Tae Min Kim, MD[8]; Won Seog Kim, MD, PhD[9]; Muhit Ozcan, MD[10]; Jamie Hirata, PharmD[11]; Elicia Penuel, PhD[11]; Joseph N. Paulson, PhD[11]; Ji Cheng, PhD[12]; Grace Ku, MD[11]; and Matthew J. Matasar, MD[13]

Median age	67
Median prior rx	2
Rx refractory	75%
Prior CAR-T	0%

Outcome	Pola-BR (n = 40)	Pola-BG (n = 27)*
End of treatment		
IRC, objective response	18 (45.0)	11 (40.7)
Complete response	16 (40.0)	8 (29.6)
Partial response	2 (5.0)	3 (11.1)



Sehn LH, et al., J Clin Oncol . 2020

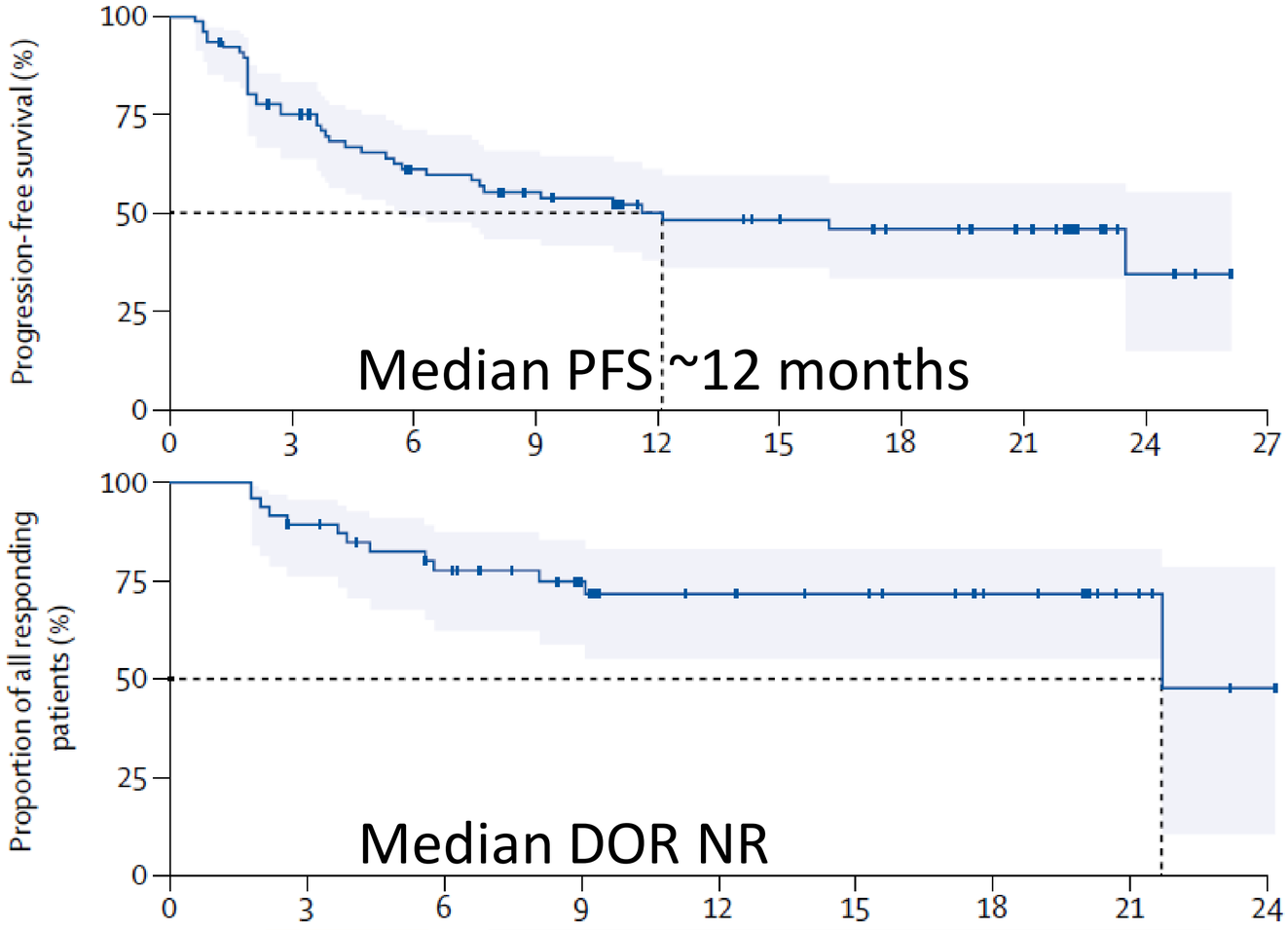
Tafasitamab + Lenalidomide

Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study

Gilles Salles, Johannes Duell*, Eva González Barca, Olivier Tournilhac, Wojciech Jurczak, Anna Marina Liberati, Zsolt Nagy, Aleš Obr, Gianluca Gaidano, Marc André, Nagesh Kalakonda, Martin Dreyling, Johannes Weirather, Maren Dirnberger-Hertweck, Sumeet Ambarkhane, Günter Fingerle-Rowson, Kami Maddocks*

Median age 72
1 prior rx 50%
2 prior rx 43%
Rx refractory 44%
Double Hit 0%

Complete response	34 (43%; 32–54)
Partial response	14 (18%; 10–28)
Stable disease	11 (14%; 7–23)
Progressive disease	13 (16%; 9–26)
Not evaluable†	8 (10%; 4–19)
PET-confirmed complete response	30/34 (88%; 73–97)
Objective response‡	48 (60%; 48–71)



Salles G, et al. *Lancet Oncol*. 2020.

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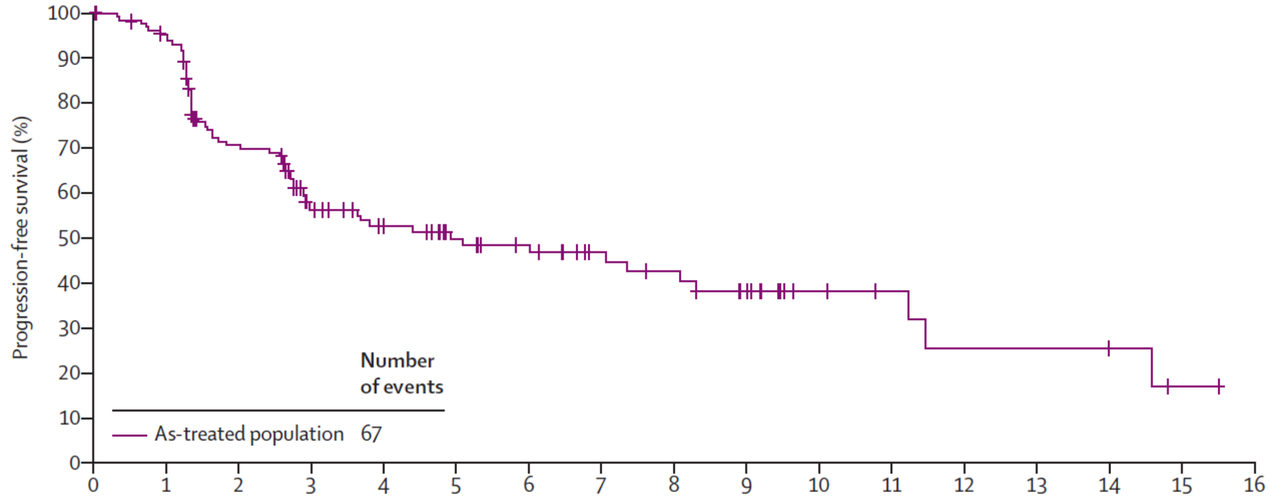
Loncasituximab

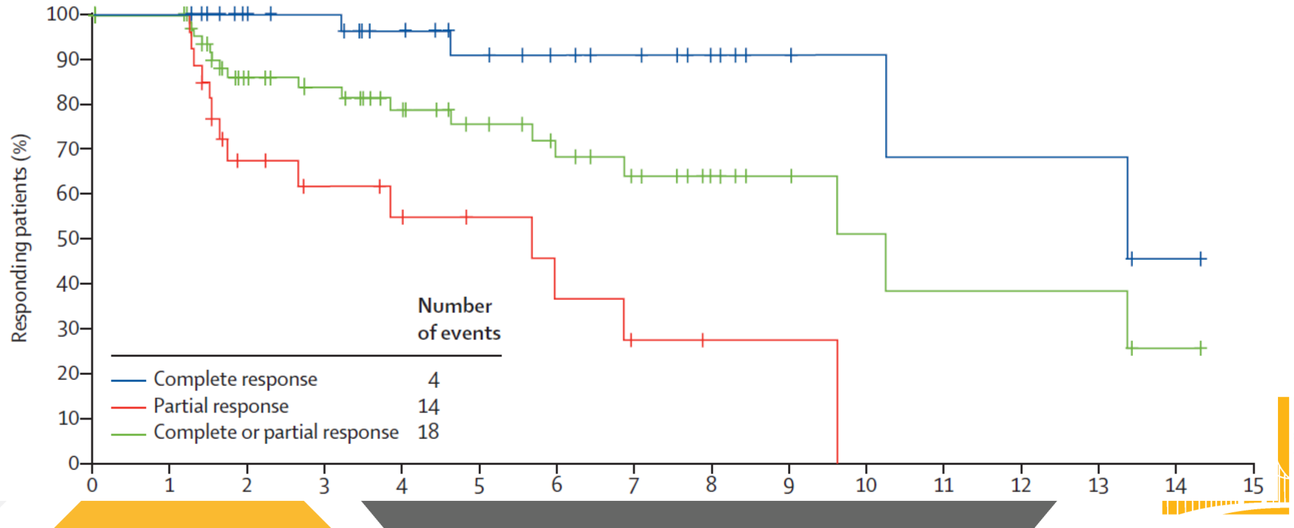
Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial

Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshna, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luiqi Zinzani, Karin Havenith, Jay Feinqold, Shui He, Yajuan Qin, David Unqar, Xiaoyan Zhanq, Carmelo Carlo-Stella

Median age 66
2 prior rx 43%
≥3 prior rx 56%
Rx refractory 58%
Double Hit 10%

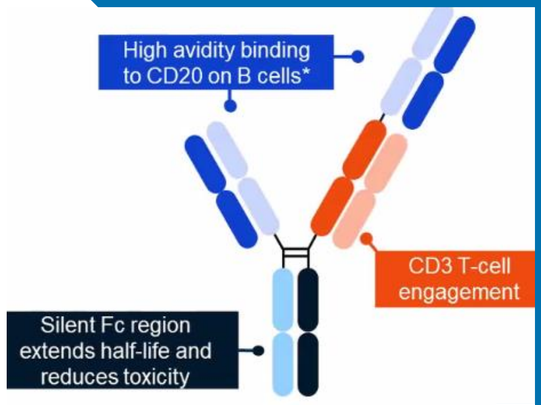
	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)





Caimi PF et al., Lancet Oncol . 2021

Glofitamab CD3xCD20

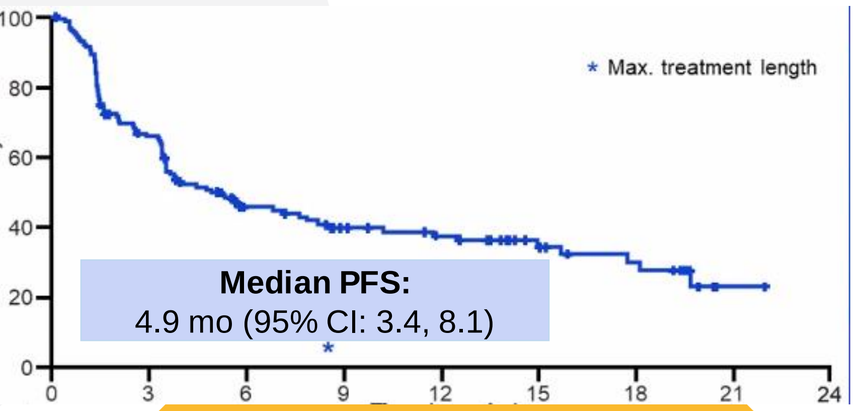


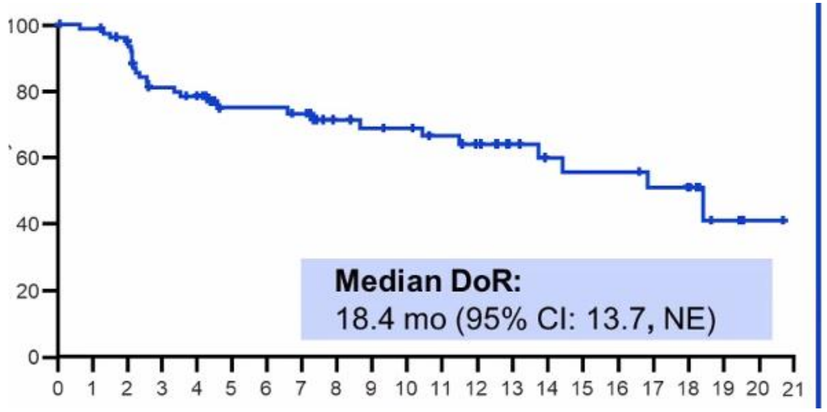
Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥2 prior therapies: pivotal Phase II expansion results

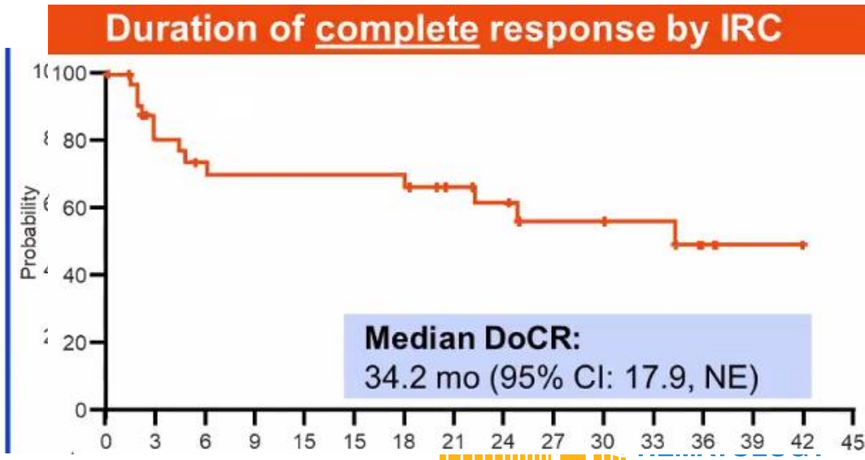
Presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting | June 3–7, 2022

Median age	66
Median prior rx	3
Rx refractory	86%
Prior CAR-T	33%

CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]





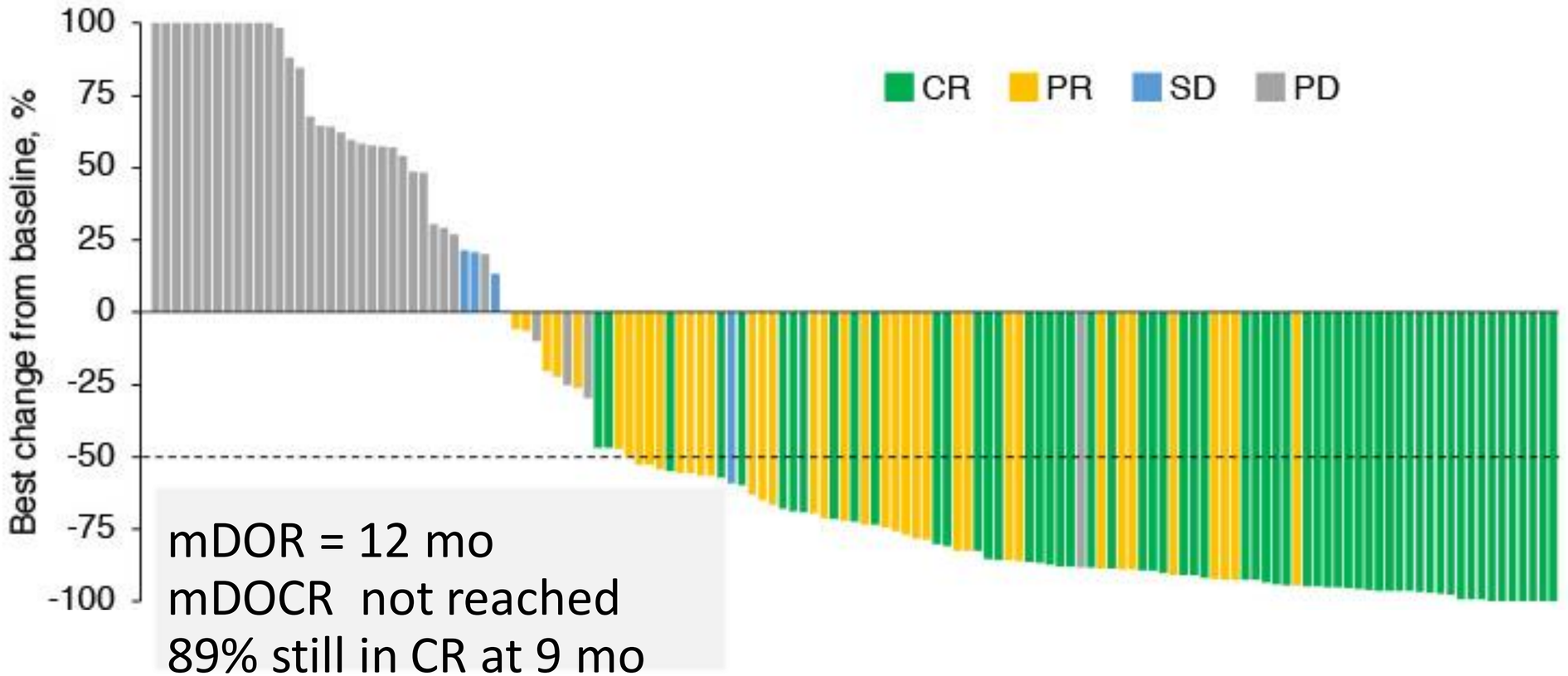


Dickinson M et al., Abstract ASCO 2022 ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.7500

Epcoritamab CD3xCD20

Relapsed / Refractory Large B-cell Lymphoma: A Phase 2 Study

Median age	64
Median prior rx	3
Rx refractory	83%
Prior CAR-T	39%



mDOR = 12 mo
mDOCR not reached
89% still in CR at 9 mo

CAR T–naive
ORR = 69%
CR = 42%

Prior CAR T
ORR = 54%
CR = 34%

CAR-T *versus* Bispecific Ab

False dichotomy: your patient likely wants *both*.

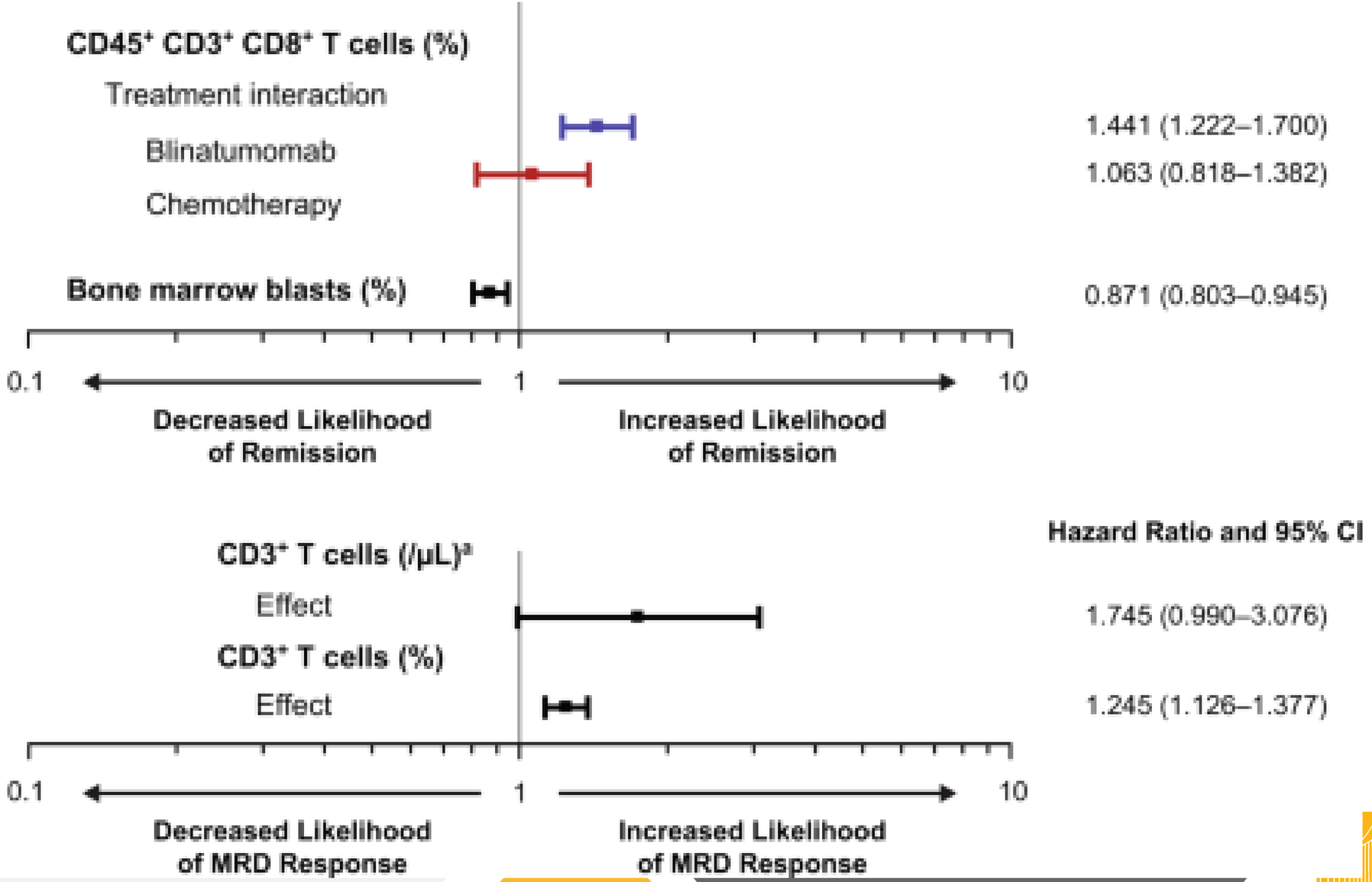
CAR-T → Bispecific Ab

versus

Bispecific Ab → CAR-T

Optimal sequencing: CAR-T and Bispecific Ab

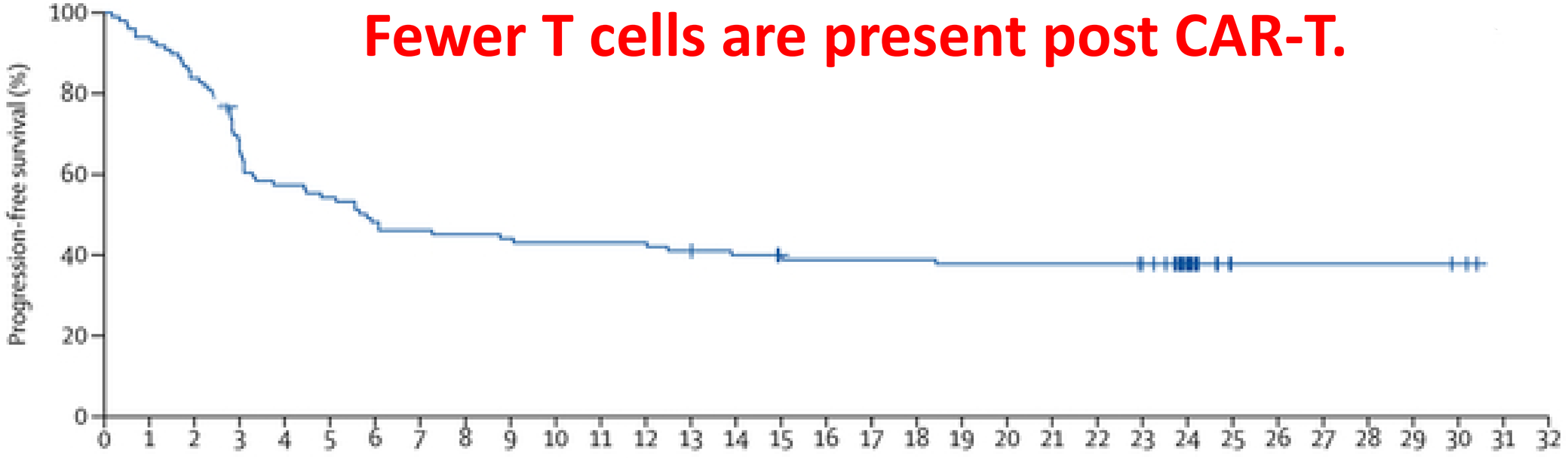
Bispecific Ab work better when T cells are present.

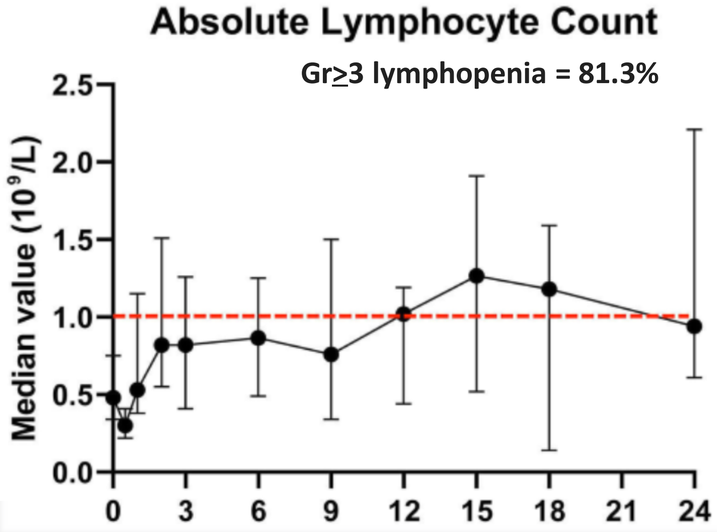


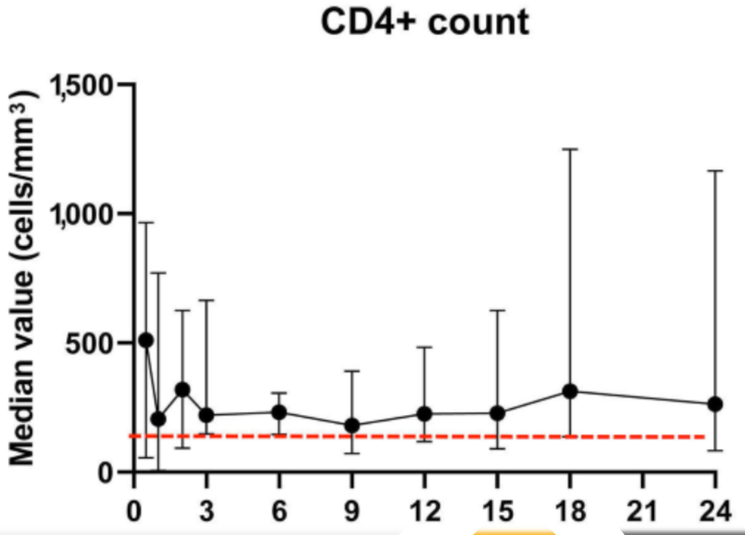
Wei, AH et al., *Leukemia* 2021

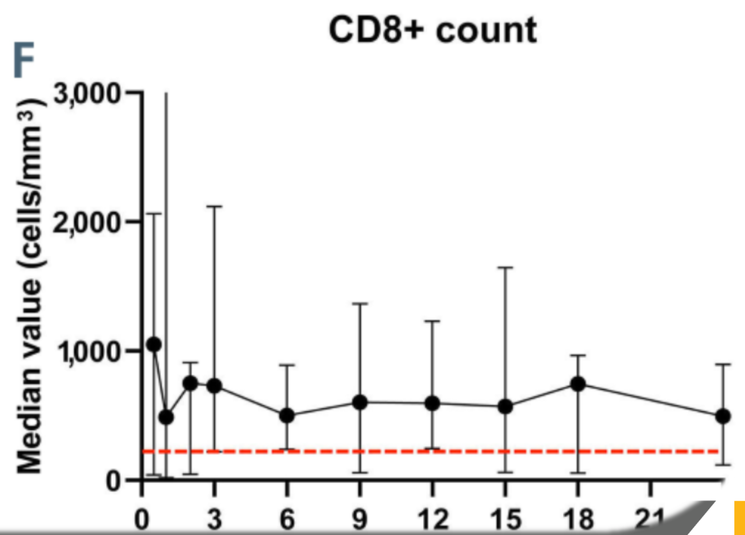
Optimal sequencing: CAR-T and Bispecific Ab

Fewer T cells are present post CAR-T.









Kato, K et al., *Int J Clin Oncol.* 2022

Strati, P et al., *Haematologica*. 2021

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CAR-T *versus* Bispecific Ab

False dichotomy: T cell rx work best after debulking rx.

Chemo → CAR-T

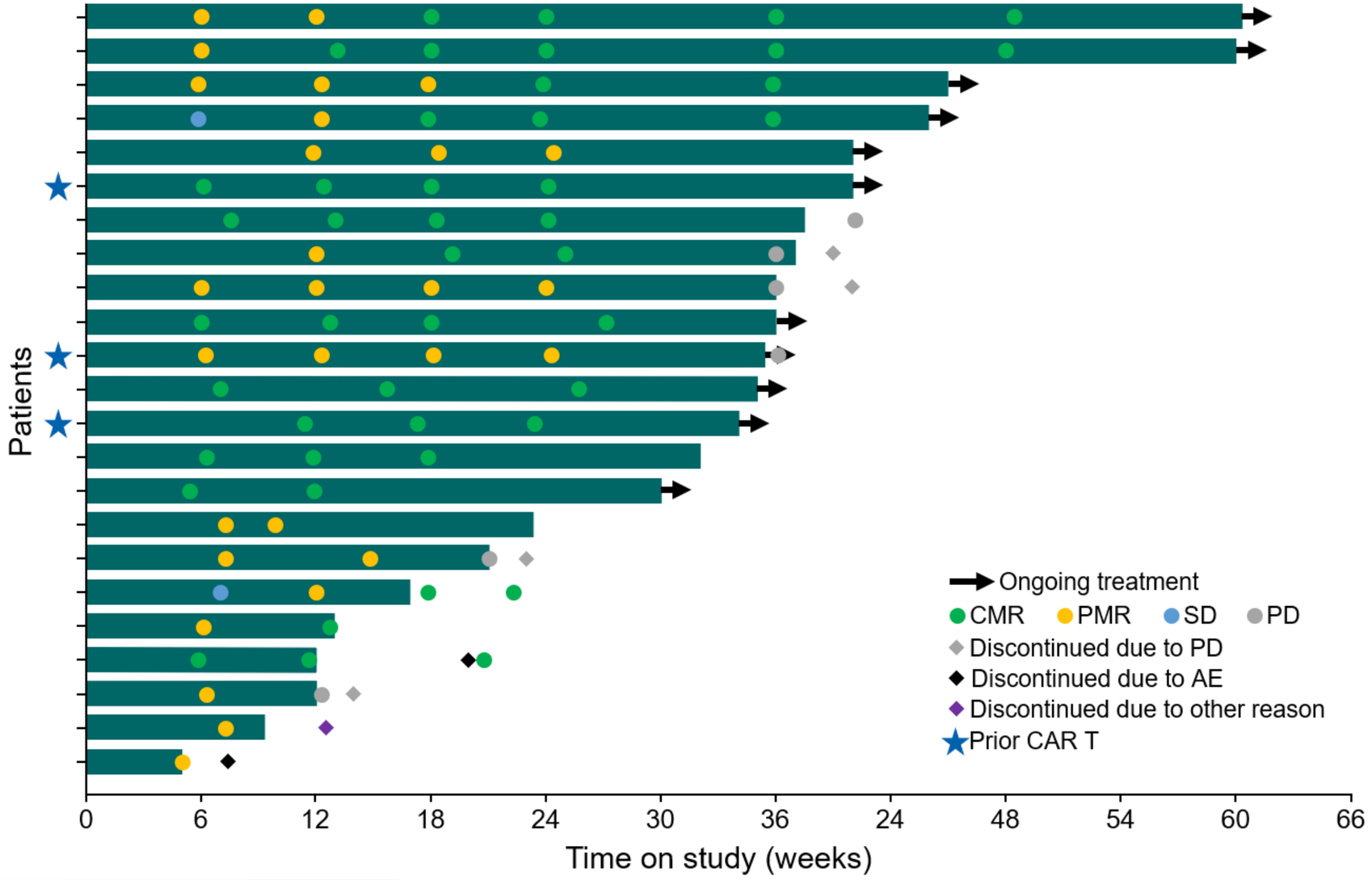
versus

Chemo + Bispecific Ab

Epcoritamab + Gemcitabine + Oxaliplatin in r/r DLBCL Transplant-Ineligible Patients Induces High Response Rate Even in Pts Failing CAR T Therapy

Median age	71
Median prior rx	2
Rx refractory	73%
Prior CAR-T	12%

Response, n (%)	n=25
Overall response	23 (92)
CMR	15 (60)
PMR	8 (32)
Not assessed	2 (8)



Brody J et al., ASCO Annual Meeting 2022 - https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.7527

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Thieblemont C et al., Abstract LB2364 EHA2022: Presidential Symposium - https://bit.ly/3DHI2Lr

Wei, AH et al., *Leukemia* 2021

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