

High Grade B-cell Lymphomas: *Impact of New Therapeutic Approaches*

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Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BMS, Caribou, Foresight Diagnostics, Genentech, Johnson & Johnson, Lilly, Miltenyi Biotec, Novartis, Roche

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Initial Therapy: *ADC*



POLARIX trial: Polatumumab-R-CHP versus R-CHOP

Multicenter, double-blind, placebo-controlled phase III trial

Patients

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

R 1:1

6 Cycles: Pola-R-CHP

2 additional cycles of rituximab

6 Cycles: R-CHOP

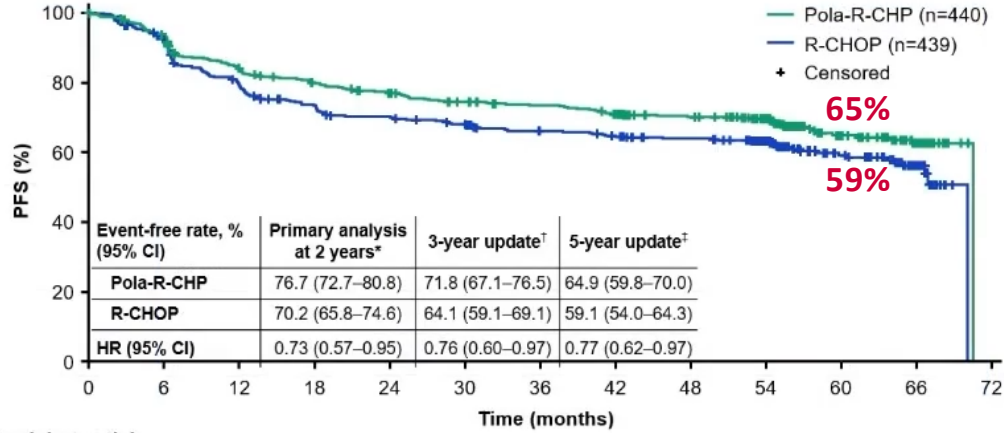
2 additional cycles of rituximab

Primary endpoint: Investigator-assessed PFS

Characteristics	Pola-R-CHP N=500	R-CHOP N=500
Expanded population		
Age, median (range)	65 (19-80)	65 (19-80)
Advanced stage, n (%)	447 (89)	444 (89)
IPI 3-5, n (%)	273 (62)	272 (62)
HGBCL, NOS/DHL, n (%)	44 (9)	52 (10)
NOS	23 (5)	24 (5)
DHL/THL	21 (4)	28 (6)
Double hit, n (%) centrally confirmed	26 (5)	19 (4)
ABC subtype, n (%)	131/377 (35)	143/390 (37)

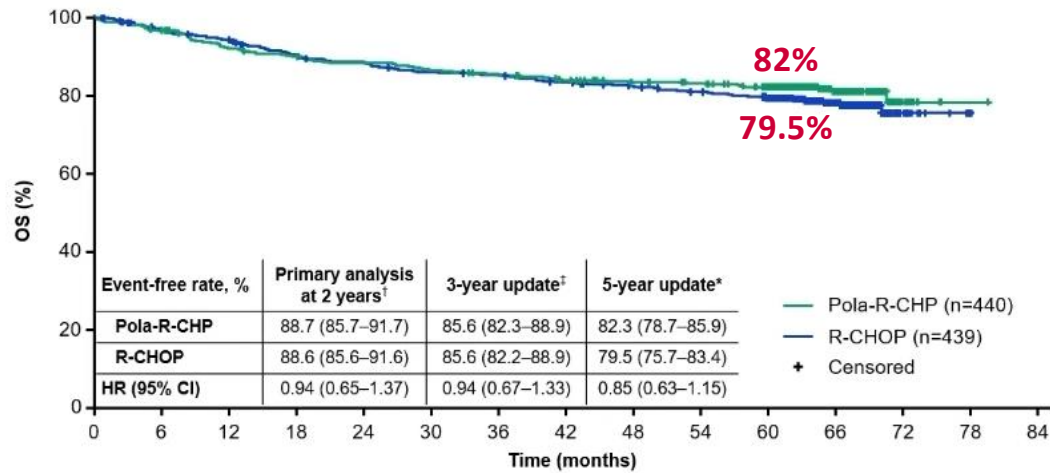


Pola-R-CHP significantly improved PFS versus R-CHOP



Patients remaining at risk

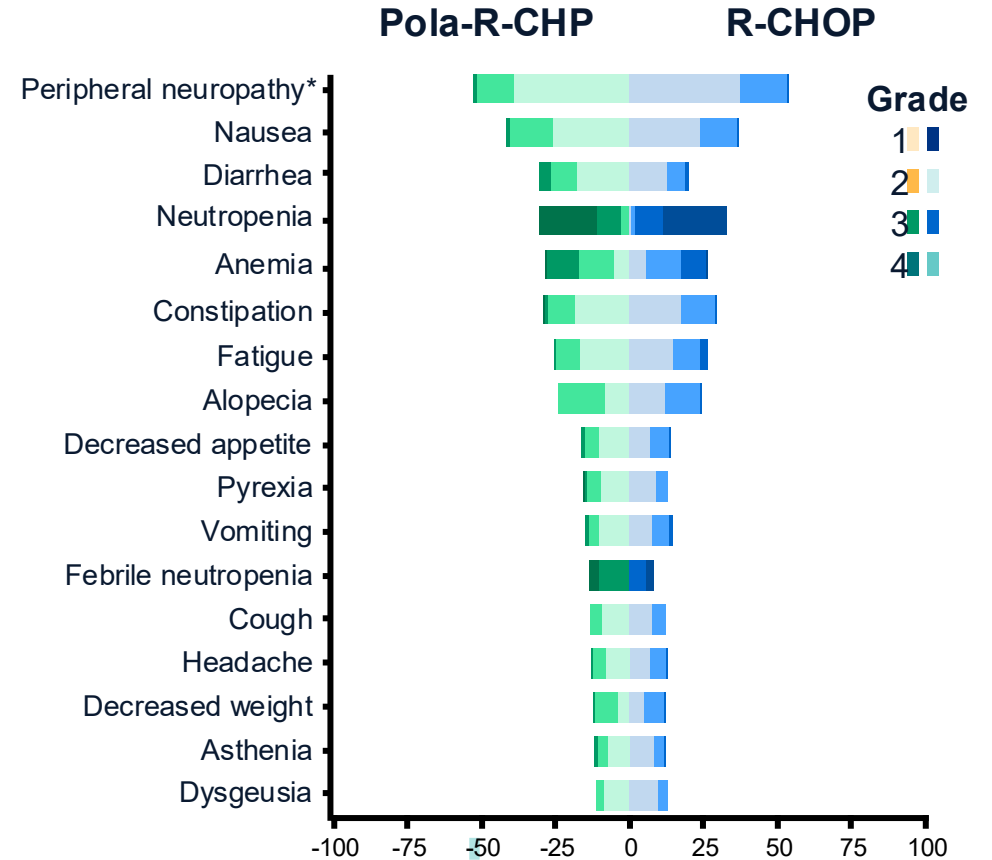
	0	6	12	18	24	30	36	42	48	54	60	66	72	NE
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE	
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE	



Patients remaining at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	NE
Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

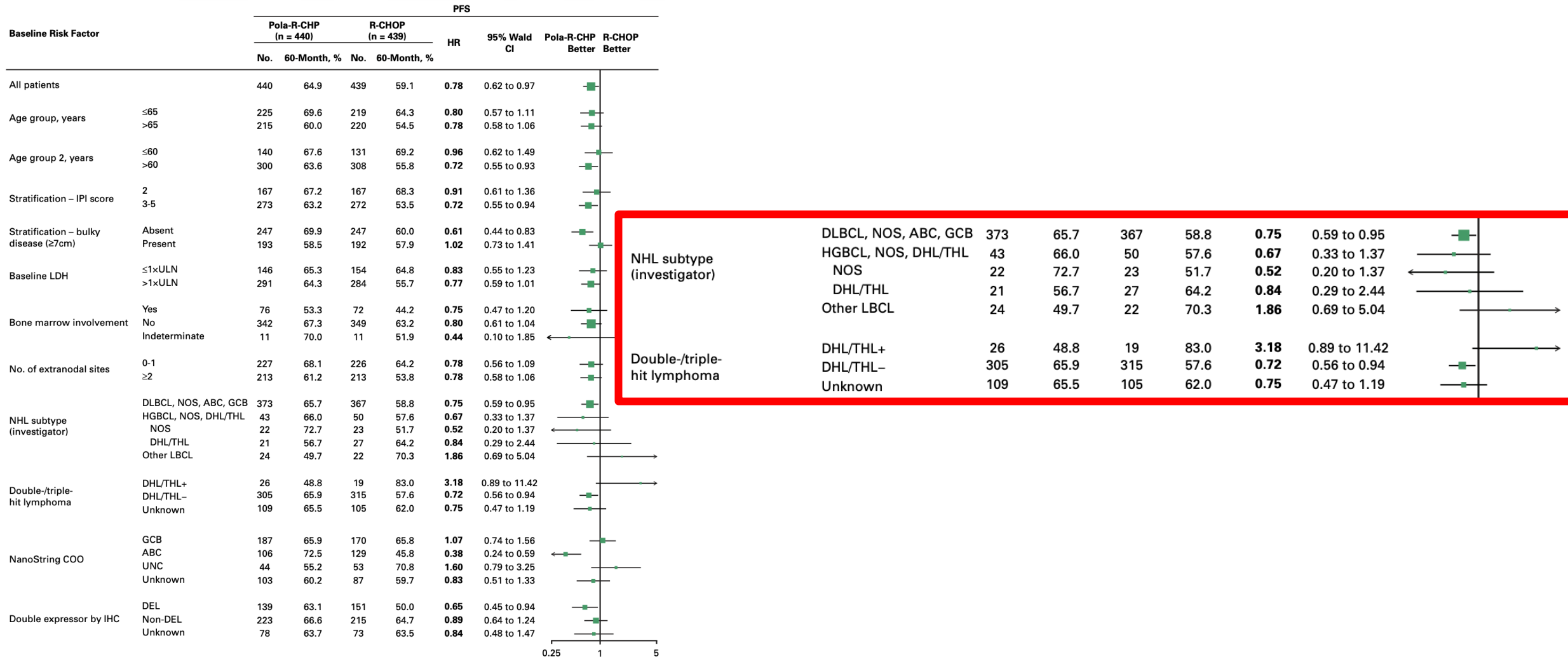
No significant increase in toxicity



*predominant benefit seen ABC, non-bulky and IPI 3-5 patients



POLARIX: PFS subset analysis (exploratory)



Relapsed/Refractory: CAR T-cells

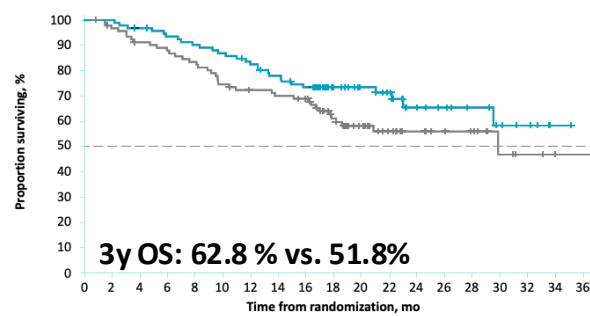
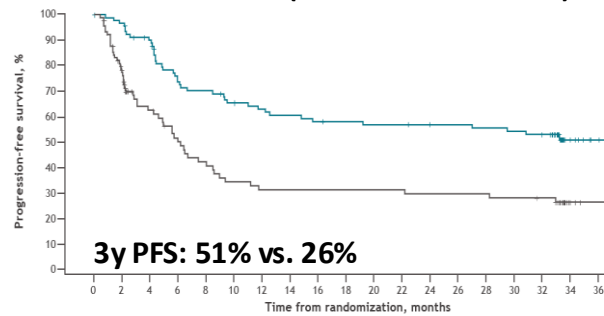


Liso-cel and Axi-cel are superior to chemotherapy as 2nd line therapy in primary refractory or early relapsed LBCL

Liso-cel vs. SOC in 2nd line

Median PFS NR vs. 6.2 mos
HR 0.422 (0.279—0.639)

Median OS NR vs. NR
HR 0.757 (0.481—1.191)



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Liso-cel arm	92	88	79	63	60	55	52	50	48	47	46	46	44	44	43	42	41	7	2
SOC arm	92	66	42	33	27	22	20	20	20	20	20	20	19	19	19	18	17	3	1

No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Liso-cel	92	92	88	84	81	78	74	68	63	43	34	30	16	13	10	7	5	1	0
SOC	92	88	81	79	74	66	62	60	58	41	30	21	15	12	10	5	3	1	1

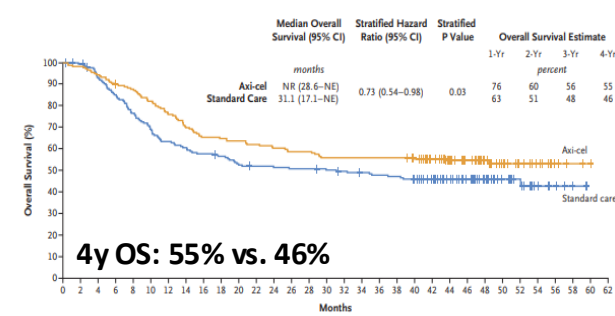
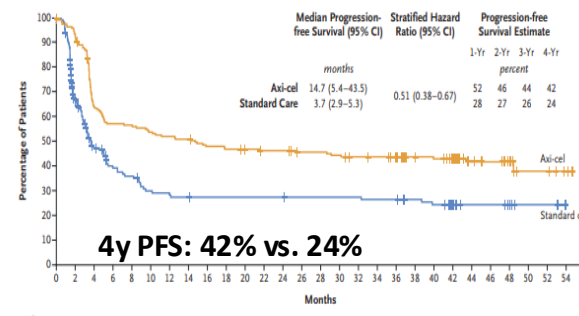
Improved QOL for Liso-cel over SOC by PRO

Toxicity	%
CRS	
Any grade	49
Grade 3	1
Neurotoxicity	
Any grade	11
Grade 3	4

Axi-cel vs. SOC in 2nd line

Median PFS 14.7 vs. 3.7 mos
HR 0.51 (0.38-0.67)

Median OS NR vs. 31.1 mos
HR 0.73 (0.54-0.98)



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
Axi-cel	180	166	112	100	99	94	91	89	83	81	79	77	77	73	71	68	67	63	54	52	45	32	29	22	7	7	3	0	
Standard care	179	94	61	47	43	35	33	32	31	31	31	31	31	30	30	30	29	29	25	23	18	10	10	8	4	4	0	0	

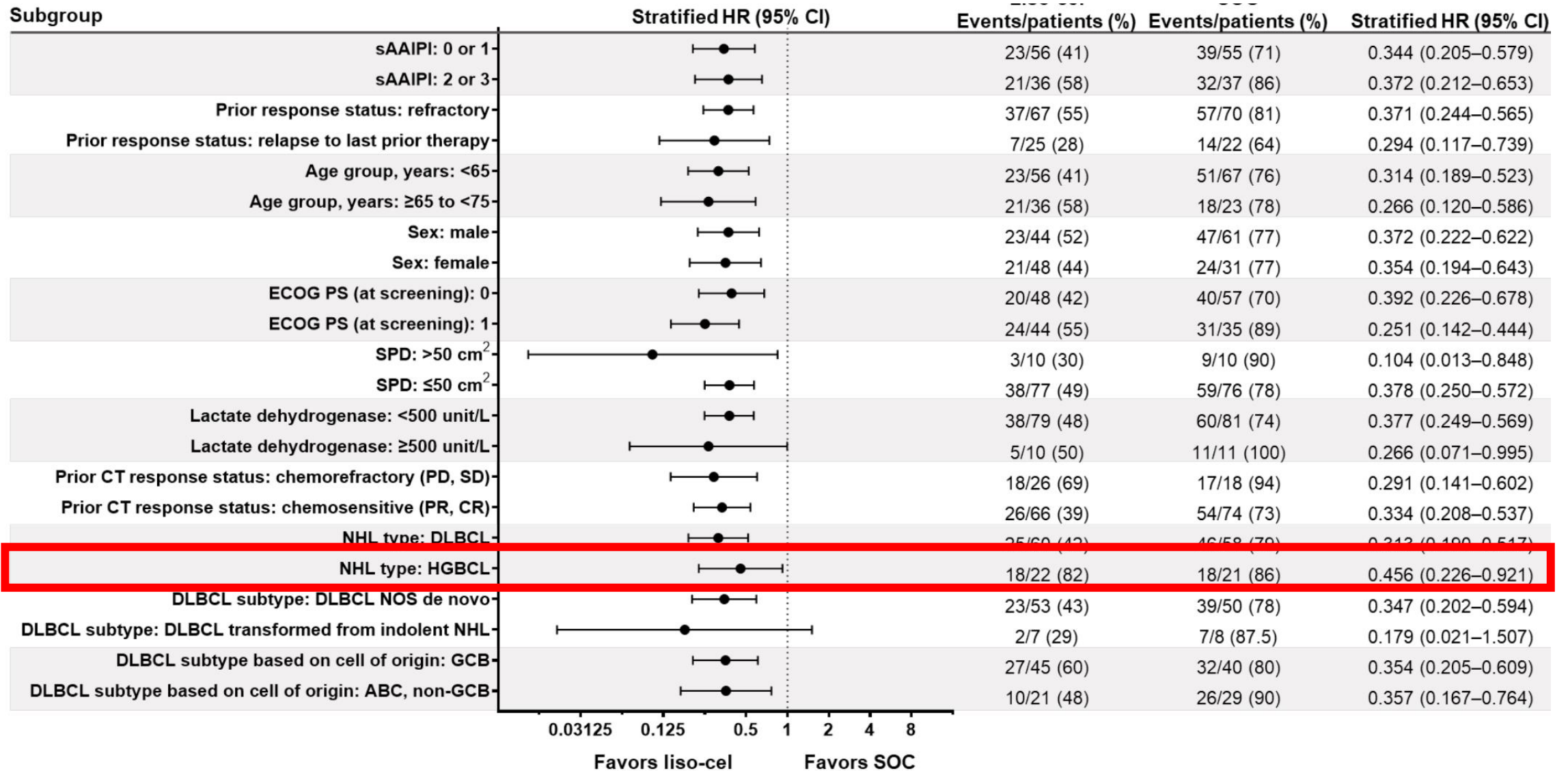
No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	60	62
Axi-cel	180	177	170	161	157	147	136	125	117	116	114	111	108	105	105	100	100	100	100	96	80	67	54	41	29	20	14	4	2	1	0
Standard care	179	176	163	149	134	121	111	106	101	98	91	89	88	87	87	85	83	81	79	78	73	63	51	41	31	19	14	7	4	1	0

Improved QOL for Axi-cel over SOC by PRO

Toxicity	%
CRS	
Any grade	92
Grade ≥3	6
Neurotoxicity	
Any grade	60
Grade ≥3	21

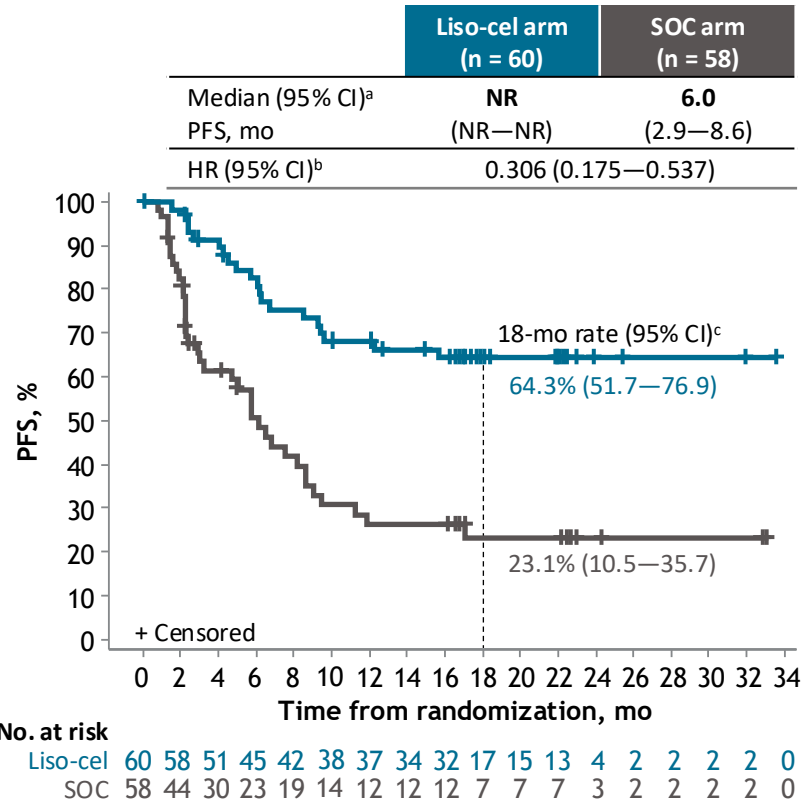


TRANSFORM Subset Analysis for EFS (ITT population)

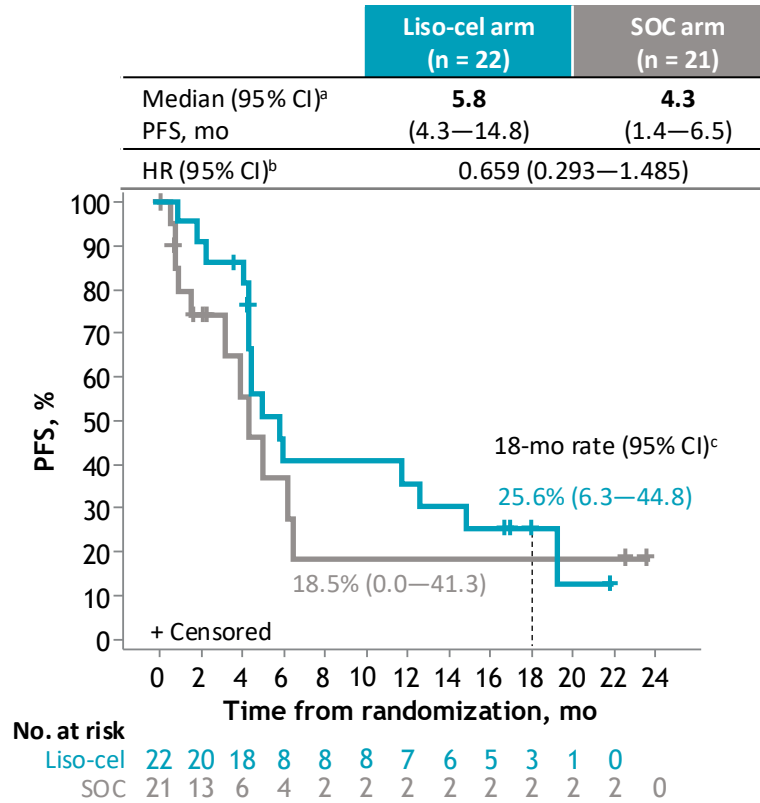


TRANSFORM PFS by LBCL type (ITT set)

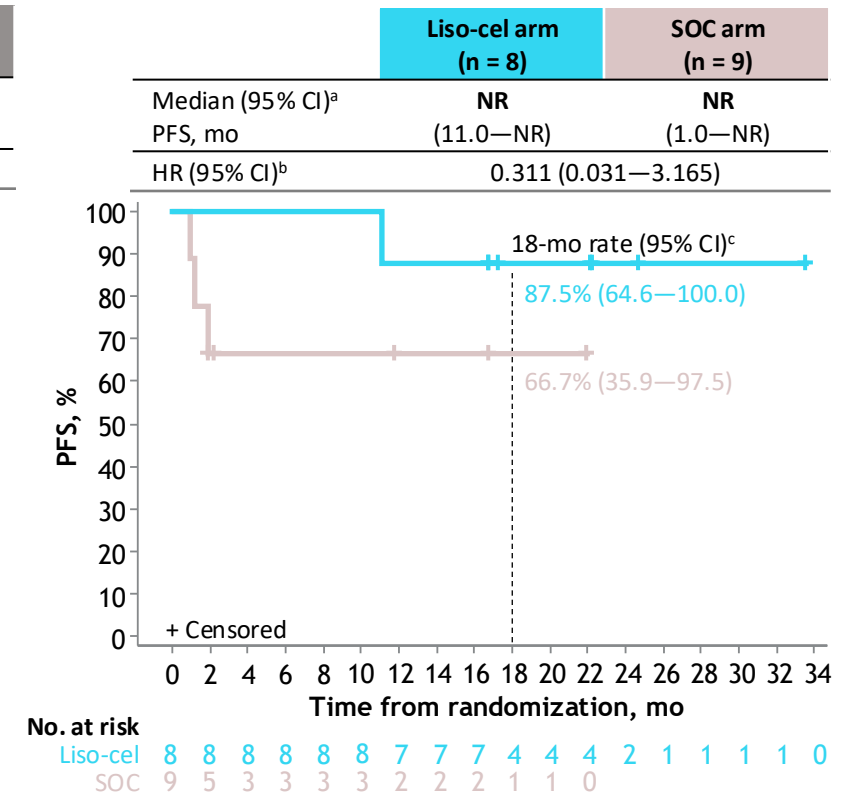
DLBCL



HGBCL



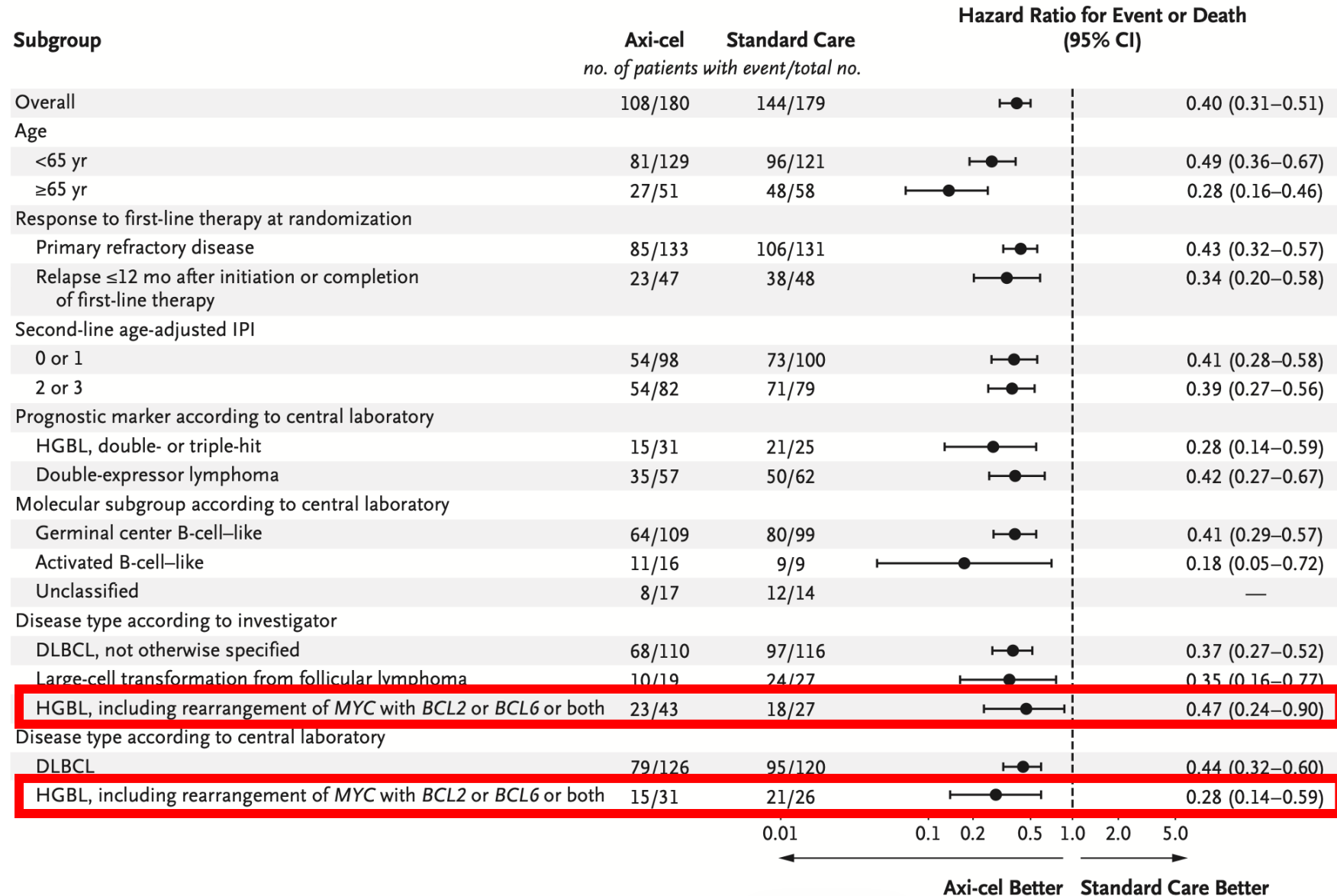
PMBCL



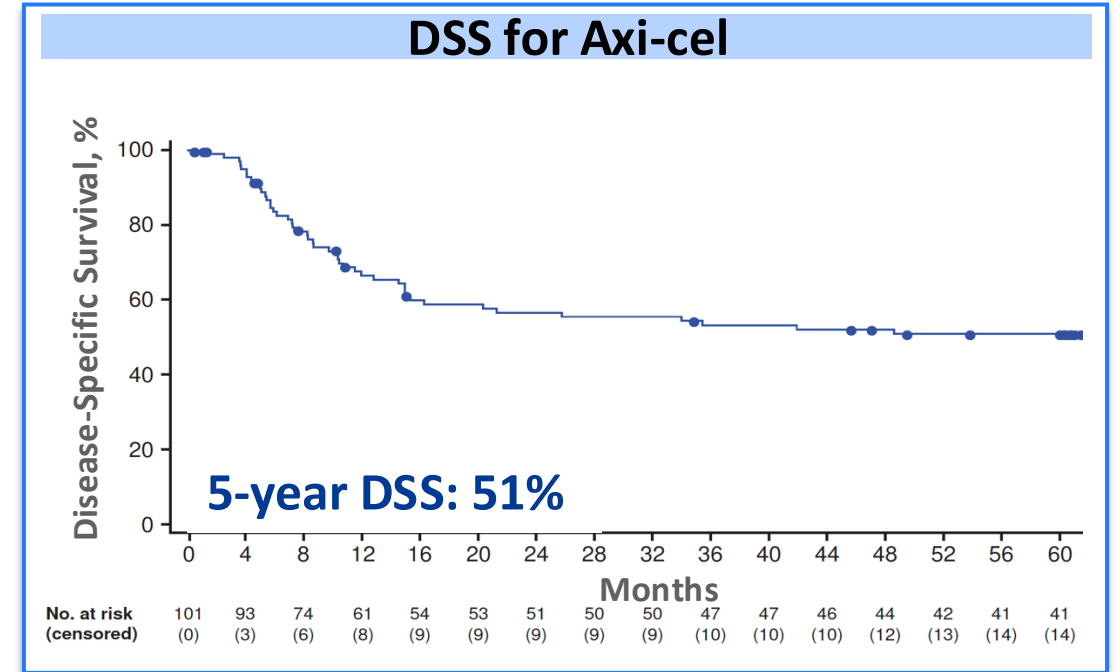
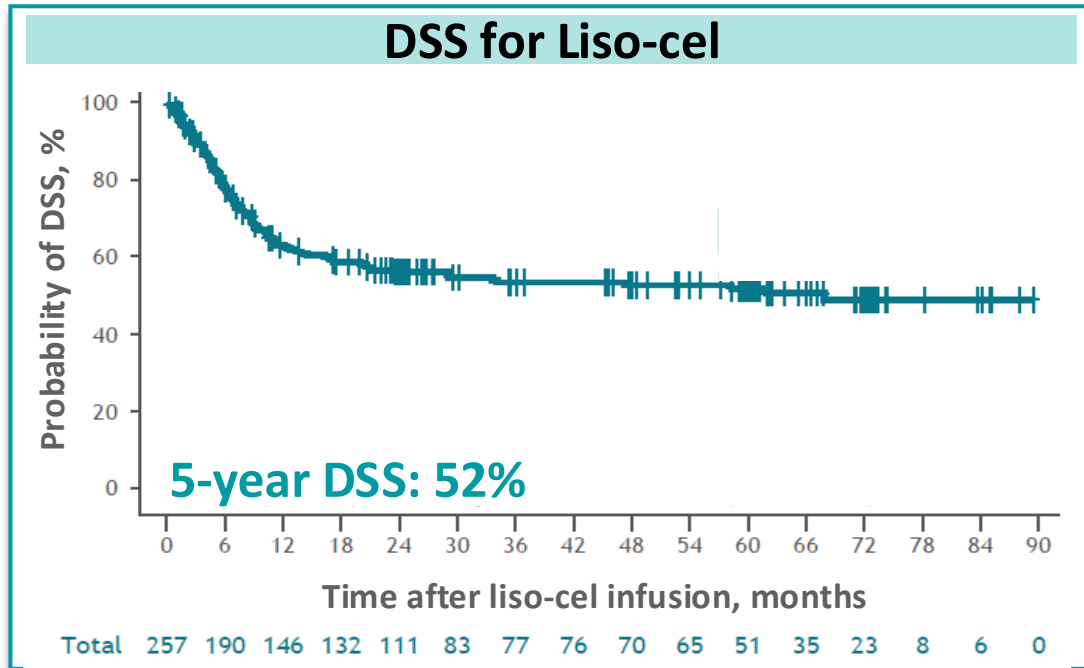
- Many patients were censored for PFS, and analyses were limited by small numbers in the HGBCL and PMBCL subgroups



ZUMA-7 Subset Analysis for EFS



CAR T-cells can CURE Large B-cell Lymphomas as 3rd line or later therapy: 5-year Follow up From ZUMA-1 and TRANSCEND



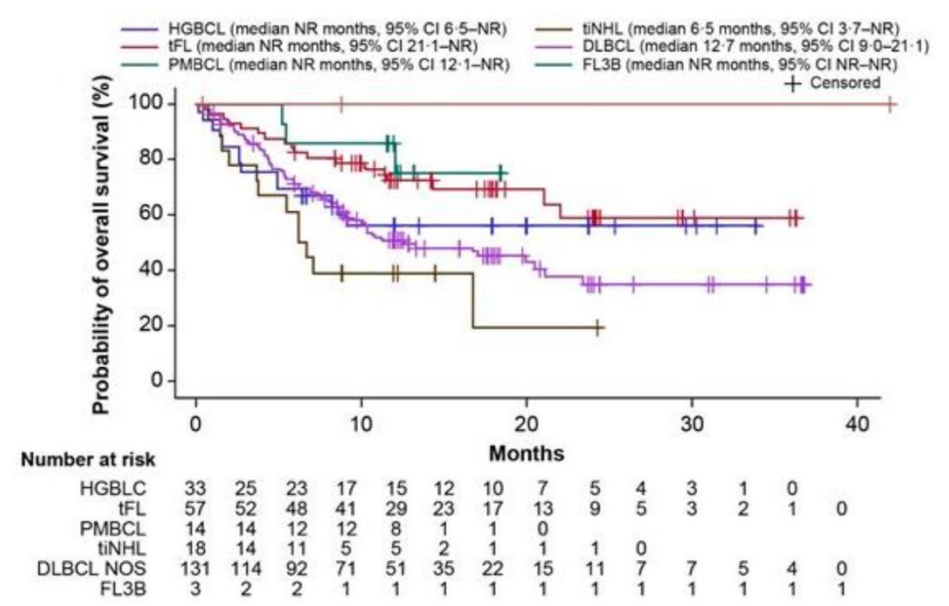
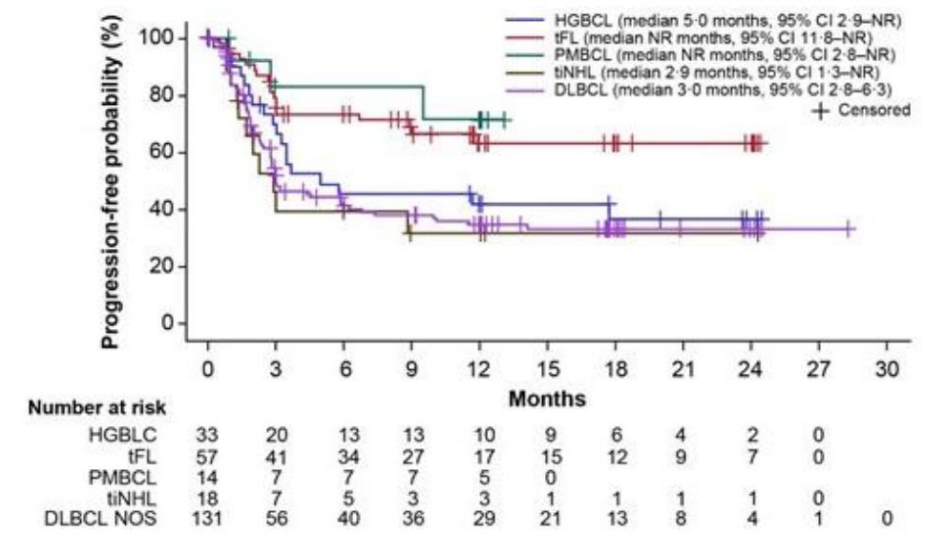
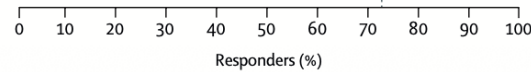
Liso-cel durable efficacy	
Overall response	73%
Complete response	53%
Median DOCR	NR at 5y
Median PFS	7 m
Median OS	28 m

Axi-cel durable efficacy	
Overall response	74%
Complete response	54%
Median DOCR	62 m
Median PFS	6 m
Median OS	26 m



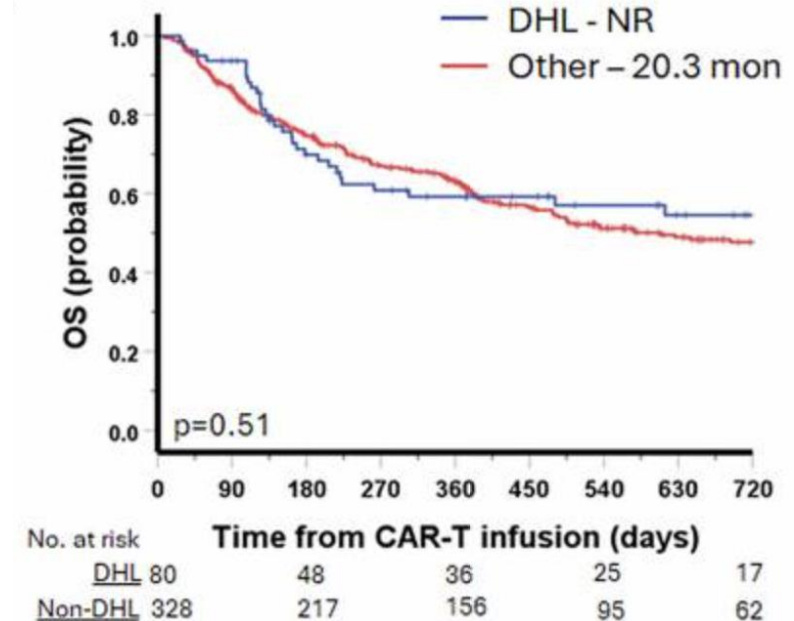
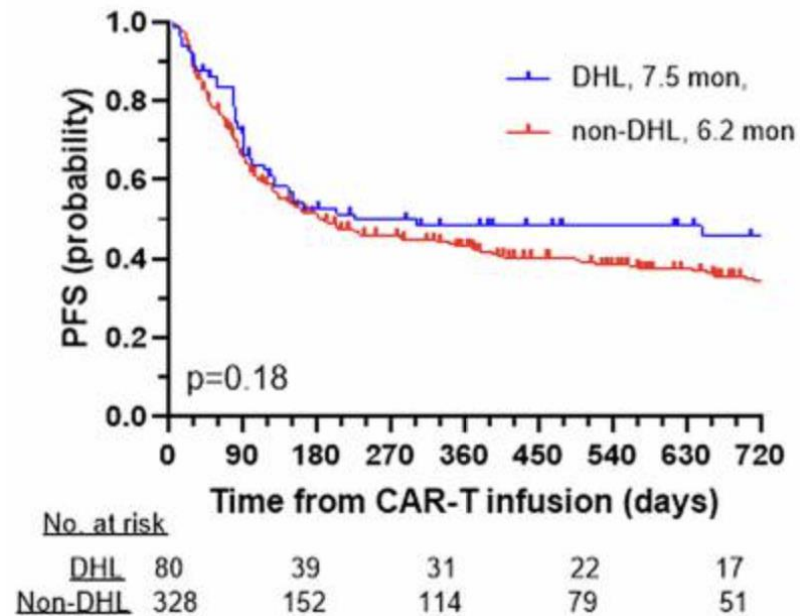
TRANSCEND: No difference between HGBCL and DLBCL

Objective response	Evaluable patients (n)	Patients with objective response (n)	Objective response rate (95% CI)
Dose level			
DL1	40	27	67.5 (50.9-81.4)
DL2	169	125	74.0 (66.7-80.4)
DL3	41	30	73.2 (57.1-85.8)
Age, years			
≥65	108	82	75.9 (66.7-83.6)
<65	148	104	70.3 (62.2-77.5)
Sex			
Male	169	125	74.0 (66.7-80.4)
Female	87	61	70.1 (58.1-78.5)
NHL histology			
DLBCL NOS	131	89	67.9 (59.2-75.8)
HGBCL	33	25	75.8 (57.7-88.9)
Transformed iNHL			
Yes	18	11	61.1 (35.7-82.7)
No	14	11	78.6 (49.2-95.3)
Bridging therapy			
Yes	150	101	67.3 (59.2-74.8)
No	106	85	80.2 (71.3-87.3)
SPD*			
≥50 cm ²	70	43	61.4 (49.0-72.8)
<50 cm ²	177	136	76.8 (69.9-82.8)
C-reactive protein†			
≥20 mg/L	146	101	69.2 (61.0-76.5)
<20 mg/L	109	84	77.1 (68.0-84.6)
Response to last therapy‡			
Refractory	203	141	69.5 (62.6-75.7)
Relapsed	53	45	84.9 (72.4-93.3)
Chemotherapy response			
Refractory	171	120	70.2 (62.7-76.9)
Sensitive	85	66	77.6 (67.3-86.0)
HSCT			
Yes	87	68	78.2 (68.0-86.3)
No	169	118	69.8 (62.3-76.6)
Lactate dehydrogenase			
≥500 U/L	57	36	63.2 (49.3-75.6)
<500 U/L	199	150	75.4 (68.8-81.2)
Secondary CNS lymphoma			
Yes	6	3	50.0 (11.8-88.2)
No	250	183	73.2 (67.3-78.6)
Comorbidities§			
Yes	60	45	75.0 (62.1-85.3)
No	196	141	71.9 (65.1-78.1)
Overall	256	186	72.7 (66.8-78.0)



Real World Data from US Consortium: No impact of DHL

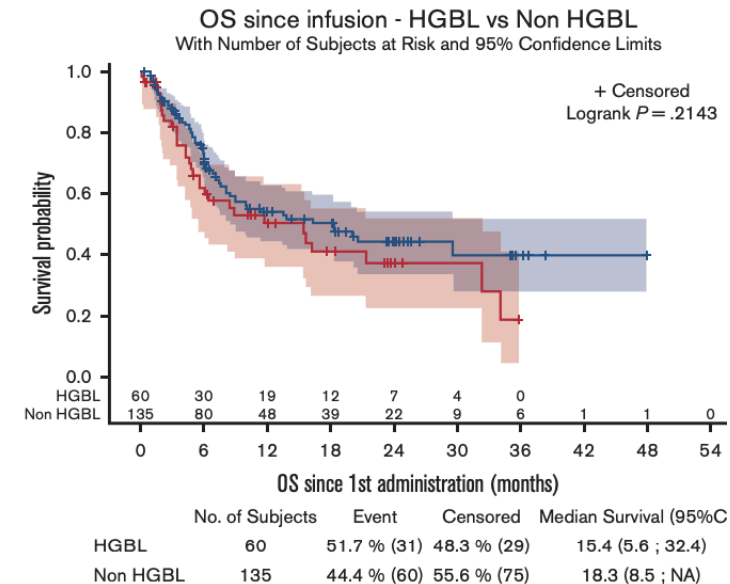
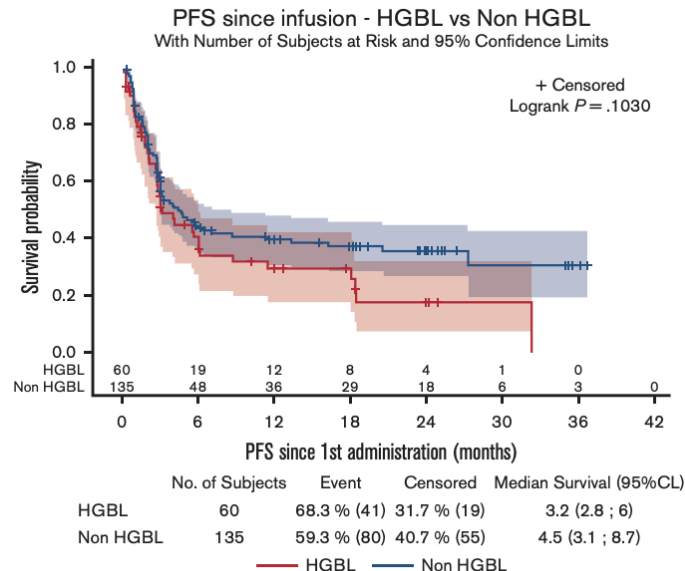
Characteristics	DHL N=80
Age, median	58
Advanced stage, n (%)	68 (90)
IPI 4-5, n (%)	12 (21)
Elevated LDH, n (%)	41 (80)
2 nd line CAR, n (%)	16 (20)
R/R within 12mo, n (%)	59 (75)
Axi-cel, n (%)	55 (68)
Liso-cel, n (%)	5 (6)
Tisa-cel, n (%)	21 (26)



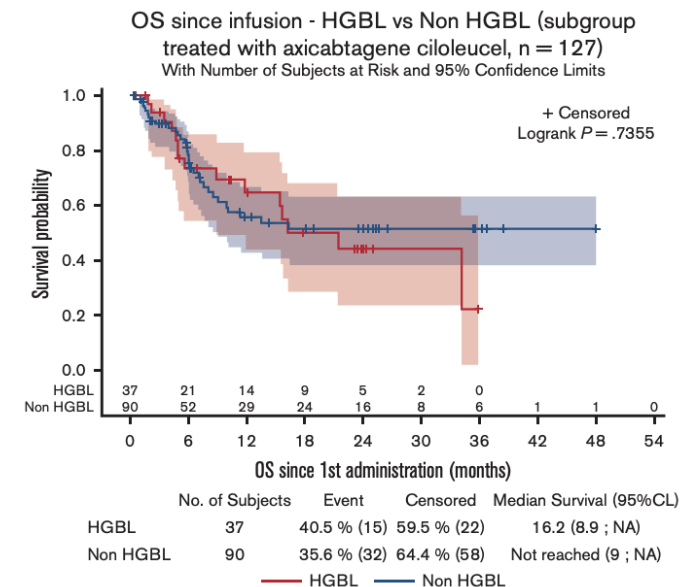
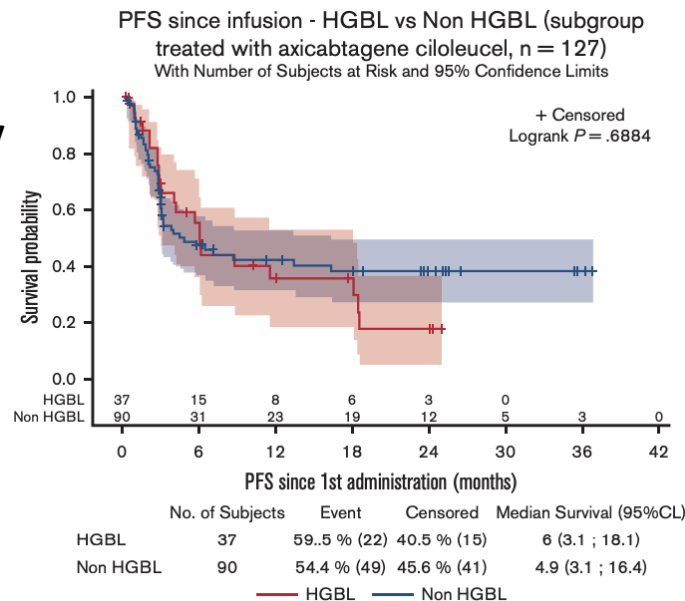
Real World Data from DESCAR-T: No impact of HGBCL

Characteristics	HGBCL N=73
Age, median	62
Advanced stage, n (%)	63 (86)
aalPI >1, n (%)	45 (62)
Elevated LDH, n (%)	52 (71)
DHL/THL, n (%)	42 (58)
Prior lines, median (range)	2 (2-7)
R/R within 12mo, n (%)	59 (75)
Axi-cel, n (%)	37 (62)
Tisa-cel, n (%)	23 (38)

All

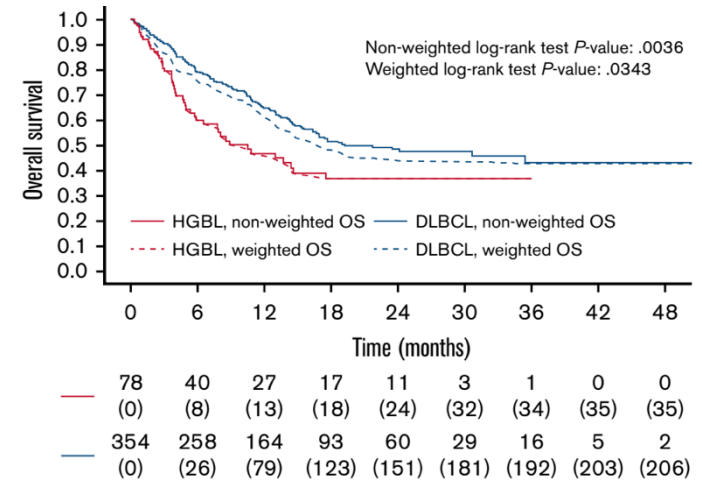
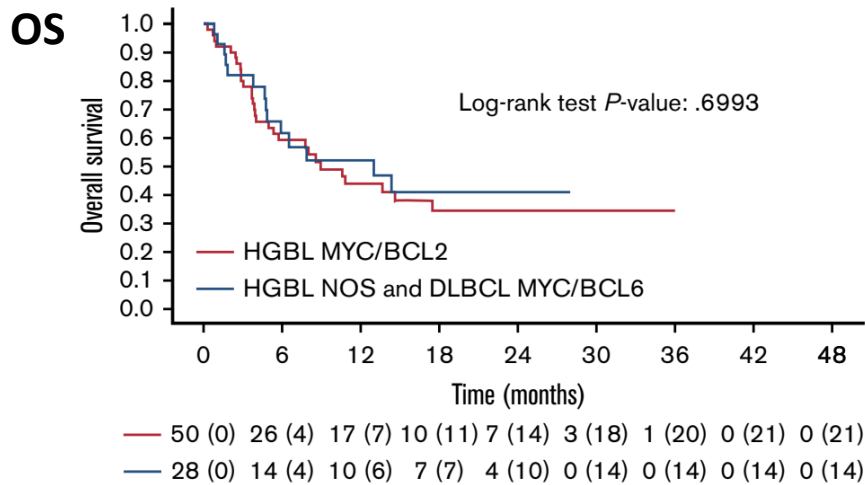
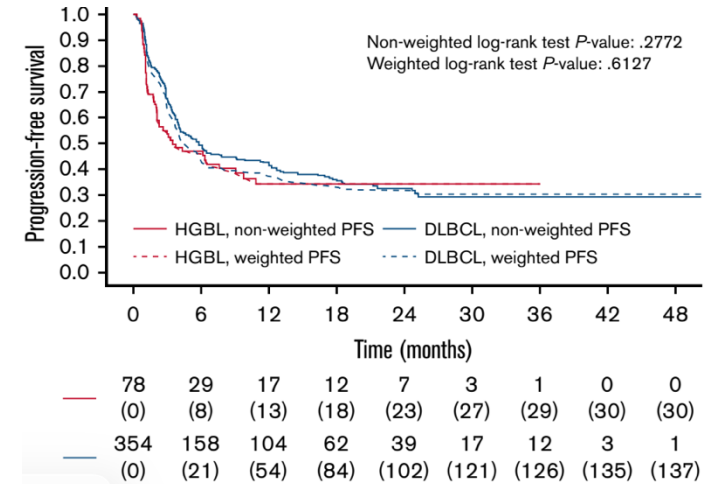
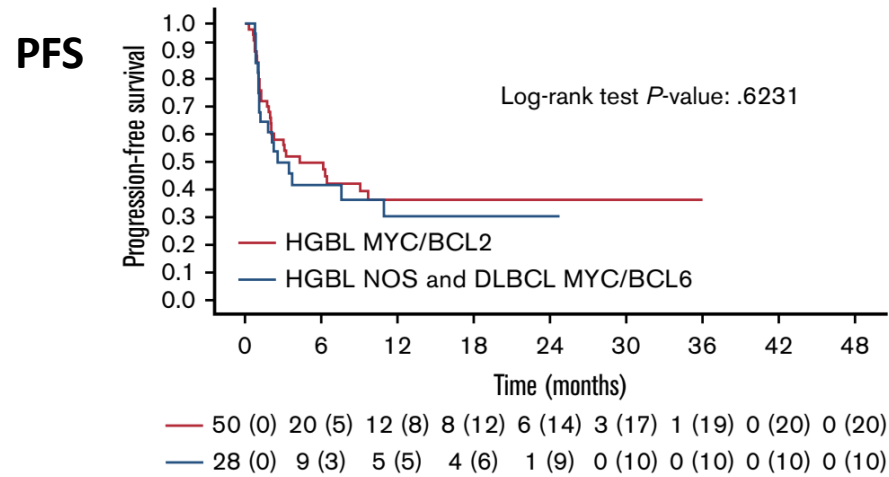


Axi only



Real World Data from the Most Important Analysis (Italia!)

Characteristics	HGBCL N=78	DLBCL N=354
Age, median	63	60
DHL-BCL2, n (%)	50 (64)	
DLBCL-BCL6, n (%)	5 (6)	
HGBCL NOS, n (%)	23 (30)	
Elevated LDH, n (%)	18 (23)	90 (26)
1-2 prior lines, n (%)	56 (72)	232 (66)
Refractory, n (%)	60 (77)	246 (69)
Axi-cel, n (%)	38 (49)	172 (49)
Tisa-cel, n (%)	40 (51)	182 (51)



Relapsed/Refractory: Bispecific antibodies +/- ADCs



Anti-CD20/CD3 Bispecific antibodies for 3rd line+ LBCL

Glofitamab

Fixed duration IV therapy for 12 cycles

Baseline Characteristics	N=154
Median age (range)	66 (21-90)
Median prior tx (range)	3 (2-7)
Prior ASCT	28 (18%)
Prior CAR	51 (33%)
Refractory to last tx	132 (86%)

Epcoritamab

Continuous SC therapy

Baseline Characteristics	N=157
Median age (range)	64 (20-83)
Median prior tx (range)	3 (2-11)
Prior ASCT	31 (20%)
Prior CAR	61 (39%)
Refractory to last tx	130 (83%)

Odronextamab

Continuous IV therapy

Baseline Characteristics	N=127
Median age (range)	67 (24-88)
Median prior tx (range)	2 (2-8)
Prior ASCT	16%
Double/triple hit	20%
Refractory to last tx	86%

Best response

ORR: 52%
CRR: 39%
Median DoR: 18.4 mo
Median PFS: 4.9 mo
CRS 63% (gr≥3, 4%)

11 HGBCL
2 PR, no CR

Best response

ORR: 63%
CRR: 39%
Median DoR: 12.0 mo
Median PFS: 4.4 mo
CRS 50% (gr≥3, 2.5%)

9 HGBCL, 13 DHL
“consistent with DLBCL”

Best response

ORR: 52%
CRR: 32%
Median DoR: 10.0 mo
Median PFS: 4.4 mo
CRS 55% (gr≥3, 4%)

11 DHL
Response NR



Bispecifics in LBCL: Real World Data

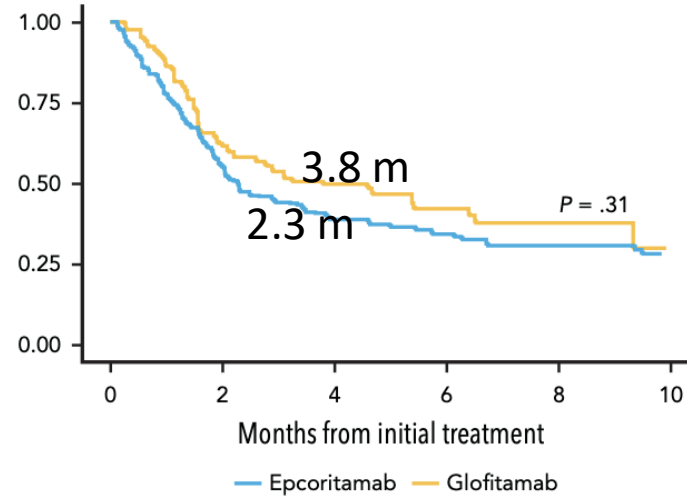
CR rate

Glofit 30%

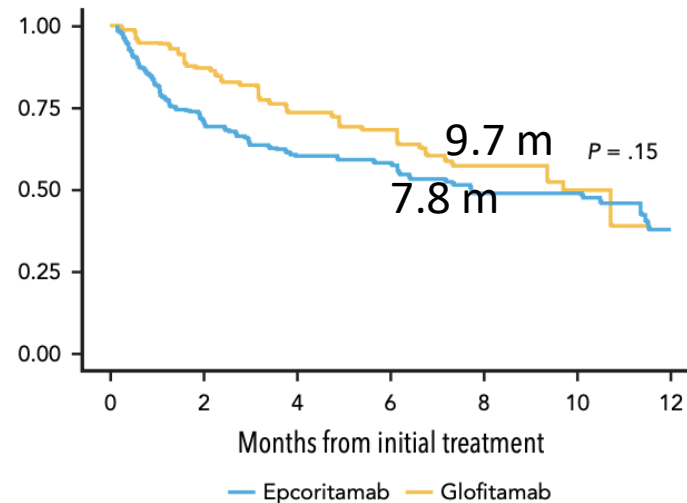
Epc 23%

By Product

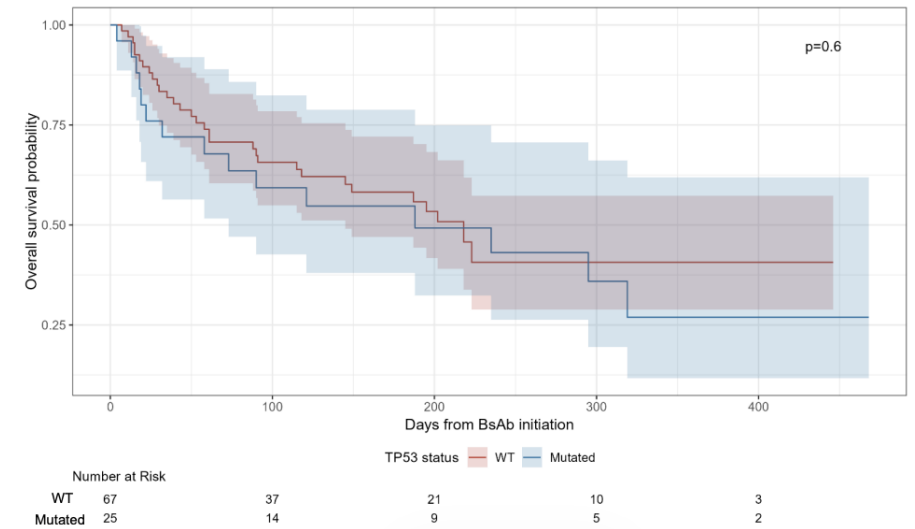
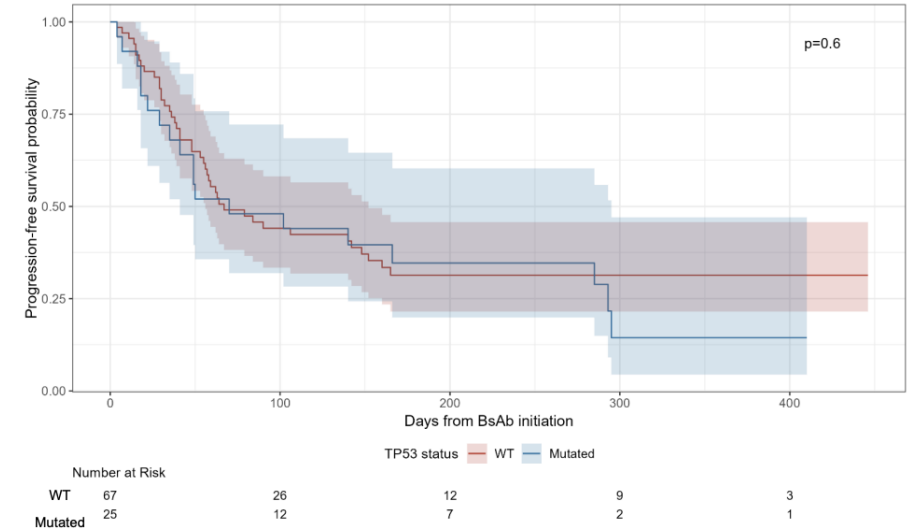
PFS



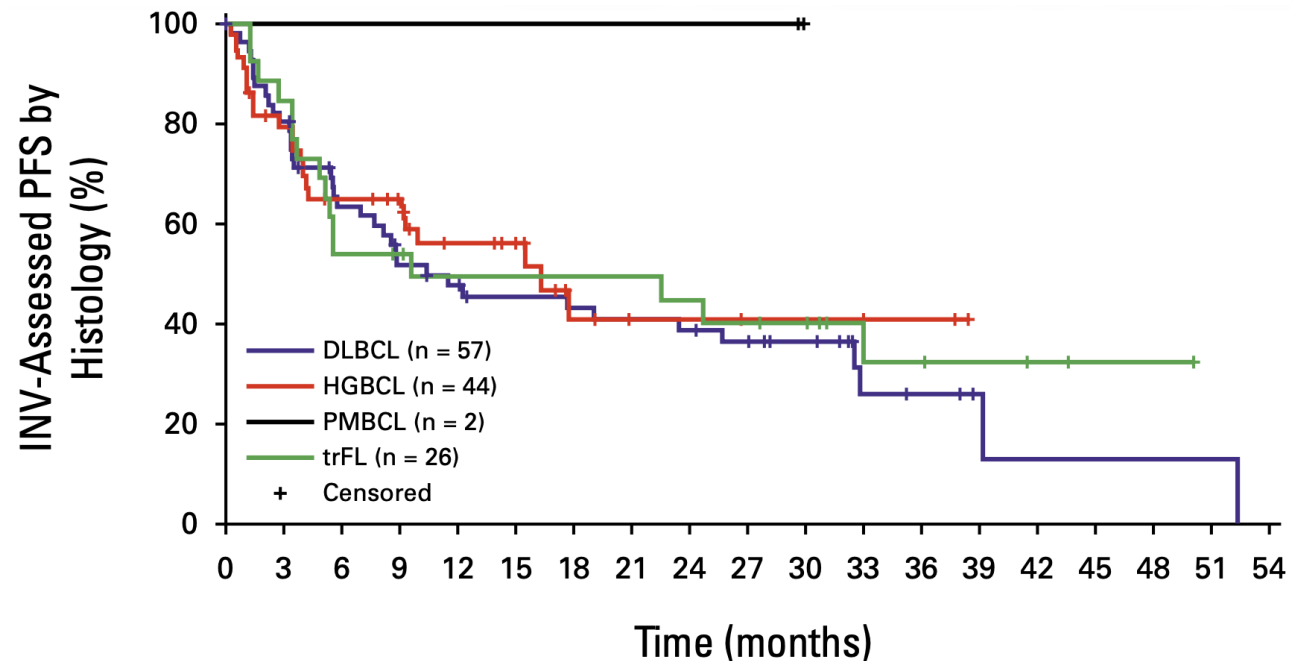
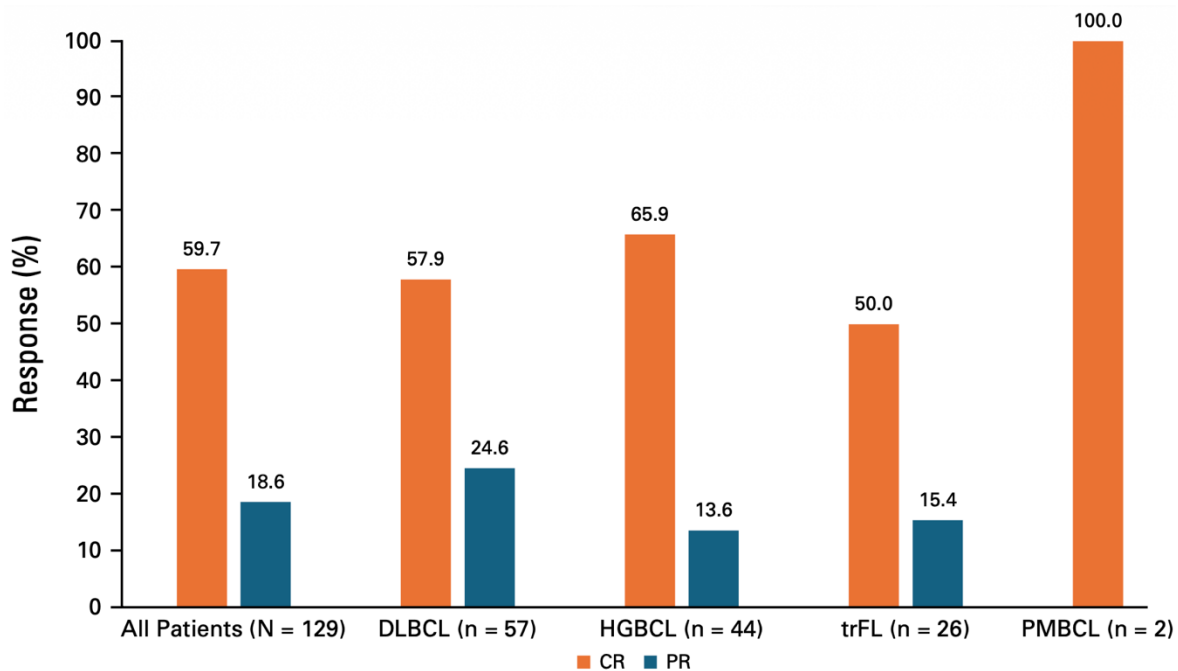
OS



By TP53 mut



Glofitamab-Polatuzumab in Relapsed/Refractory LBCL subsets

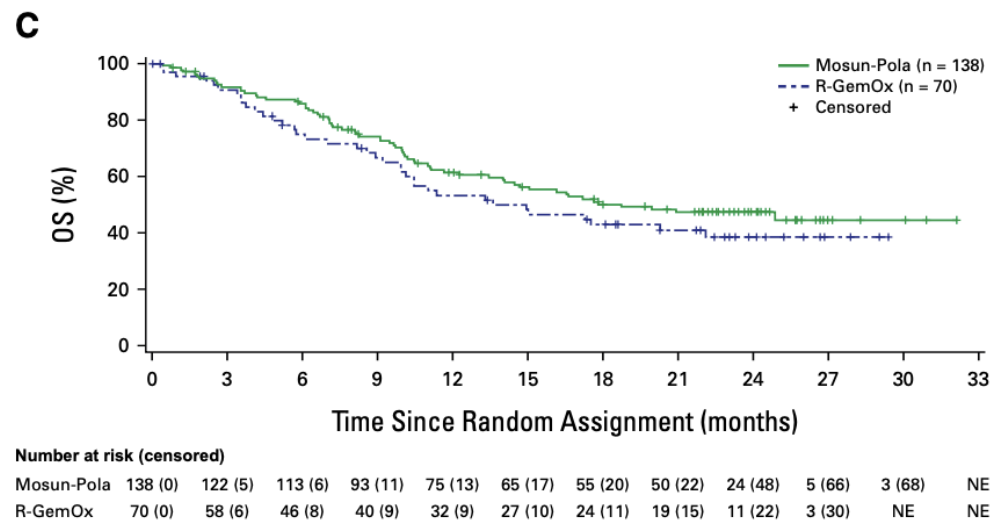
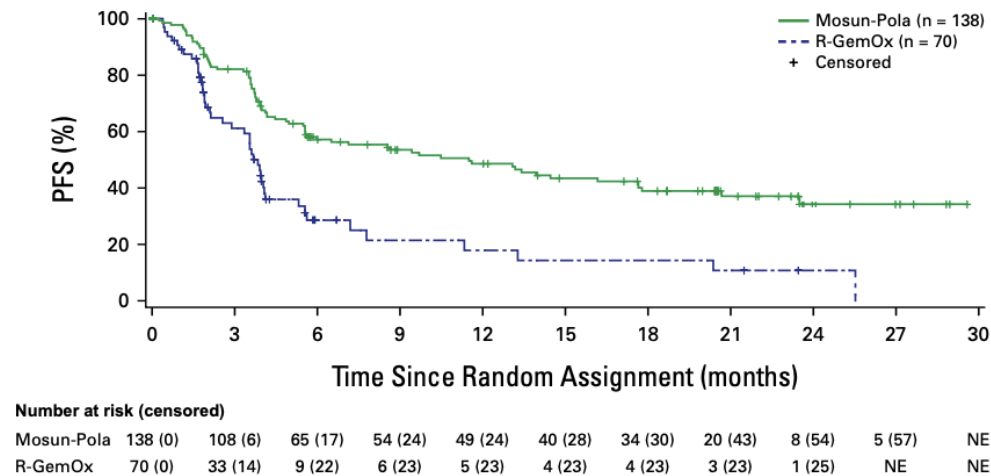


Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
DLBCL	57	45	33	26	23	20	19	18	17	15	12	5	4	2	1	1	1	1	NE
HGBCL	44	33	26	23	17	14	7	4	4	3	3	2	2	NE	NE	NE	NE	NE	NE
PMBCL	2	2	2	2	2	2	2	2	2	2	NE	NE	NE	NE	NE	NE	NE	NE	NE
trFL	26	22	14	13	11	11	11	11	10	9	8	5	4	3	2	1	1	NE	NE



Mosun-Pola in LBCL: SUNMOO trial



		Mosun-Pola (n = 138)			R-GemOx (n = 70)					Mosun-Pola Better	R-GemOx Better
Baseline risk factors	Total No.	No.	Events	Median (months)	No.	Events	Median (months)	HR	95% CI		
All patients	208	138	76	11.5	70	45	3.8	0.41	(0.28 to 0.61) ^a		
Age group (years)											
<65	122	84	46	11.5	38	25	3.5	0.39	(0.23 to 0.64)		
≥65	86	54	30	13.1	32	20	4.0	0.47	(0.27 to 0.84)		
No. of previous lines of therapy											
1	91	61	32	14.5	30	22	3.6	0.38	(0.22 to 0.67)		
≥2	117	77	44	8.6	40	23	3.9	0.49	(0.29 to 0.82)		
Status of last previous therapy											
Refractory	145	97	63	5.5	48	36	2.6	0.39	(0.26 to 0.60)		
Relapse	63	41	13	NE	22	9	11.3	0.37	(0.16 to 0.88)		
Status of first previous therapy											
Refractory	121	79	54	4.2	42	31	2.6	0.46	(0.29 to 0.72)		
Relapse	87	59	22	22.5	28	14	5.6	0.25	(0.18 to 0.70)		
NHL subtype											
DLBCL	163	109	58	11.5	54	34	3.5	0.38	(0.24 to 0.59)		
HGBCL	40	26	18	9.7	14	9	4.0	0.78	(0.35 to 1.77)		
FL3b	5	3	0	NE	2	2	12.0	<0.01	(0.00 to NE)		



Conclusions

- New therapeutic approaches are making an impact for patients with HGBCL/DHL
- DHL patients still in need of improved outcomes. Combination strategies warrant ongoing evaluation.
- HGBCL NOS likely no different from DLBCL NOS
- We still need more data for bispecific monotherapy in HGBCL/DHL
- CAR, bispecifics and ADCs should be offered at standard therapy to patients with HGBCL and DHL



Thank you for your attention!



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