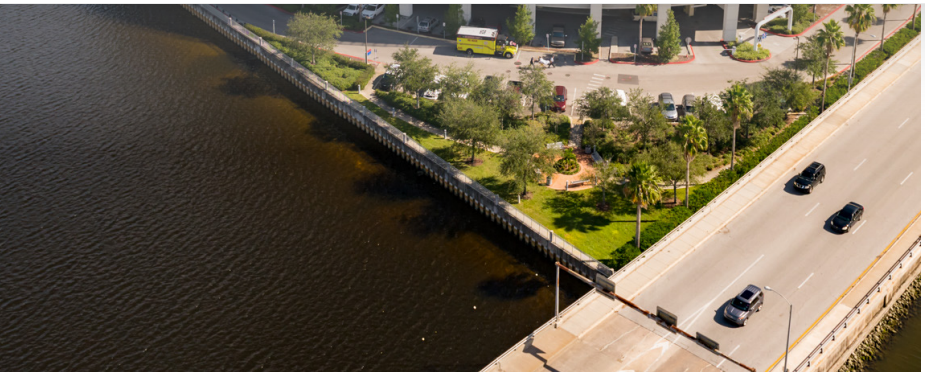
TGH Tampa General Hospital | CANCER INSTITUTE

USF HEALTH MORSANI COLLEGE OF MEDICINE UNIVERSITY OF SOUTH FLORIDA

"What is New for DLBCL & Hodgkin's Disease?"



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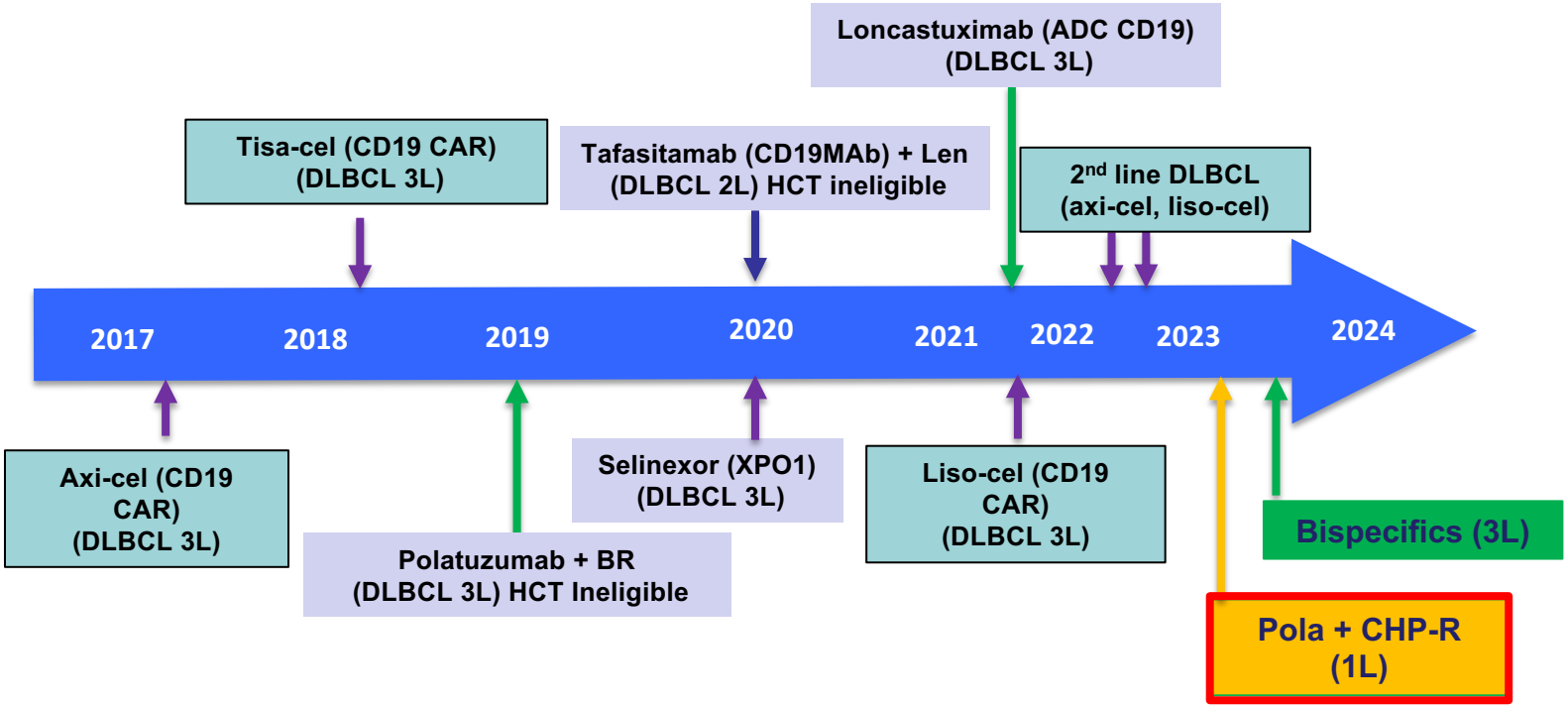
Professor, USF Health Morsani College of Medicine

Frontline Advanced DLBCL

Frontline Hodgkin's disease

FDA Approvals for Frontline DLBCL (2000-2016)

FDA Approvals for DLBCL (2017-2024)



Chavez, J. et al.

POLARIX: Study design overview

- **Double-blind, randomized controlled**
- Collaboration with LYSA
- NCT03274492

Patients
- **Previously untreated DLBCL**
- **Age 18–80 years**
- **IPI 2–5**
- **ECOG PS 0–2**

N=879

Stratification factors
- **IPI score (2 vs 3–5)**
- **Bulky disease (≥7.5cm vs absence)**
- **Geographic region***

R 1:1

ARM A

Polatuzumab vedotin
1.8mg/kg
R-CHP + vincristine placebo
Q21D x 6 cycles

→ **Rituximab** 375mg/m^2 Cycles 7 & 8

1 Cycle=21 days

ARM B

R-CHOP + polatuzumab vedotin placebo
Q21D x 6 cycles

→ **Rituximab** 375mg/m^2 Cycles 7 & 8

Primary endpoint	**PFS by INV**
Key secondary endpoints	**$EFS_{efficacy}$ by INV, PET CR at EOT by BICR, OS, and safety**

*Western Europe, United States, Canada and Australia vs Asia vs Rest of World. BICR, blinded independent central review; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; $EFS_{efficacy}$, event-free survival for efficacy causes (time from randomization to the earliest occurrence of disease progression/relapse, death due to any cause, initiation of any non-protocol specified anti-lymphoma treatment, or biopsy-confirmed residual disease after treatment completion)

Tilly H, et al. New Engl J Med 2022;386:351–63.

Pola-R-CHP | ***R-CHOP***

HR 0.73 (p=0.02)

Pola-R-CHP → 27% reduction in risk of progression, relapse or death[1]

- Relapsing or being refractory to 1L treatment remain the main causes of morbidity and mortality in DLBCL[2]

1.Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Maurer MJ, et al. Ann Oncol 2018;29:1822–27.

Pola-R-CHP	R-CHOP

6.5%

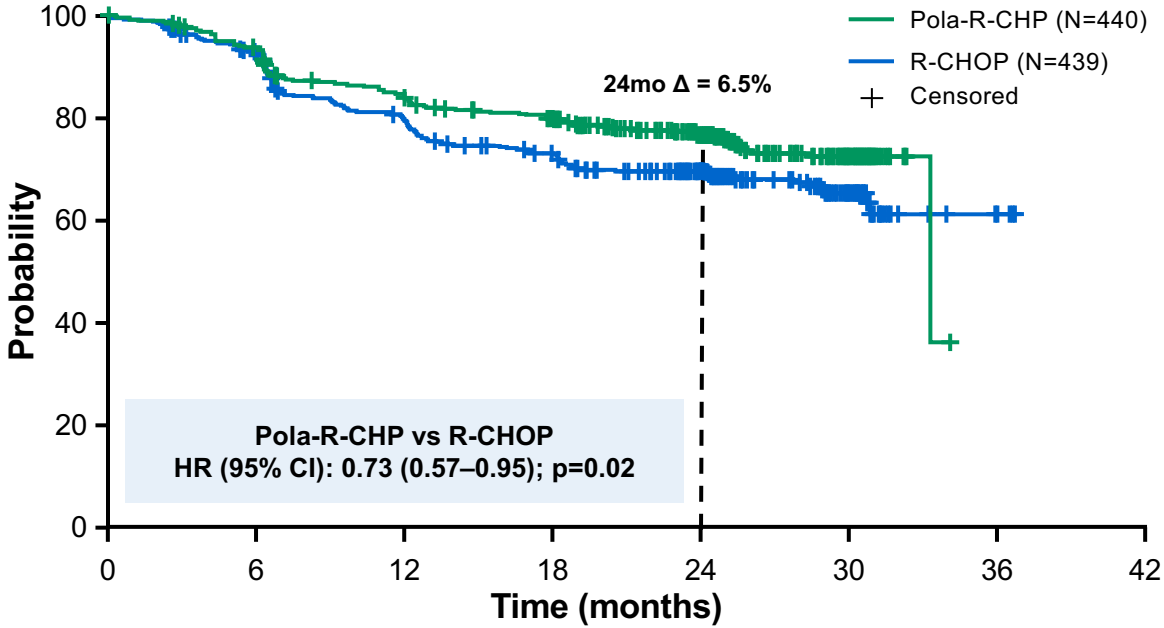
improvement[1]

76.7%	**70.2%**
24 months	24 months
Progression-free survival	*Progression-free survival*

- Most relapses in patients with previously untreated DLBCL occur in the first 2 years, and outcomes with salvage therapy remain poor for a variety of patients[2]
- **Landmark analysis at 24 months** showed a clinically meaningful improvement in the number of patients avoiding relapse with Pola-R-CHP vs R-CHOP

1.Tilly H, et al. New Engl J Med 2022;386:351–63;
2. Maurer MJ, et al. Ann Oncol 2018;29:1822–27.

Investigator-assessed PFS (global ITT population)

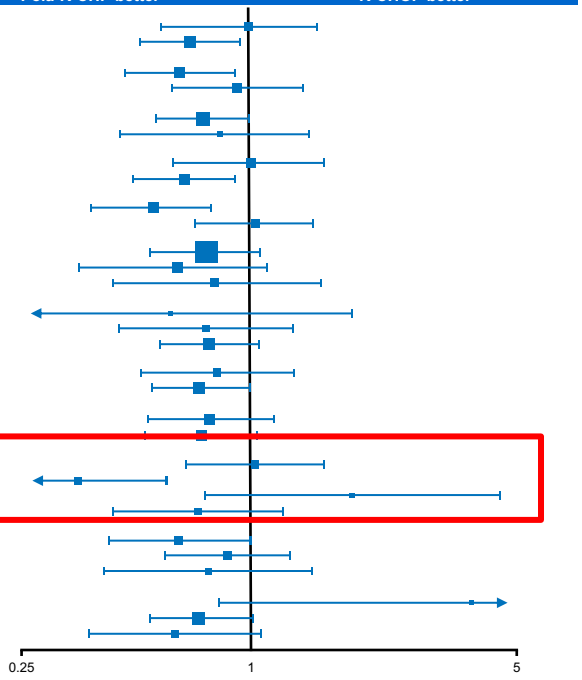


Number at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Tilly H, et al. New Engl J Med 2022;386:351–63.

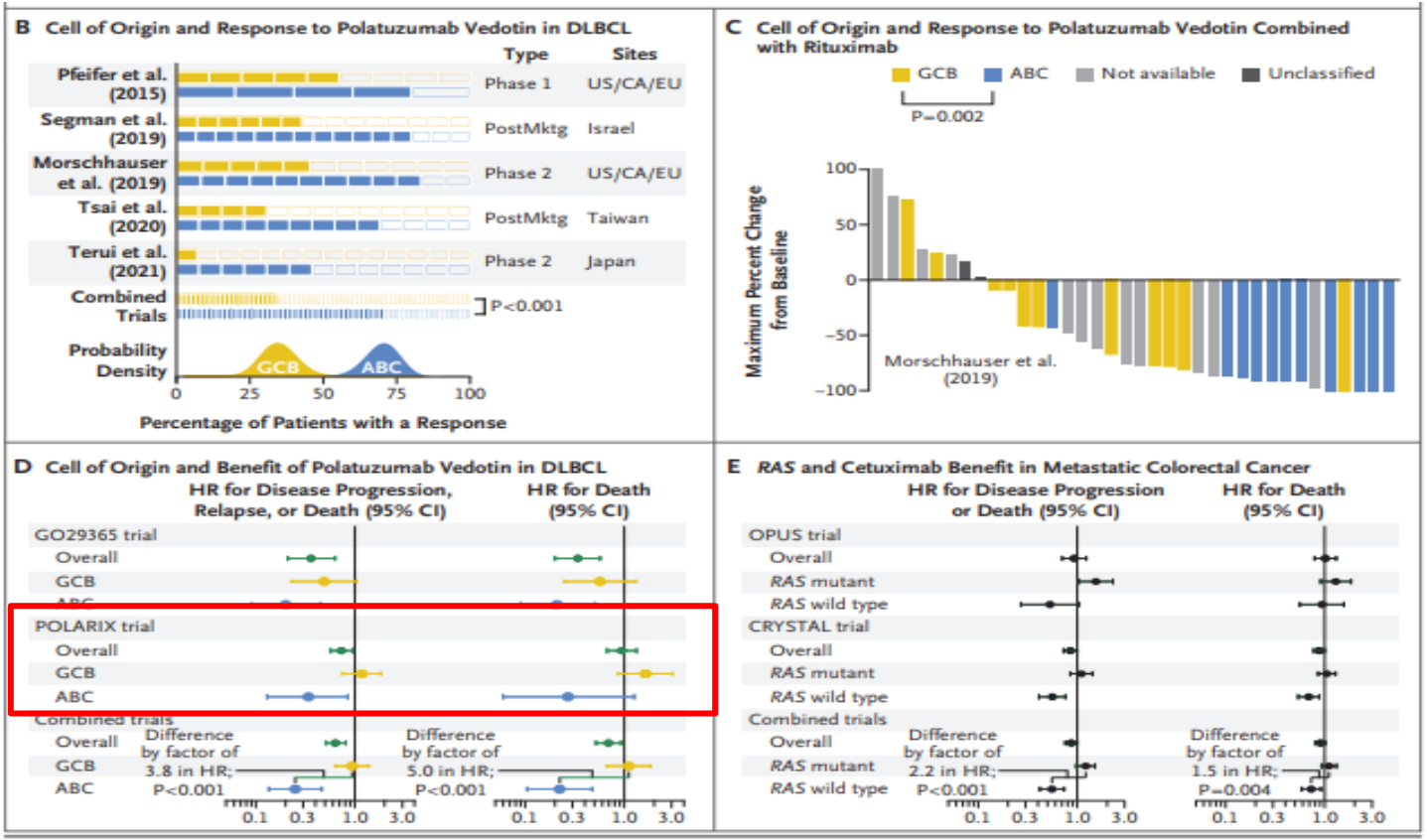
Investigator-assessed PFS by subgroup (global ITT, unstratified)

Baseline risk factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year rate	HR	95% Wald CI
Age group							
≤60	271	140	74.1	131	71.9	0.9	(0.6 to 1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5 to 0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5 to 0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6 to 1.4)
ECOG PS							
0–1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)
IPI 3–5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)
Geographic region							
W. Europe, US, Canada, Australia	603	302	78.6	301	72.0	0.8	(0.6 to 1.1)
Asia	160	81	74.3	79	65.6	0.6	(0.4 to 1.5)
Rest of world	116	57	70.8	59	67.3	0.9	(0.6 to 1.5)
Ann Arbor stage							
I–II	99	47	89.1	52	85.5	0.6	(0.2 to 1.8)
III	232	124	80.7	108	73.6	0.8	(0.5 to 1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6 to 1.1)
Baseline LDH							
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)
No. of extranodal sites							
0–1	453	227	80.2	226	74.5	0.8	(0.5 to 1.1)
>2	426	213	73.0	213	65.8	0.7	(0.5 to 1.0)
Cell-of-origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)
Non DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8 to 17.6)
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)



Tilly H, et al. New Engl J Med 2022;386:351–63.

Cell of Origin and Response to Polatuzumab Vedotin in DLBCL

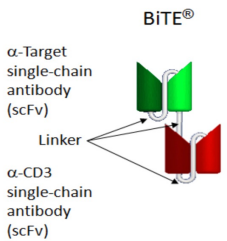
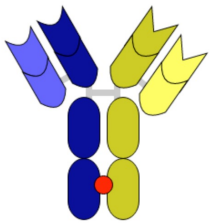
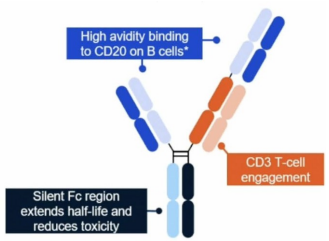
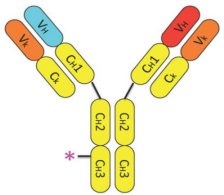


Palmer et al. NEJM 2023

Frontline Trials in DLBCL

(with Bispecifics or Venetoclax)

Bispecific Antibodies in B-cell NHL

The Original: Proof of Concept	The New Ones ….and more to come			
Blinatumomab[1]	**Epcoritamab[2]**	**Mosunetuzumab[3]**	**Glofitamab[4]**	**Odronextamab[5]**
				
CD3 (scFV) x CD19 (scFV)	**DuoBody- CD3 x CD20 BsAb**	**CD3 x CD20 Knobs-in-hole Fc BsAb**	**CD3 (Fab) x CD20 (Fab x2) Fc BsAb**	**CD3 x CD20 Common LC Fc BsAb**

- Numerous bispecific antibody structures exist
- **Properties of the BsAbs vary by construct**

- Distinguishing features of BsAbs include:
  - ***"Off-the-shelf"*** *– rapid access, relative ease of delivery* [6,7]
  - ***Adaptable*** *– lack of persistence and ability to modulate dosing may improve tolerability*[6]

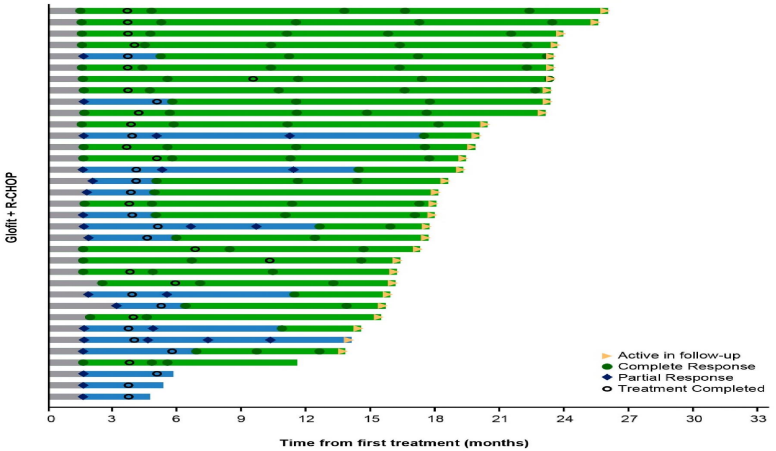
1. Queudeville M, et al. Onco Targets Ther. 2017;10:3567-3578. 2. Clausen MR, et al. J Clin Oncol. 2021;39(suppl 15):7518. 3. Budde LE, et al. Blood. 2018;132(suppl 1):399. 4. Hutchings M, et al. Blood. 2020;136(suppl 1):45-46. 5. Bannerji R, et al. Blood. 2020;136(Suppl_1):42-43. Presented at: ASH 2020. Abstract 400. 6. Husain B, et al. BioDrugs. 2018;32(5):441-464. 7. Schuster S. SurvivorNet. Bispecific antibodies: an off-the-shelf approach to treating lymphoma. Accessed June 23, 2022. https://www.survivornet.com/articles/bispecific-antibodies-an-off-the-shelf-approach-to-treating-lymphoma/

Improving on R-CHOP or Pola-R-CHP in DLBCL

- **Glofitamab + R-CHOP**
  - 56 pts (96% stage III/IV). Median IPI 3
  - 6-8 cycles of R-CHOP with glofitamab dose ramp-up starting C2
    - Glofitamab maintenance for up to 1y
  - 10.7% CRS, no G3/4
  - Median 17m follow-up:
    - 84% CMR (91% remained in CMR at 1y)

Topp et al, ASH 2023 Abst #3085

Figure. Durability of response in patients with previously untreated DLBCL who received Glofit + R-CHOP

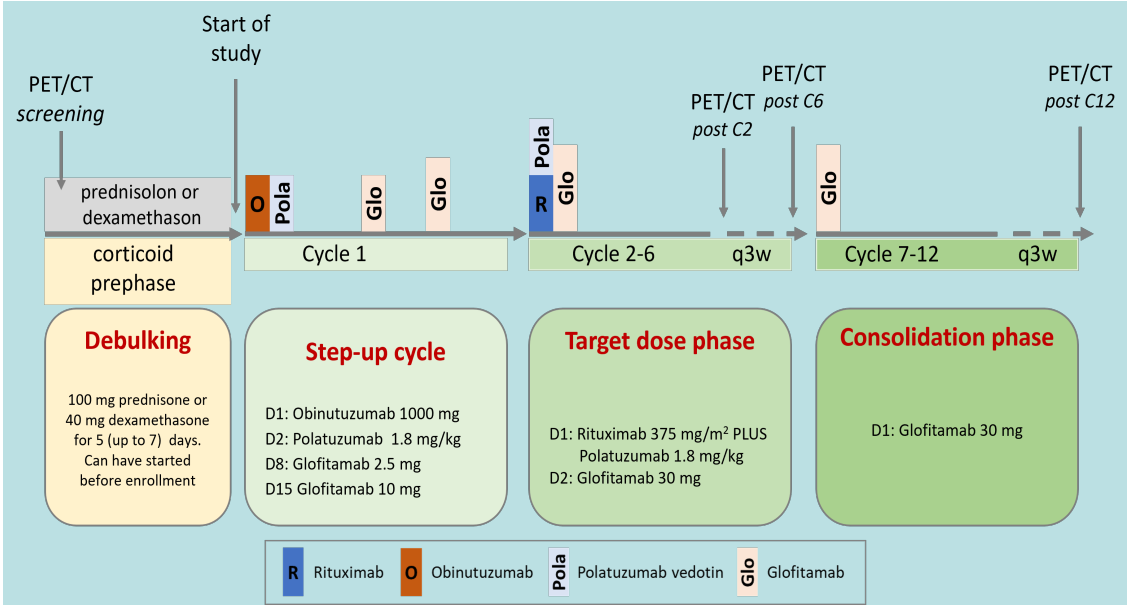


Clinical cut-off date: April 4, 2023; DLBCL, diffuse large B-cell lymphoma; Glofit, glofitamab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

- **Epcoritamab + Pola-R-CHP**
  - Ongoing, open at TGH Cancer Institute
  - Adding Epco with dose ramp-up to Pola-R-CHP
  - 6 cycles of Pola-R-CHP+Epco followed by 2 cycles of Epco

Pola + Glofitamab + Rituximab in Frontline DLBCL:

- **Not eligible for R-CHOP**
- **First 10 pts:**
  - **Median age 79**
  - **70% stage III/IV**
  - **70% IPI 3-5**
  - **1 G3 bleeding, 1 G3 AKI**
  - **3 G1 CRS**
  - **no ICANS/neuropathy**
- **ORR 63%, CR 51%**

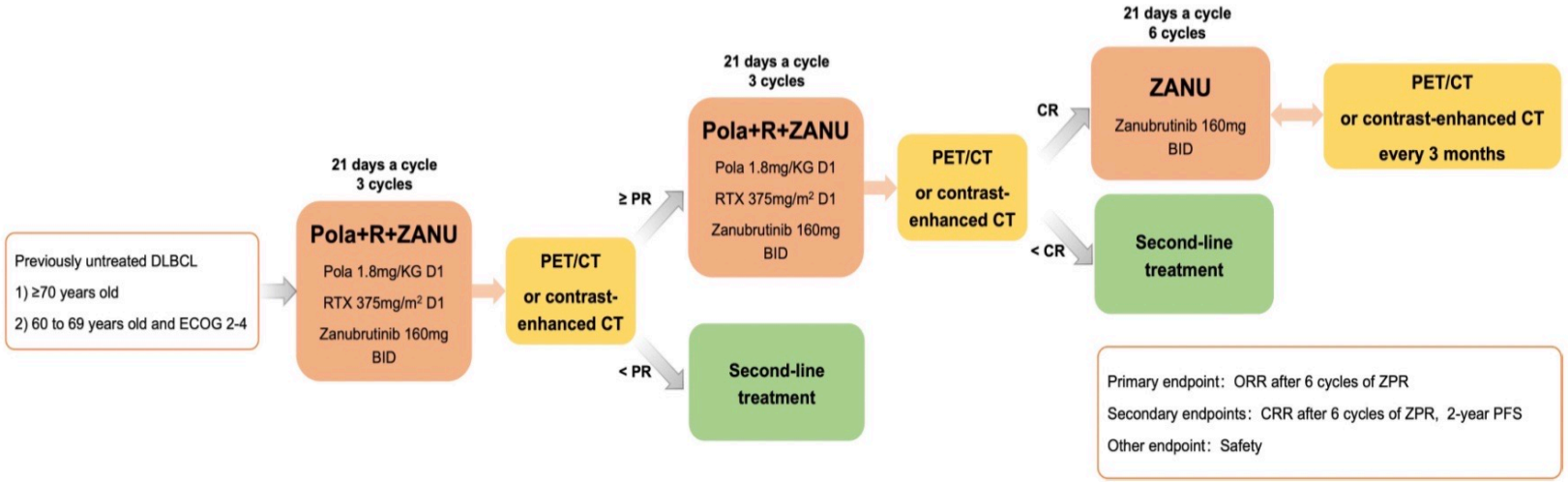


Melchardt et al., ASH 2023 Abst #1734

“Chemo-free” frontline therapy for elderly/frail DLBCL patients: Polatuzumab, Zanubrutinib & Rituximab

- 12 pts, 9 non-GCB, 1 double-hit
- Age > 70 or 60-69 & ECOG 2-4
- 1 G3 transaminitis, 1 G3 pneumonitis
- 4 patients evaluable after C3: 100% CMR

Figure 1. Scheme of ZPR regimen study

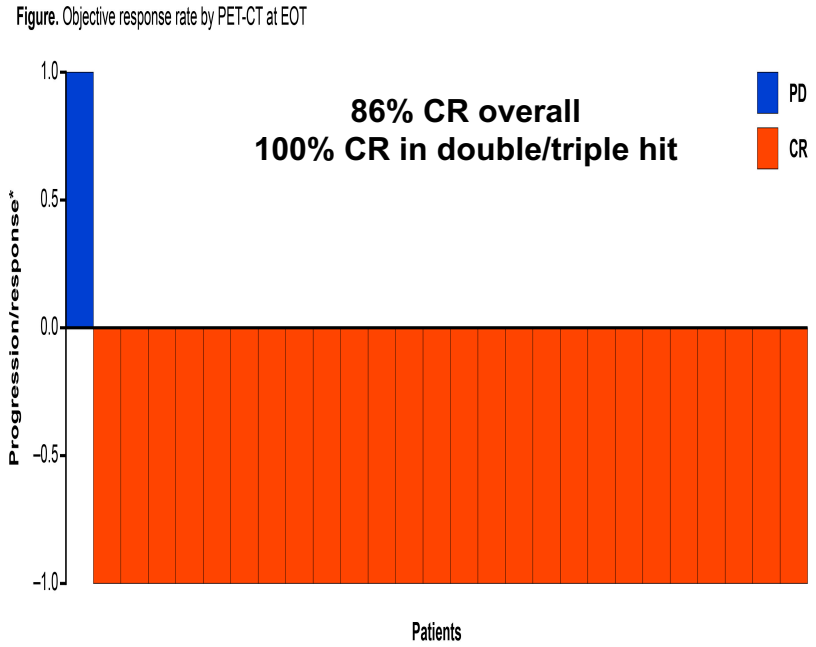


Ren et al., ASH 2023 Abst #1747

Venetoclax + Pola-R-CHP

- Cavalli study (Blood 2021) using 10d venetoclax with significant AEs

- Shorter course, 5-day venetoclax:
  - 30 pts evaluable for response
  - BCL2+, R-IPI 2-5, 90% stage III/IV, 25% double/triple hit
  - Venetoclax 800mg x 5 days (C1D4, then D1 subsequent cycles)
  - 2 G5 AE (cardiac, sepsis), 10% febrile neutropenia



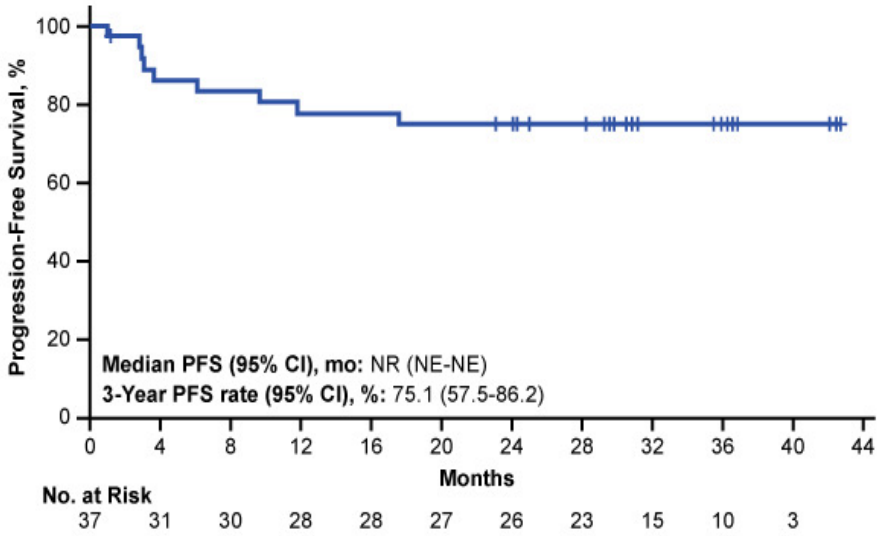
Zelenetz et al., ASH 2023 Abst #439

Frontline Trials in DLBCL

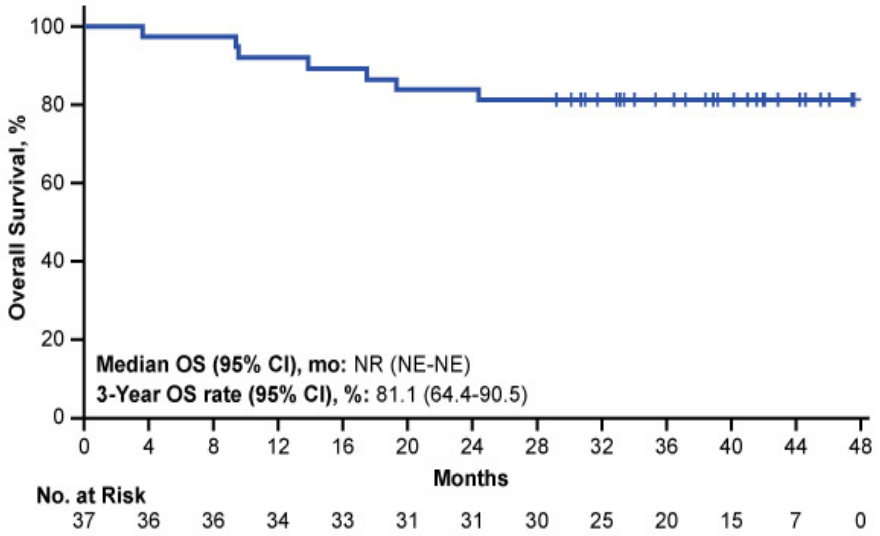
(with CAR T cells)

ZUMA-12: Axi-Cel as Frontline Therapy for High Risk DLBCL: 3-year follow up *(Chavez, JC et al. ASH 2023)*

PFS



OS

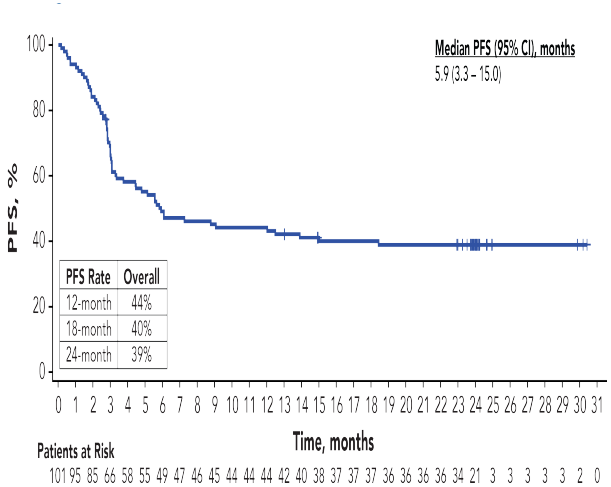


- **Medians for PFS and OS were not reached** in efficacy-evaluable patients
- Among patients who achieved a CR as best response, **3-year PFS: 84.4% and OS: 90.6%**

Chavez JC et al. ASH Meeting 2023

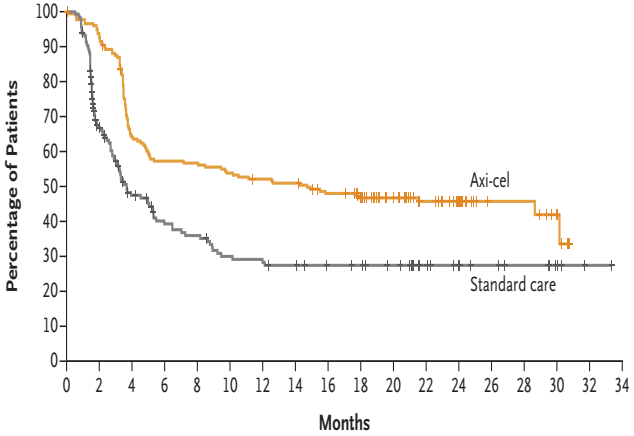
Earlier use of CAR T cells seems to further improve outcomes in DLBCL

ZUMA-1 (3rd Line)



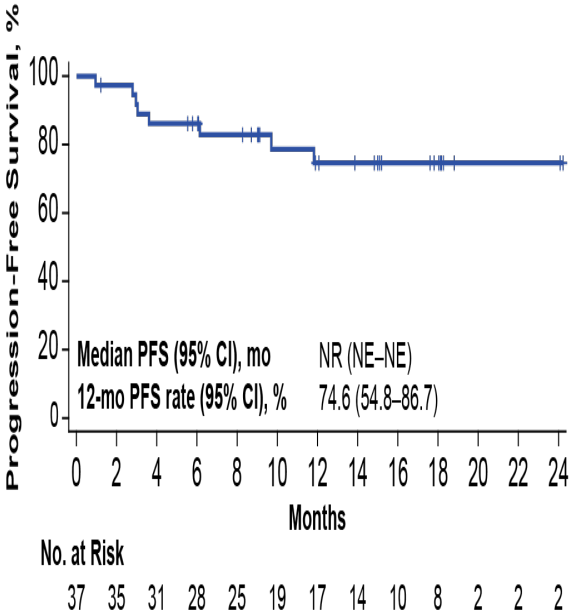
Median PFS 5.9 m

ZUMA-7 (2nd Line)



Median PFS (axi-cel arm): 14.6 m

ZUMA-12 (1st Line)



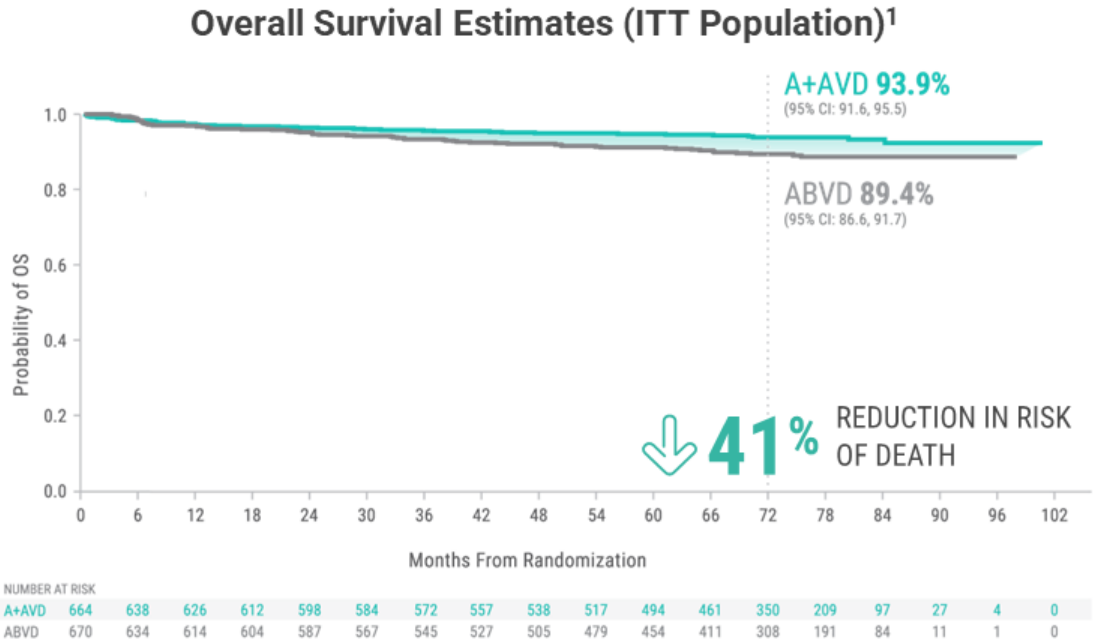
Median PFS: Not reached

Westin, J. et Al. N Eng. J. Med 2023

Frontline Advanced DLBCL

Frontline Advanced Hodgkin's disease

Bv+AVD in advanced stage Hodgkin Lymphoma: 6-year OS



HR: 0.59 (95% CI: 0.40, 0.88)
P = 0.009

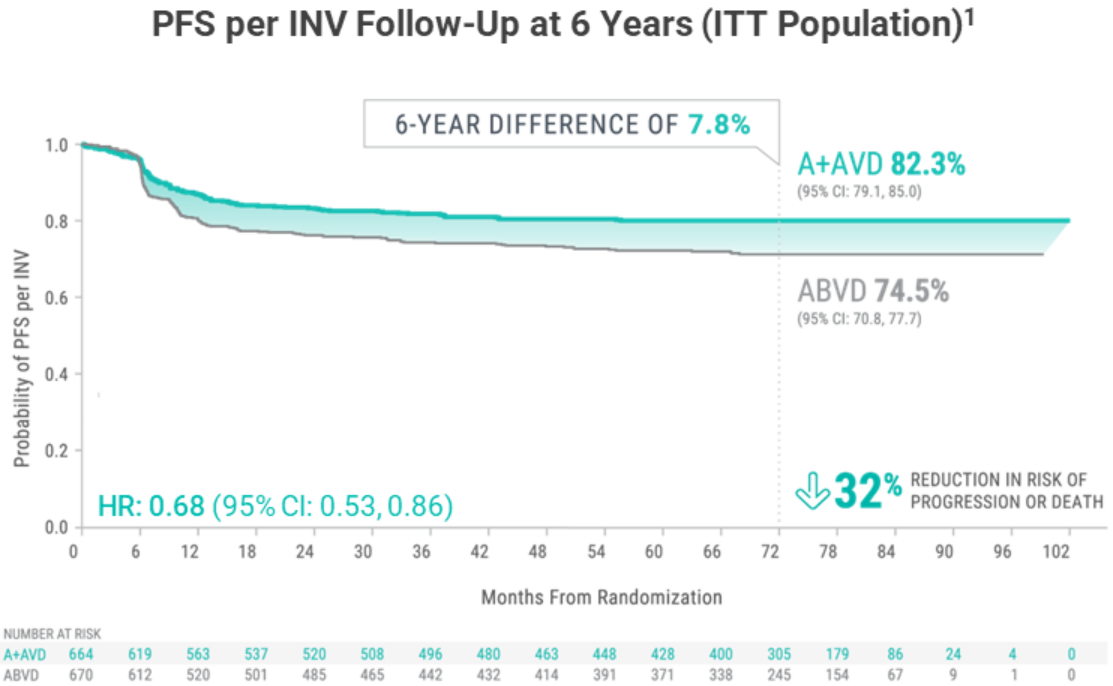
- At 103 events, a benefit was considered statistically significant at P<0.0365[1]
- Median follow-up: 73.0 months[1]
- Median overall survival was not reached in either arm[1,2]
- At 2 years (the time of the modified PFS analysis), an interim overall survival did not demonstrate a significant difference[2]

ASCO 2024 (S. Ansell et al)

7year OS: 93.5% with Bv+AVD vs. 88.8% with ABVD

(HR: 0.62; 95% CI: 0.42,0.90) p=0.011

Bv+AVD in advanced stage Hodgkin Lymphoma: 6-year PFS



ECHELON-1 primary endpoint: Modified PFS per IRF at 2 years[2,3]

- HR (95% CI): 0.77 (0.60, 0.98), *P* = 0.035; median follow-up: 24.6 months
- 23% reduction in event risk†

ECHELON-1 exploratory endpoint: PFS per INV analyzed at 6 years

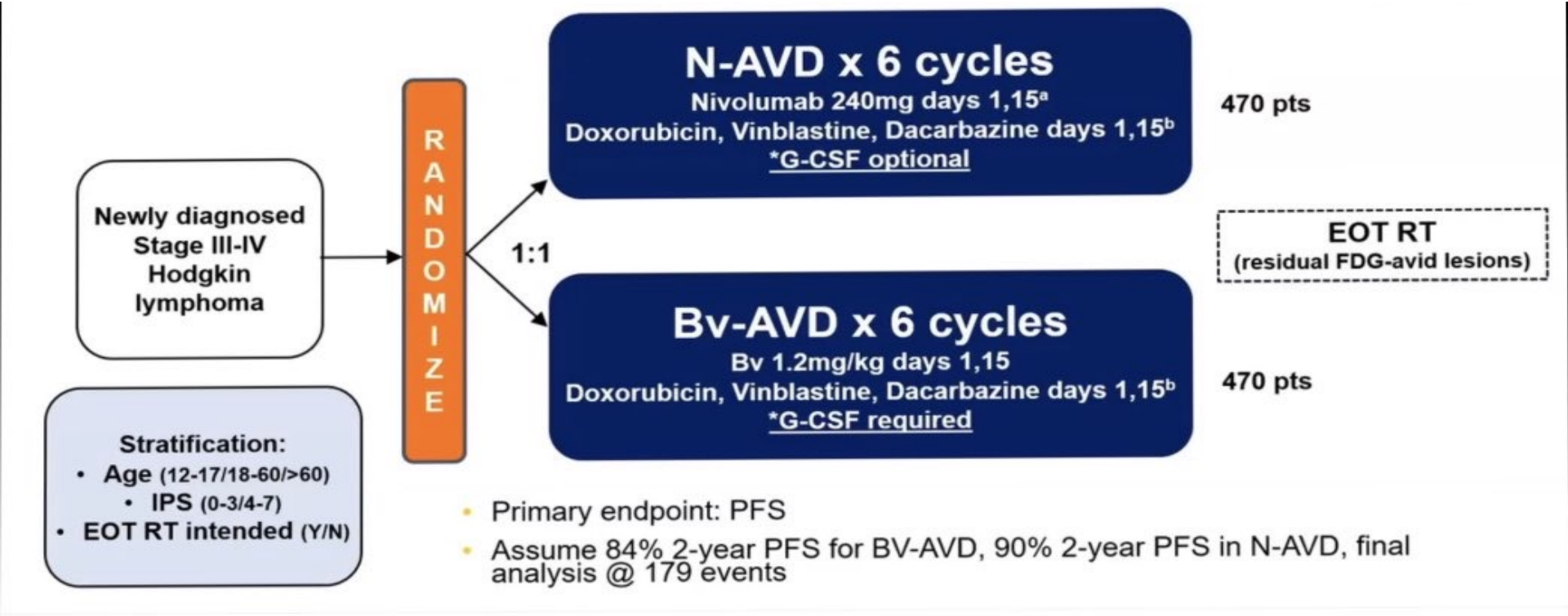
- PFS per INV was defined as time from randomization to the first occurrence of disease progression or death[1]
- Median progression-free survival was not reached in either arm[1]

* PFS per INV at 6 years was a post-hoc exploratory analysis. This analysis was not powered to determine differences between treatment arms and offers supportive, but not conclusive, clinical information only.

ASCO 2024 (S. Ansell et al)

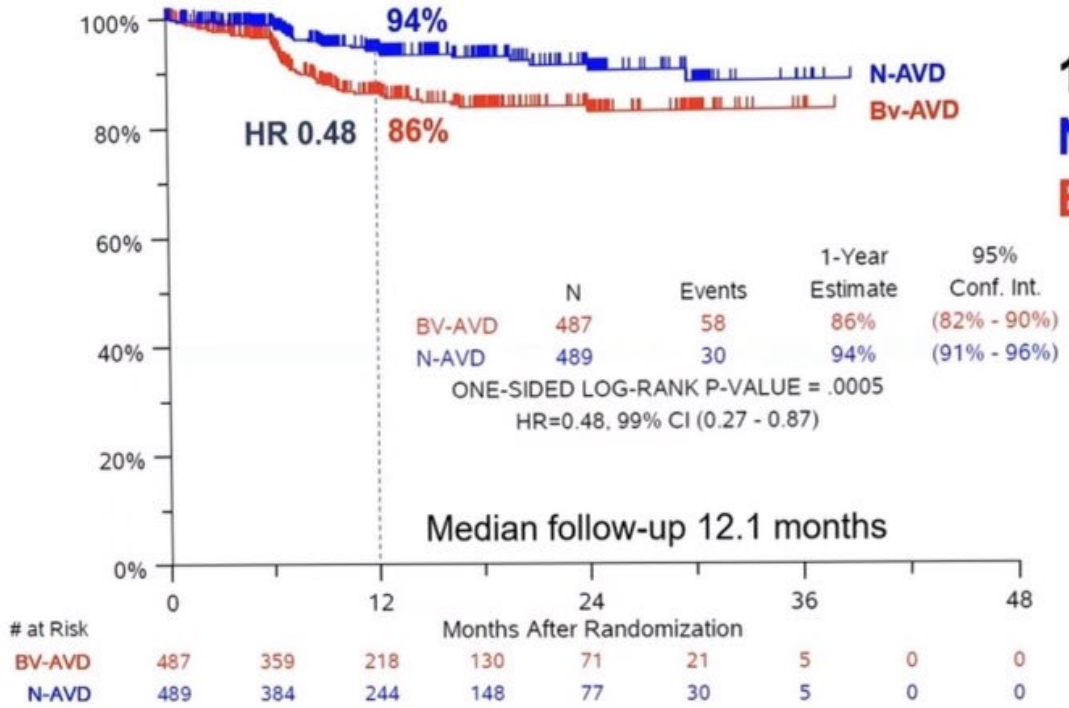
7year PFS: 82.3% with Bv+AVD vs. 74.5% with ABVD
(HR: 0.68; 95% CI: 0.53,0.86) p=0.001
PFS rates at 7 years indicate potential curability

Intergroup Study S1826



Herrera AF, et al. ASCO 2023, Plenary Session.

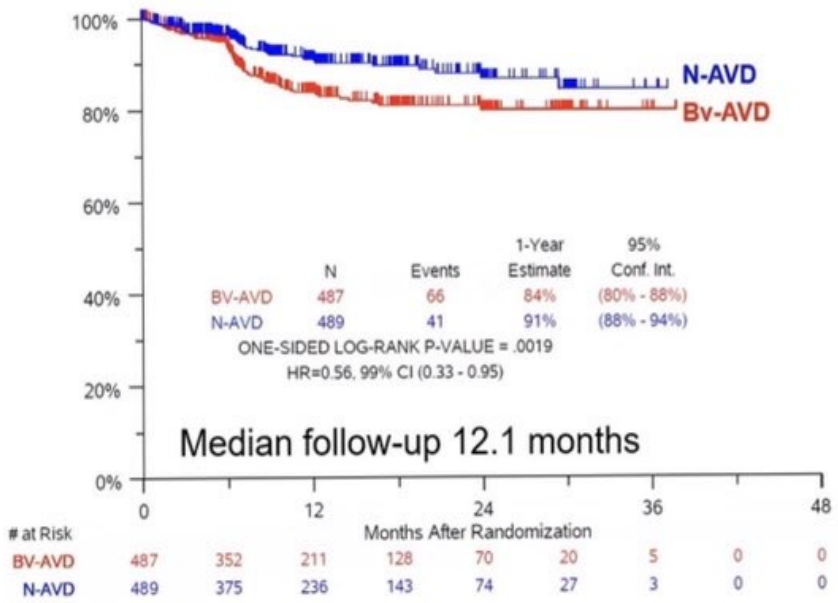
Intergroup Study S1826: PFS



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

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: EFS



1-year EFS
N-AVD 91%
Bv-AVD 84%

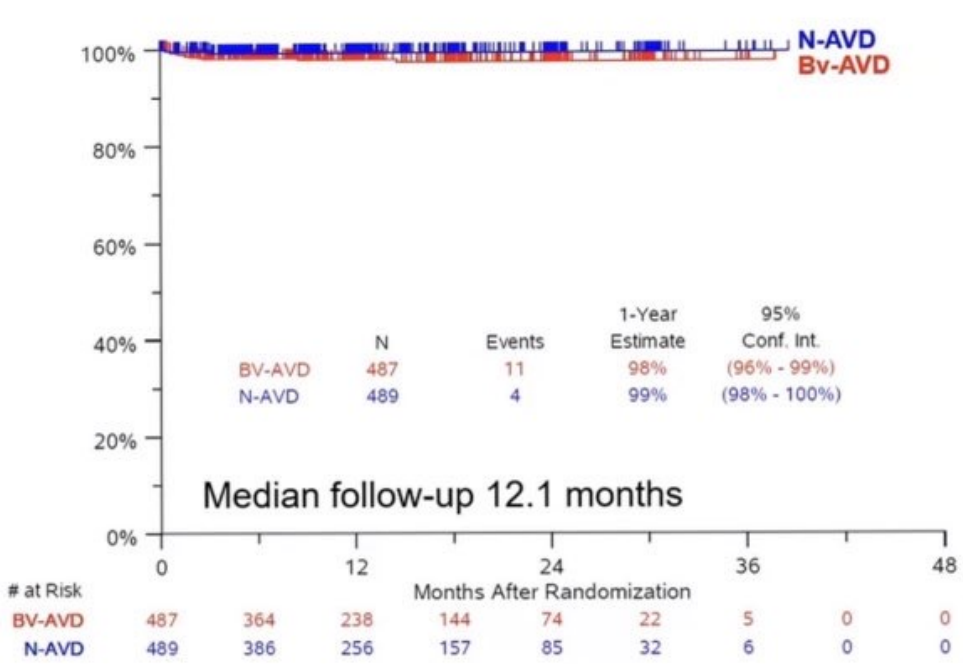
EFS events: death, progression, non-protocol treatment before progression

EFS event	N-AVD	Bv-AVD
Non-protocol chemo before PD	9	6
Non-protocol immunotx before PD	1	0
Non-protocol RT prior to PD	1*	3**
Progression/Relapse	**26**	**47**
Death without progression	**4**	**10**
Total EFS Event	**41**	**66**

* Intended for RT, EOT DS=3, received RT anyways
**1/3 intended for RT, 1 with EOT DS=2 and off tx due to AE then received RT, 2 with EOT DS=3 and received RT anyways

Herrera AF, et al. ASCO 2023, Plenary Session.

Intergroup Study S1826: OS



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

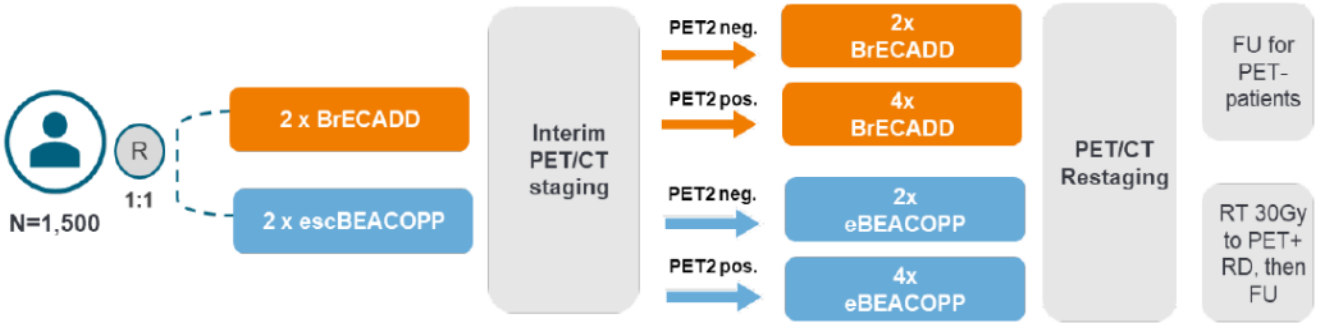
* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

Herrera AF, et al. ASCO 2023, Plenary Session.

GHSG HD21: BrECADD versus BEACOPP in advanced stage classical Hodgkin lymphoma

GHSG HD21 study design and primary endpoints

HD21 is an international randomized, open-label, phase 3 study of BrECADD versus eBEACOPP in adult patients < 60 yo with previously untreated, AS-cHL



Co-primary objectives:

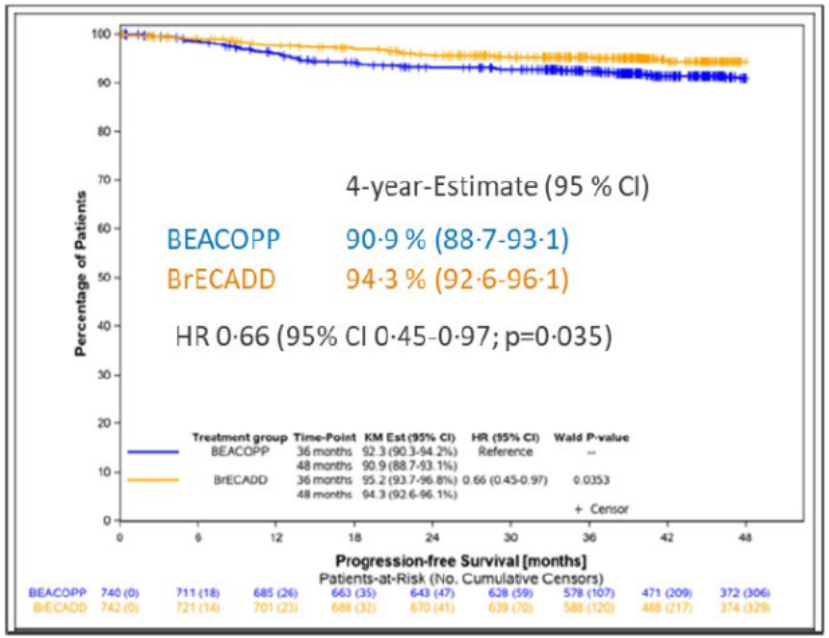
- Demonstrate **superior tolerability** defined by treatment-related morbidity (TRMB) with BrECADD.
- Demonstrate **non-inferior efficacy** of 4-6 x BrECADD compared with 4-6 x BEACOPP determined by PFS (NI margin 6%, HR to be excluded 1.69)

Borchmann, P. et al. LBA7000, ASCO 2024

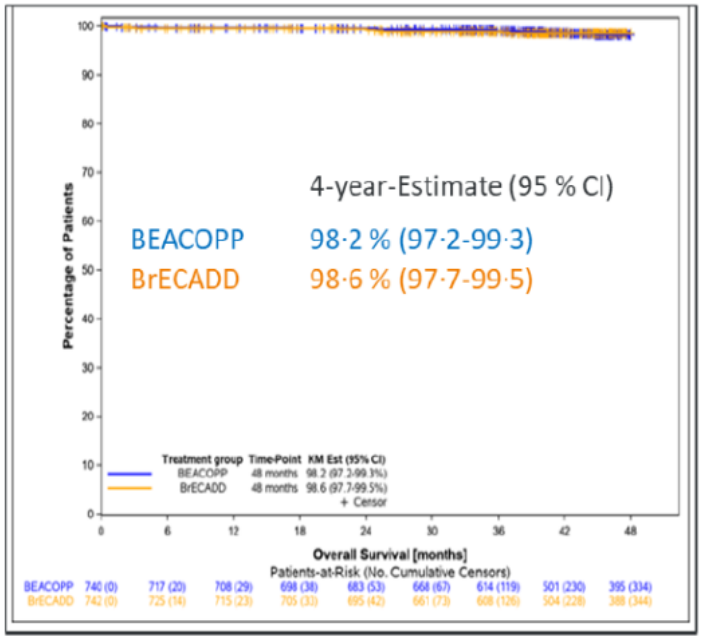
GHSG HD21: BrECADD versus BEACOPP

HD21 final analysis: BrECADD is superior to eBEACOPP (mFU 48 m)

Progression-free survival



Overall survival



Borchmann, P. et al. LBA7000, ASCO 2024

BrECADD versus BEACOPP: Key Findings

1. **BrECADD is more active than eBEACOPP** reaching
   - an unprecedentedly high 4-year PFS of 94.3%
   - with most patients (64%) receiving only 4 cycles (i.e. 12 weeks) of treatment.

2. **BrECADD is better tolerated than eBEACOPP:** TRMB relative risk 0·72 ($p<0·0001$) with
   - resolution of TRMB events in > 99% of patients at 12 months follow-up
   - a clinically highly relevant reduction of neuropathy and gonadal dysfunction

➢ PET2-guided individualized BrECADD has a very favourable risk-benefit ratio.
We thus recommend it as **standard treatment option for AS-cHL.**

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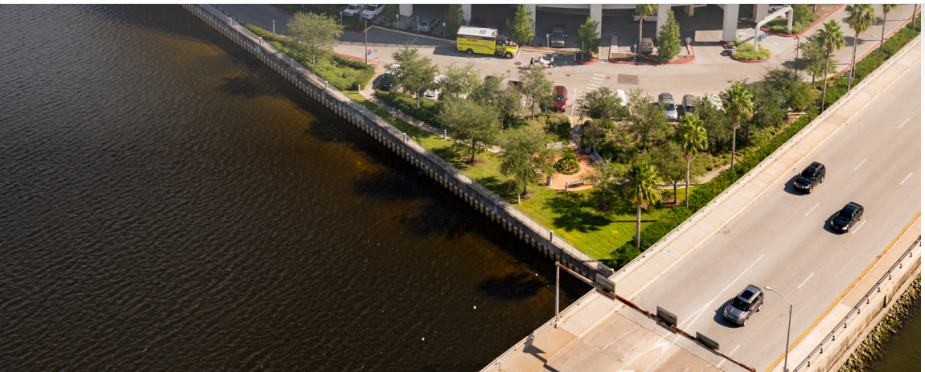
THANK YOU !



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