New data in upfront and relapsed aggressive B-cell lymphoma

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Disclosures

Consulting advice:

Sutro, Epizyme, BMS/Celgene, Bayer, Gilead/Kite, GenMab, Genentech/Roche, Abbvie, Incyte, Janssen, Eisai, Mustang Bio, Second Genome

Diffuse large B-cell lymphoma

- Most common lymphoma
- Median age 60, usually with advanced stage disease
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
  - IPI (Age, PS, LDH, Extranodal, Stage = IPI 0-5)
- Most patients treated same (R-CHOP x 6 cycles)
- AutoSCT standard for chemosensitive relapsed disease
- CAR-T, novel agents/combinations in rel/ref setting

When have we frequently treated patients with DLBCL with something other than R-CHOP x 6?

Double hit subtype (MYC, BCL2, BCL6 translocations)

Primary mediastinal

HIV associated

Testicular

Limited stage (? 4 cycles)

CNS

Elderly (mini-R-CHOP)

What's new in DLBCL from ASH 2021?

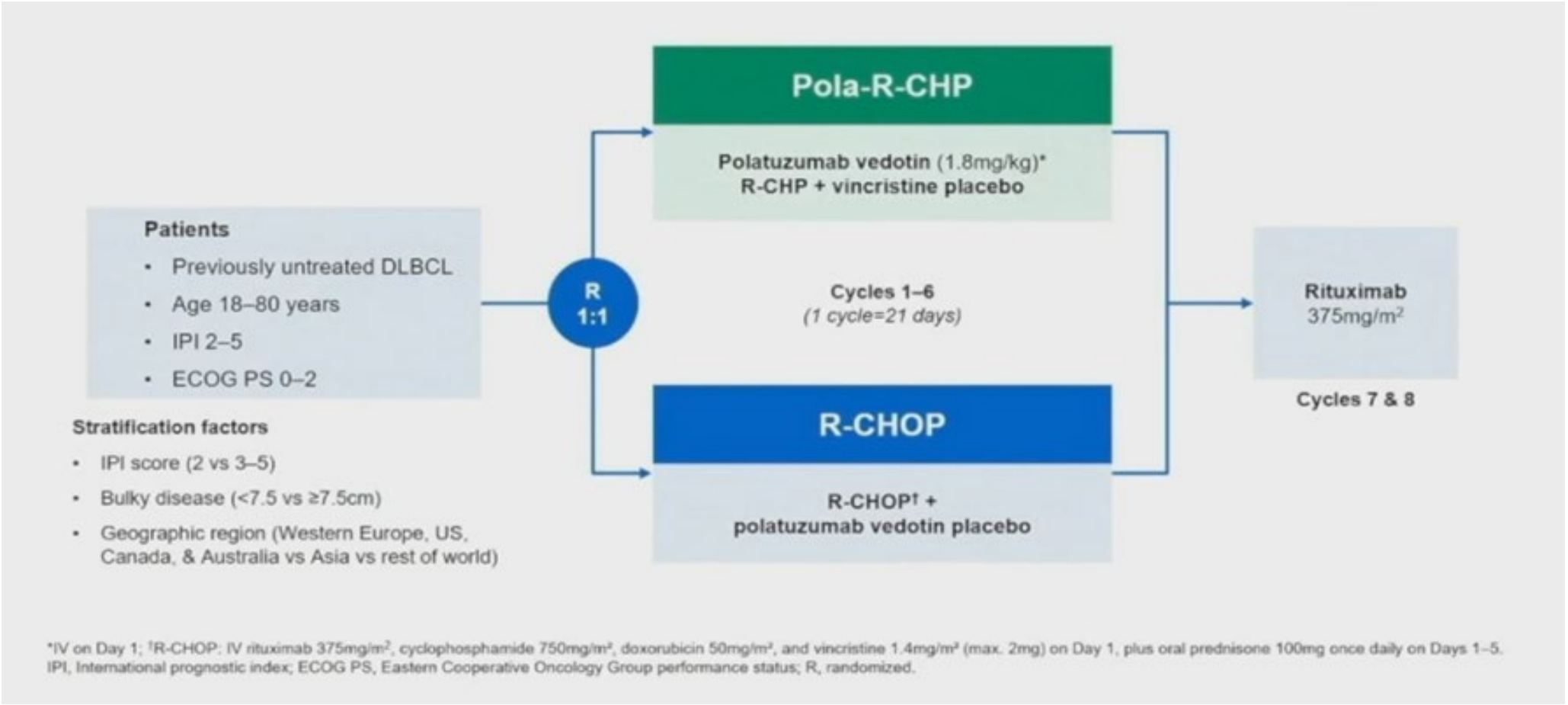
New upfront therapy for subset of patients

CAR-T as second-line therapy

Bispecific antibodies

R-CHOP vs Polatuzumab-R-CHP in DLBCL (IPI 2-5)

Tilly et al, NEJM 2021



R-CHOP vs Polatuzumab-R-CHP in DLBCL

Tilly et al, NEJM 2021

Characteristic	Pola-R-CHP (N=440)	R-CHOP (N=439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)

R-CHOP vs Polatuzumab-R-CHP in DLBCL

Tilly et al, NEJM 2021

ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

R-CHOP vs Polatuzumab-R-CHP in DLBCL - Toxicity

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Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

R-CHOP vs Polatuzumab-R-CHP in DLBCL - PFS

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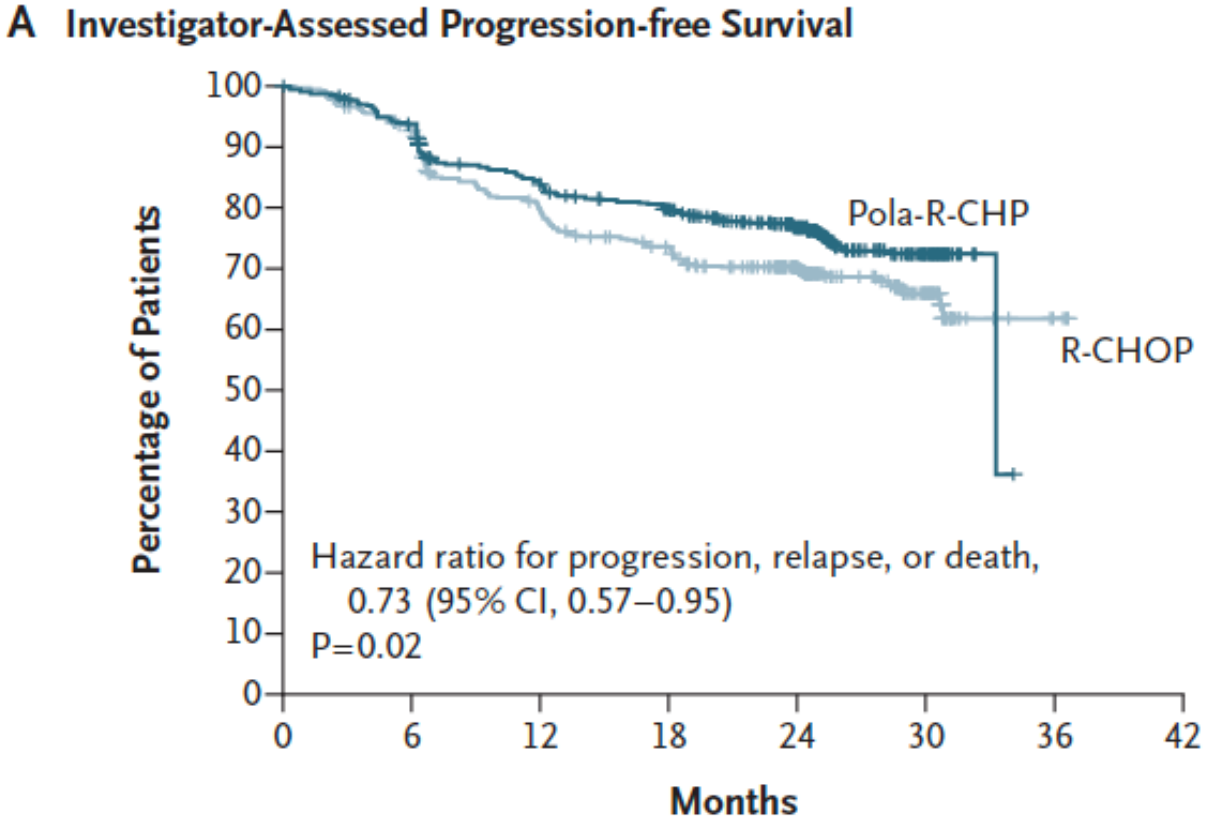

No. at Risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

24 mo PFS:
76.7% Pola-R-CHP
70.2% R-CHOP

R-CHOP vs Polatuzumab-R-CHP in DLBCL - OS

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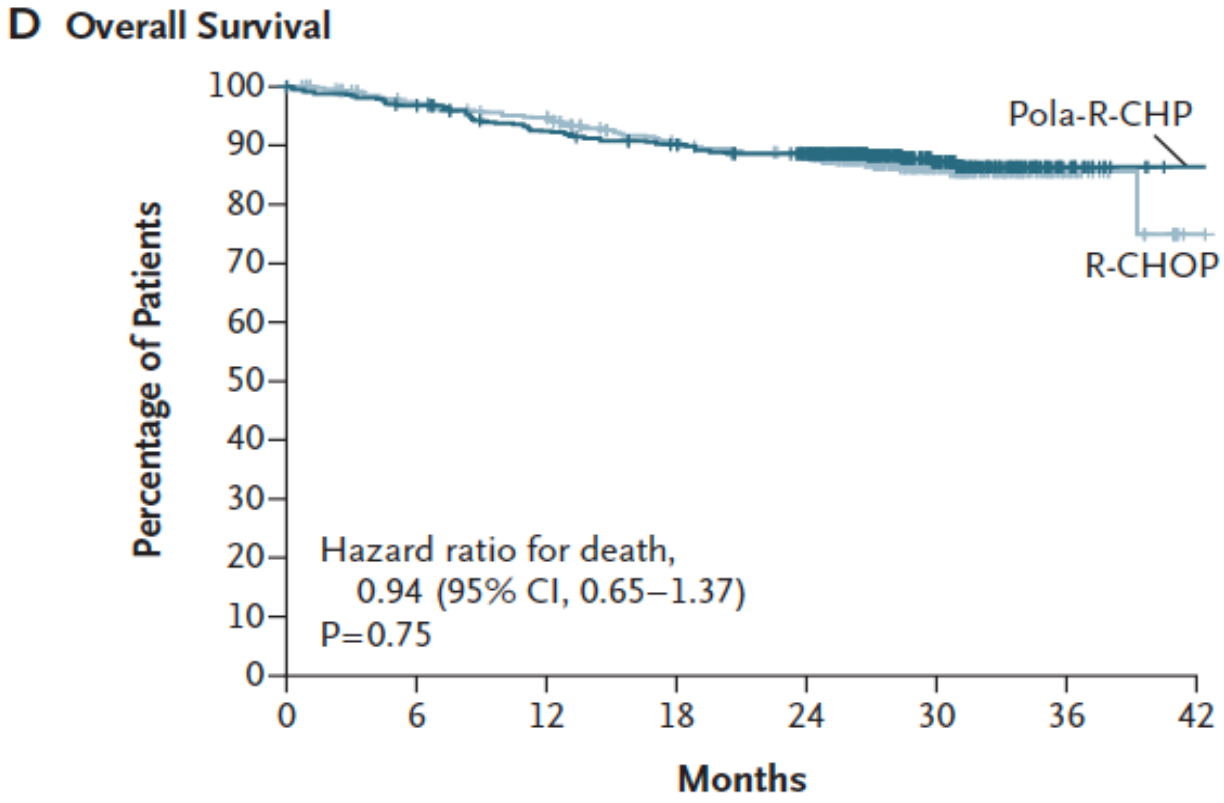

No. at Risk

Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

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R-CHOP vs Polatuzumab-R-CHP in DLBCL - Subgroups

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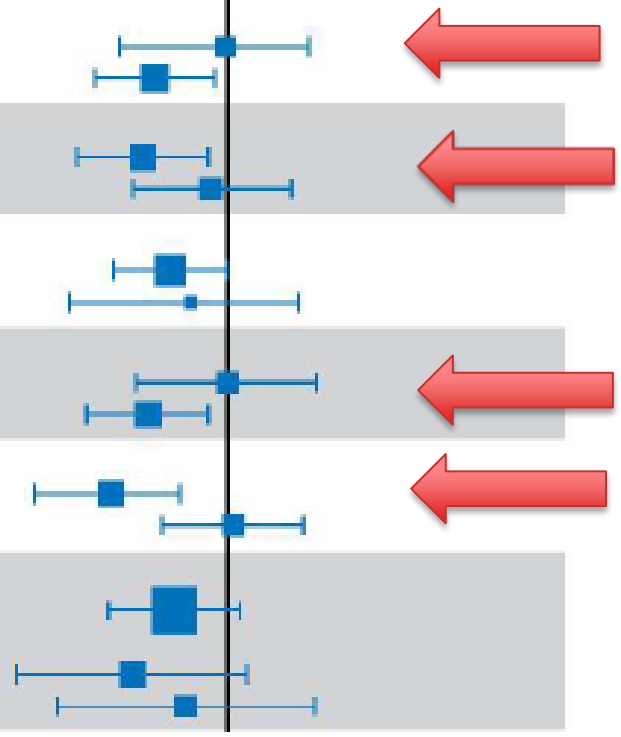
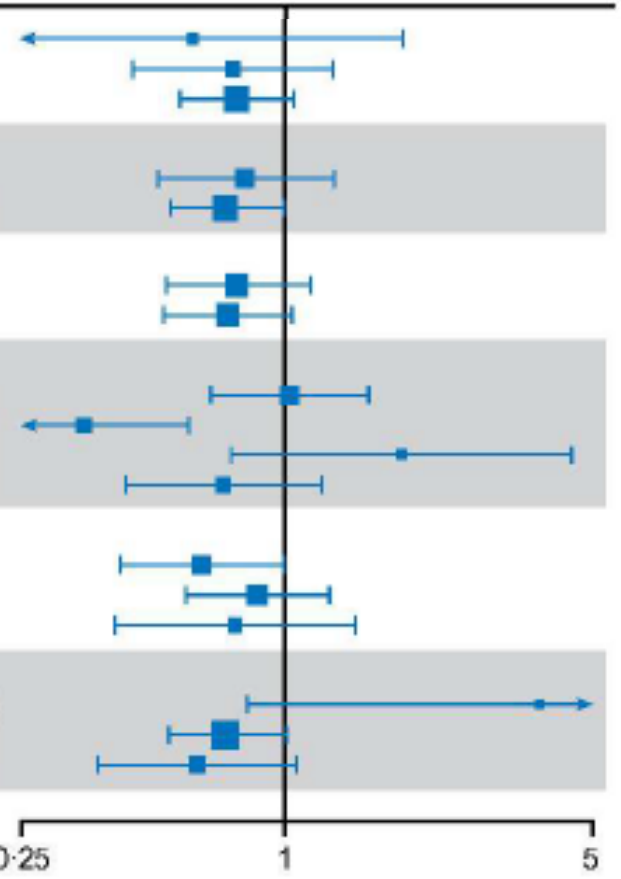
Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 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							
Western Europe, United States, Canada, and 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)



R-CHOP vs Polatuzumab-R-CHP in DLBCL – Subgroups

Tilly et all, NEJM 2021

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	Hazard Ratio	95% Wald CI
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)



Implications of POLARIX study

Positive trial (6.5% benefit in PFS), no OS benefit in IPI 2-5 DLBCL patients

Generally comparable toxicity

Older, male patients, higher risk, and ABC subtype benefitted most

Saves 6.5% (1 of 15 patients) from relapse and more therapy

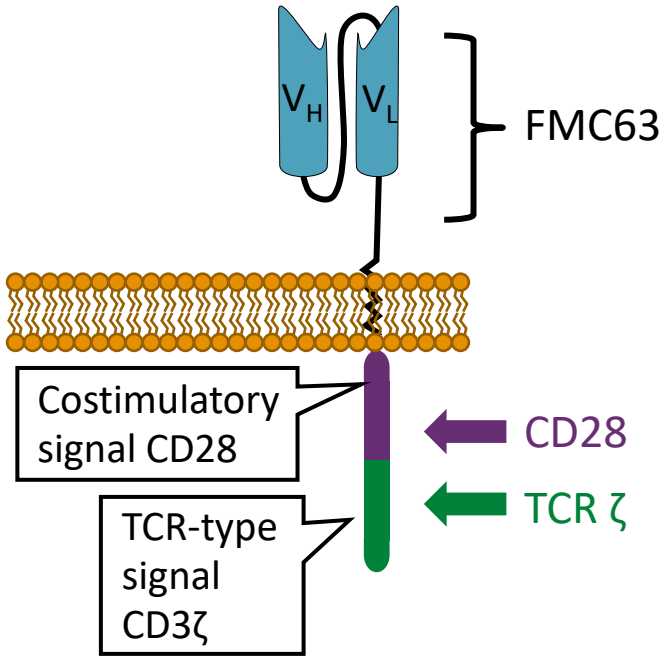
6 doses x $15,669/dose/80kg pt x 15 patients

= $1.4 million/relapse saved

CD19-directed CAR T-cell products

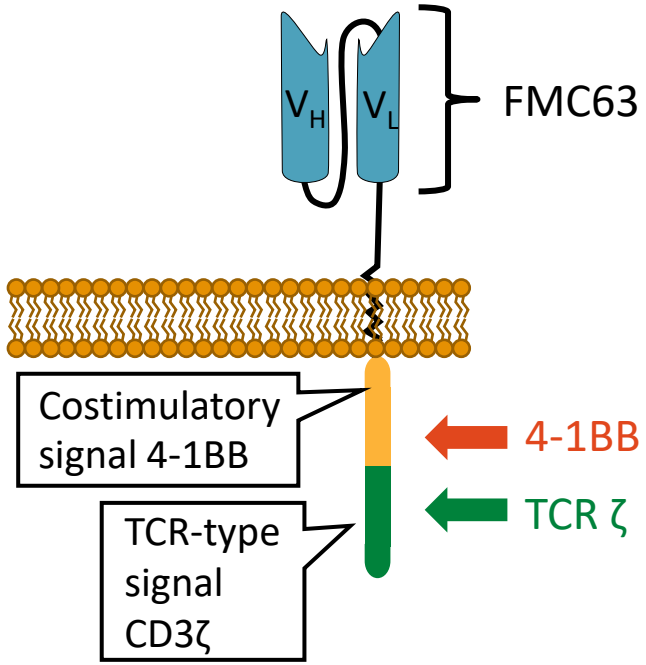
Axicabtagene ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



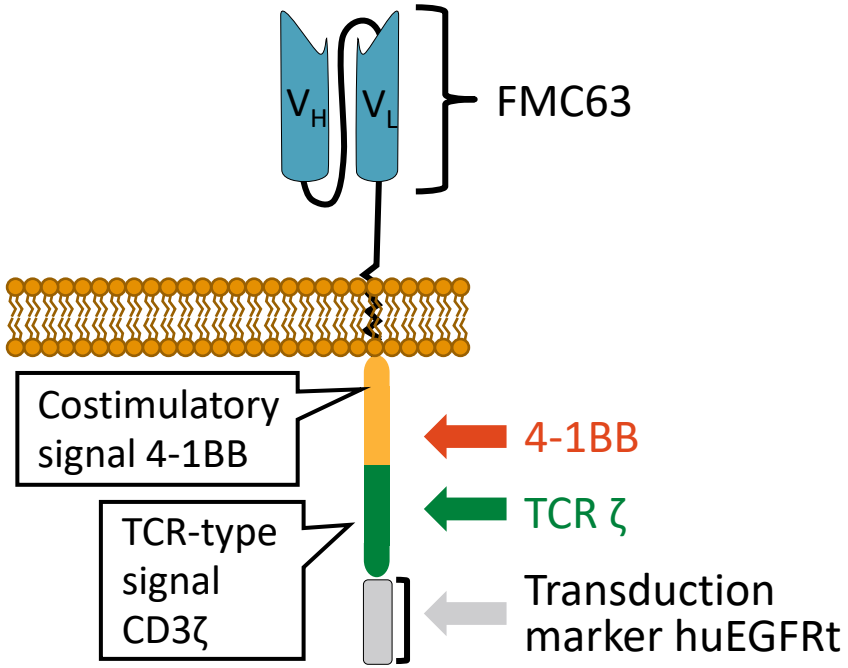
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



van der Stegen. Nat Rev Drug Discov. 2015;14:499.

CD19-directed CAR T-cell products: Indications

Axicabtagene ciloleucel (Axi-cel)

- **R/R large B-cell lymphoma after ≥2 lines of therapy**
  - DLBCL, FL3B, Transformed; after induction chemo, salvage chemo ± auto PSCT, or not a candidate
- **R/R FL after ≥2 lines of systemic therapy** (accelerated approval)

Tisagenlecleucel (Tisa-cel)

- **R/R large B-cell lymphoma after ≥2 lines of therapy**
  - DLBCL, FL3B, Transformed FL/DLBCL; after induction chemo, salvage chemo ± auto PSCT, or not a candidate
- Patients aged 25 years or younger with **B-cell precursor ALL that is refractory or at least second relapse**

Lisocabtagene maraleucel (Liso-cel)

- **R/R large B-cell lymphoma after ≥2 lines of therapy,**
  - DLBCL, FL3B, Transformed FL/DLBCL; after induction chemo, salvage chemo ± auto PSCT, or not a candidate

Brexucabtagene autoleucel: CAR T-cell therapy approved for mantle cell lymphoma (after chemoimmunotherapy and a BTK inhibitor, ± auto PSCT failure)

Others in clinical trials or many combinations with other agents or in earlier high-risk DLBCL

Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI.

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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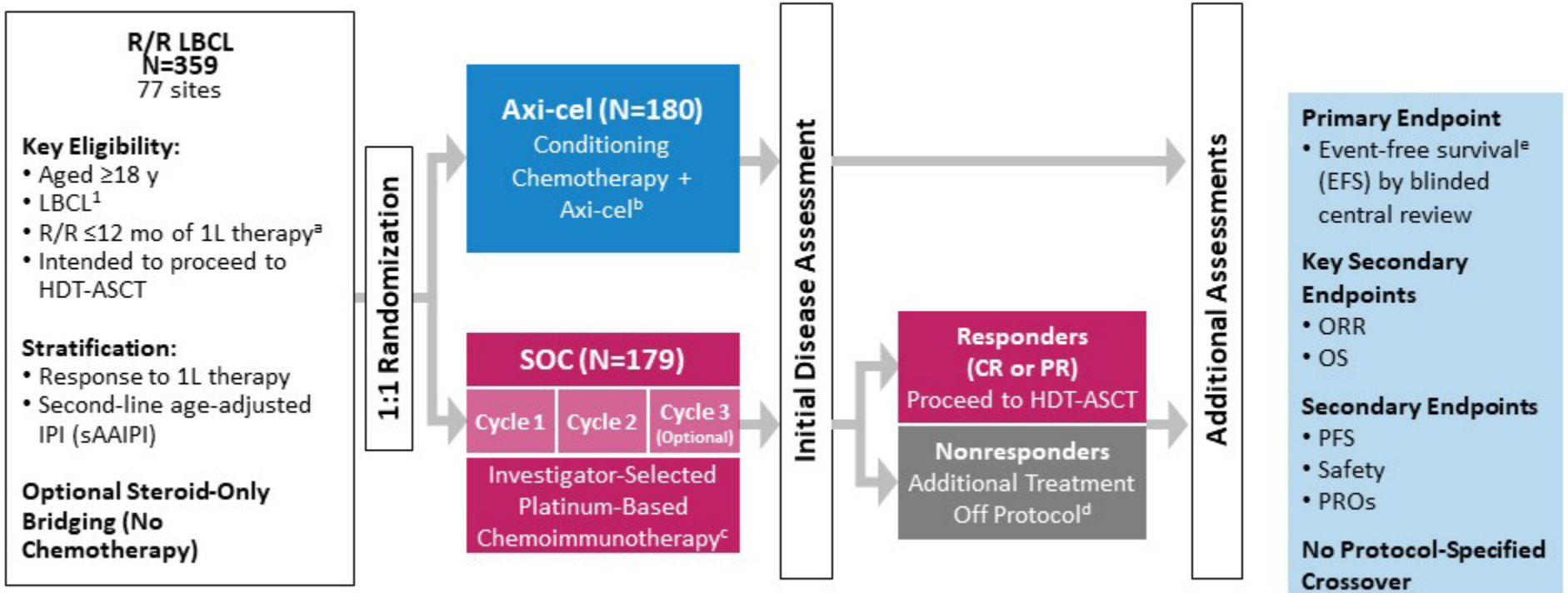
ZUMA-7 Study Schema and Endpoints: Axi-cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m^2/day) and fludarabine (30 mg/m^2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Axi-cel (N=180)	Standard Care (N=179)	Total (N=359)
Age			
Median (range) — yr	58 (21–80)	60 (26–81)	59 (21–81)
≥65 yr — no. (%)	51 (28)	58 (32)	109 (30)
Male sex — no. (%)	110 (61)	127 (71)	237 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance-status score of 1 — no. (%)‡	85 (47)	79 (44)	164 (46)
Disease stage — no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
Second-line age-adjusted IPI of 2 or 3 — no. (%)§	82 (46)	79 (44)	161 (45)

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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Molecular subgroup according to central laboratory — no. (%)¶			
Germinal center B-cell–like	109 (61)	99 (55)	208 (58)
Activated B-cell–like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to first-line therapy at randomization — no. (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse at ≤12 mo after the initiation or completion of first-line therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory — no. (%)			
Diffuse large B-cell lymphoma‖	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0	1(1)	1 (<1)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator — no. (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell– or histiocyte–rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein–Barr virus–positive diffuse large B-cell lymphoma	2 (1)	0	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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Table 2. Most Common Adverse Events, Cytokine Release Syndrome, and Neurologic Events.*

Event	Axi-cel (N=170)		Standard Care (N=168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cytokine release syndrome — no. (%)	157 (92)	11 (6)	—	—
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—
Chills — no./total no. (%)	38/157 (24)	0/157	—	—
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—
Neurologic event — no. (%)	102 (60)	36 (21)	33 (20)¶	1 (1)
Tremor	44 (26)	2 (1)	1(1)	0
Confusional state	40 (24)	9 (5)	4 (2)	0
Aphasia	36 (21)	12 (7)	0	0
Encephalopathy	29 (17)	20 (12)	2 (1)	0
Paresthesia	8 (5)	1 (1)	14 (8)	0
Delirium	3 (2)	3 (2)	5 (3)	1 (1)

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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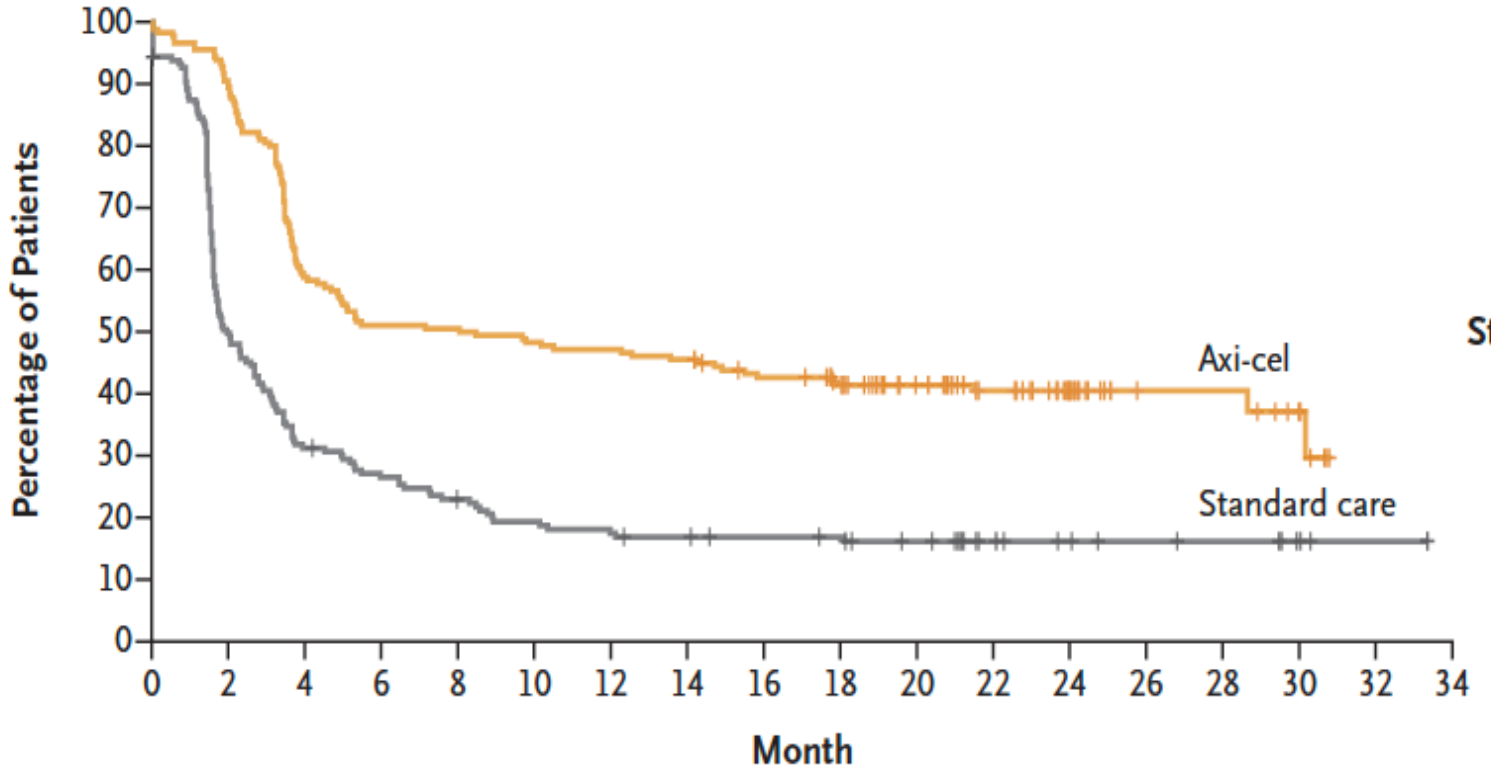
A Event-free Survival



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

No. at Risk

Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

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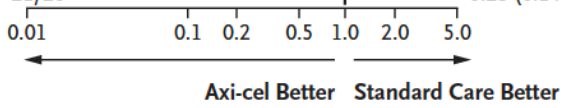
B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



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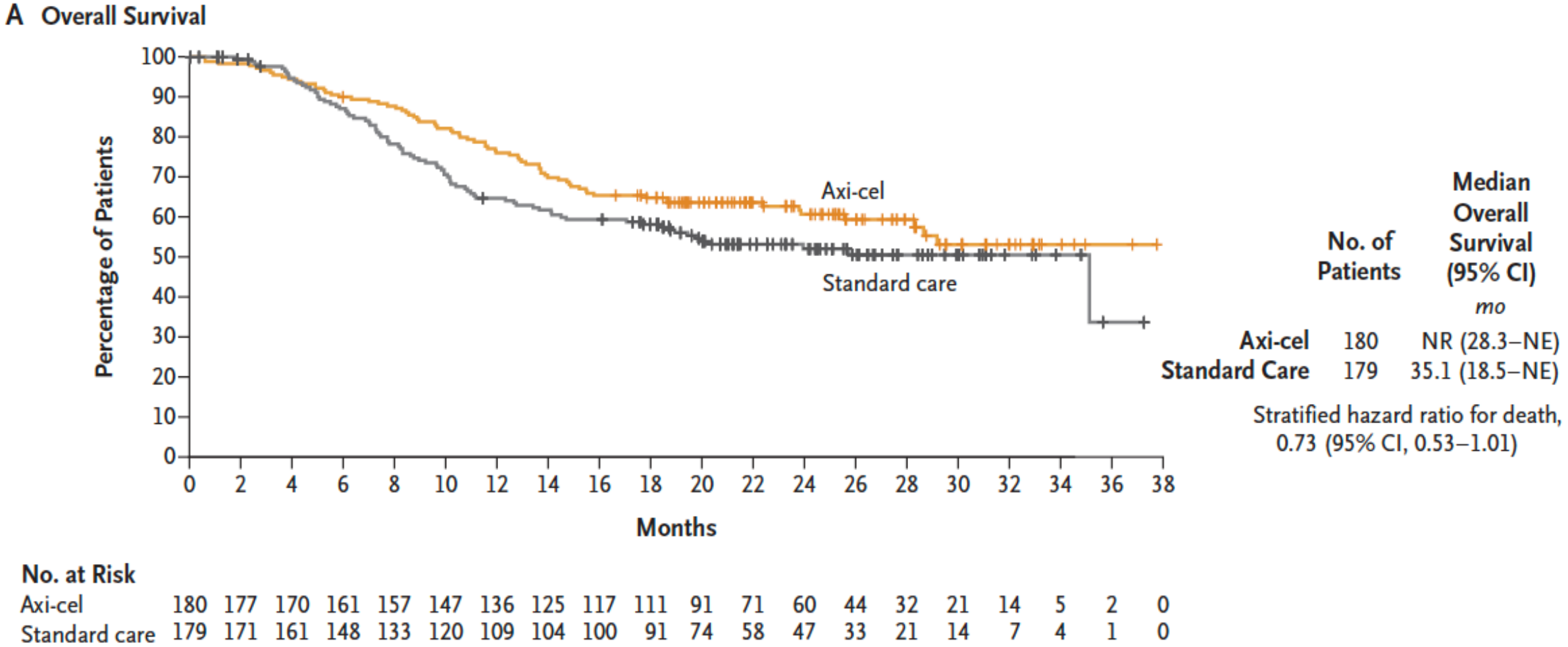
Axicabtagene ciloleucel for 2nd line (<12m) relapsed DLBCL

Locke et al, NEJM 2021



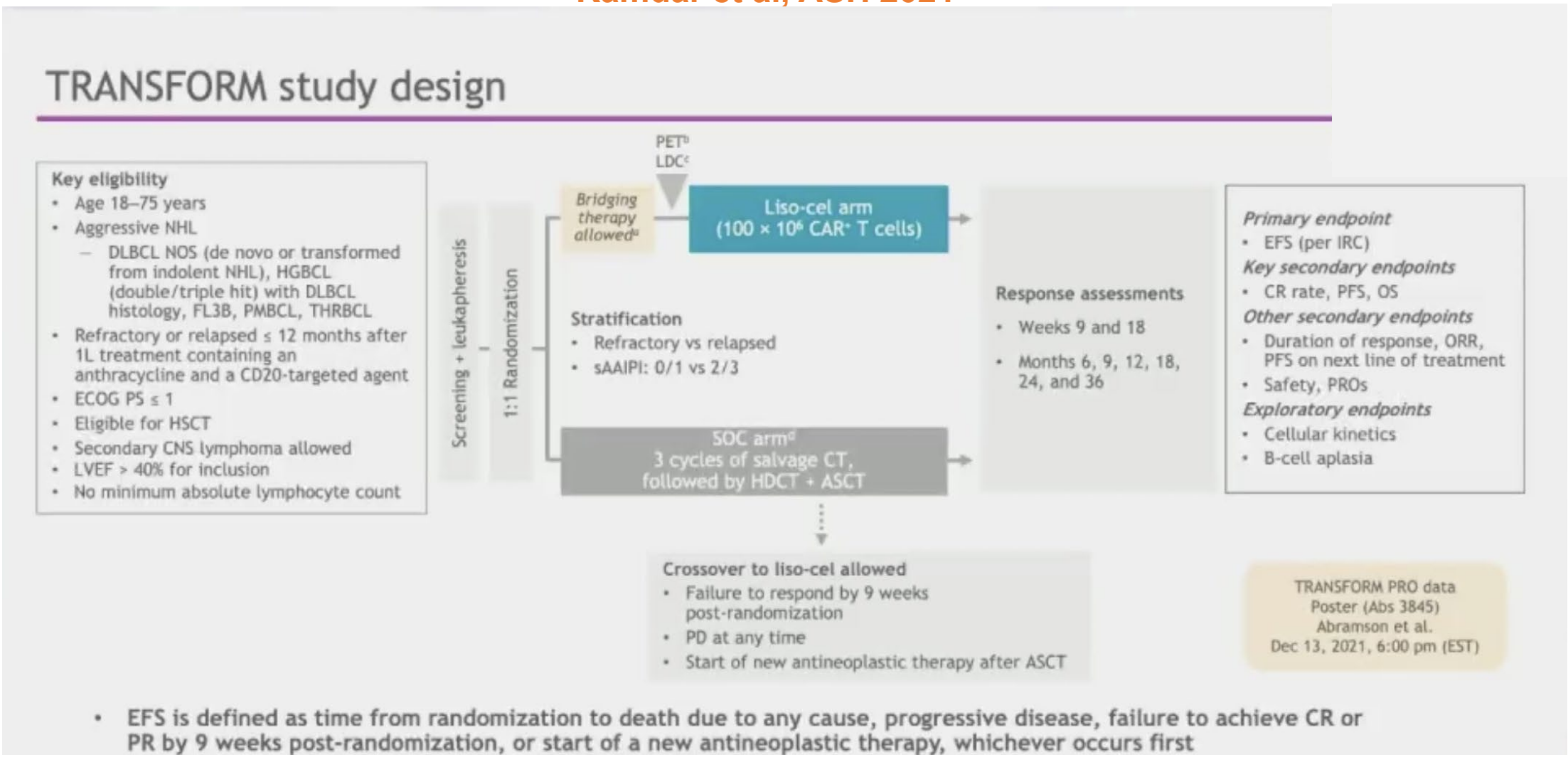
	No. of Patients	Median Overall Survival (95% CI)
		mo
Axi-cel	180	NR (28.3–NE)
Standard Care	179	35.1 (18.5–NE)

Stratified hazard ratio for death, 0.73 (95% CI, 0.53–1.01)

Weill Cornell Medicine NewYork-Presbyterian

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021



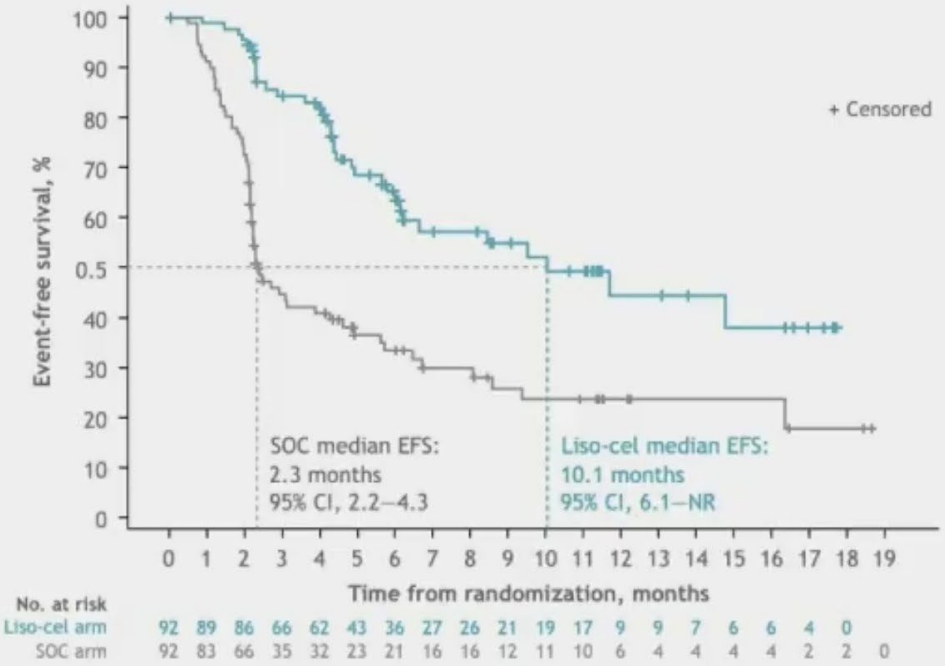
- EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021

TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)

Median follow-up in both arms: 6.2 months



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

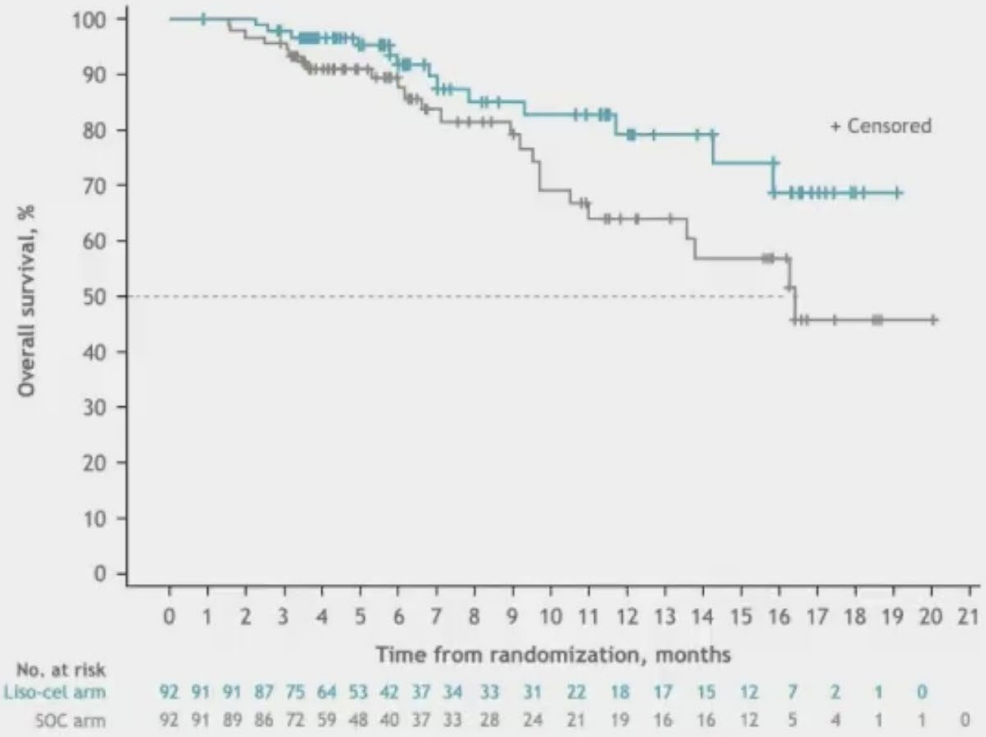
EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021

TRANSFORM: Overall survival (ITT set)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004) *P* = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

OS is defined as the time from randomization to death from any cause.

Kamdar M, et al. ASH 2021 [Abstract #91]

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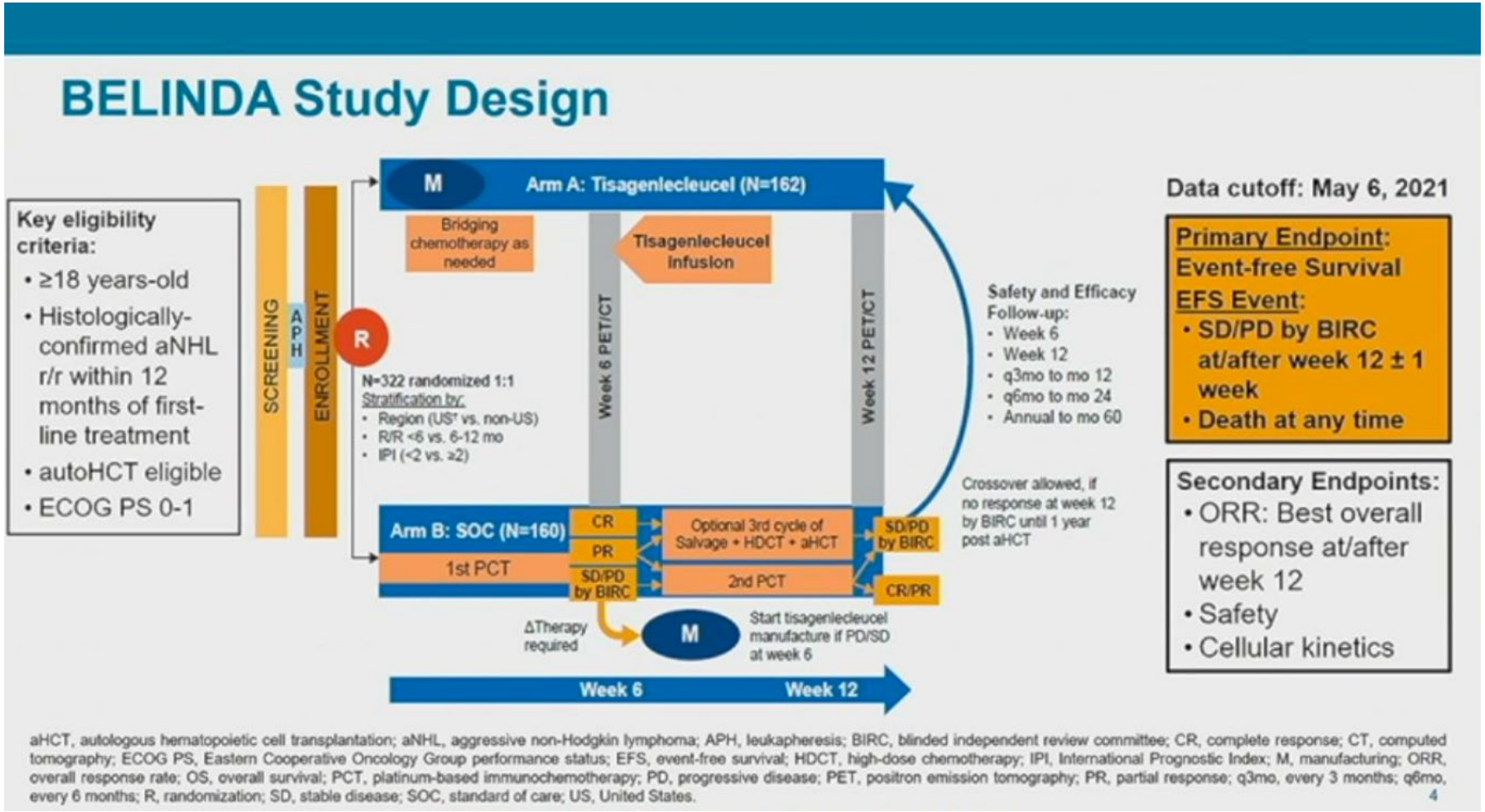
Weill Cornell Medicine NewYork-Presbyterian

Tisagenlecleucel for 2nd line (<12m) relapsed DLBCL

Bishop et al, NEJM 2021



aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

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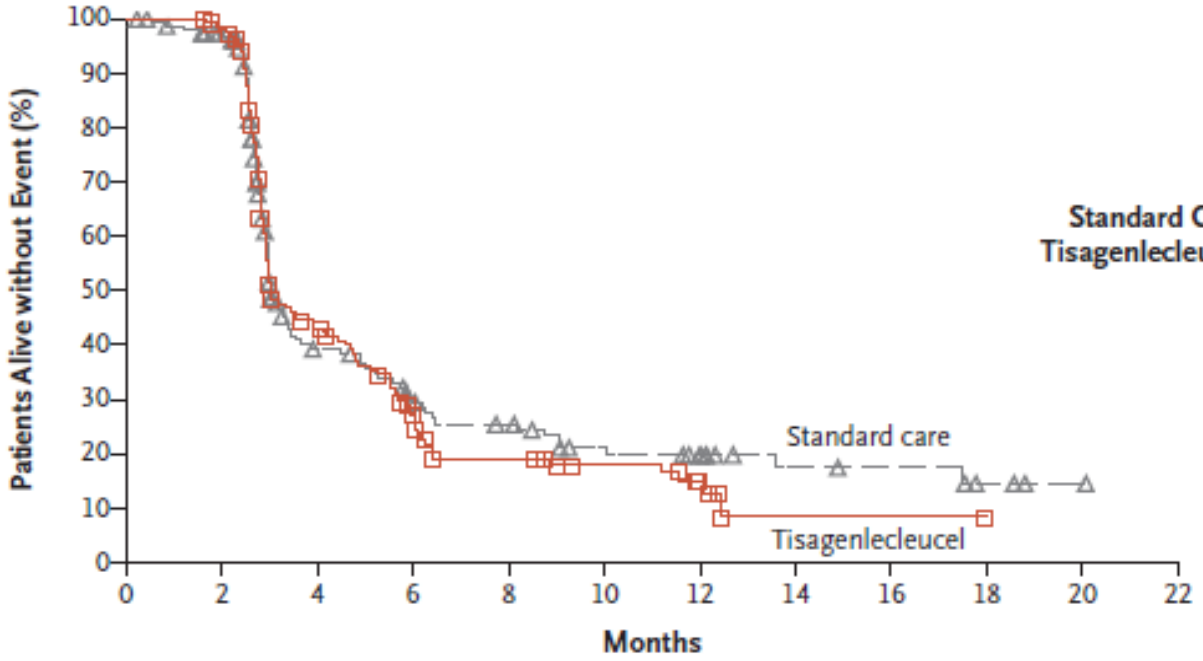
Tisagenlecleucel for 2nd line (<12m) relapsed DLBCL

Bishop et al, NEJM 2021



	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

No. at Risk

Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

Figure 2. Kaplan–Meier Plot of Event-free Survival.

An event was defined as progressive disease or stable disease on or after day 71 or death at any time (i.e., event-free survival at a given time point represents the estimated percentage of patients who had a complete or partial response at this time point among all ran-

Differences of EFS definitions in second line CAR-T studies

EFS definitions in Phase-3 trials of CAR-T vs SOC in transplant eligible patients with aggressive B-cell lymphoma

	ZUMA-7	TRANSFORM	BELINDA
EFS	**1)** Disease progression **2)** Death from any cause **3)** New therapy started **4)** SD as best response within 150 days from randomization	**1)** Disease progression **2)** Death from any cause **3)** New therapy started **4)** Not achieving CR/PR by 9-weeks.	**1)** SD or PD at or after week 12 **2)** Death (any time)
EFS TIME	From randomization	From randomization	From randomization

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Locke, F. ASH21 (#2) *Kamdar, M. ASH21 (#91)* *Bishop, M. ASH21 (#LBA-6)*

Pere Barba

Summary of second line CAR-T studies

Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P*<*0*.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

Toby Eyre

Implications of second line CAR-T studies

In patients with chemoresistant disease (short first remission), more chemo (and AutoSCT) is not effective

Why different outcome in BELINDA study with tisagenlecleucel?

- chemotherapy bridging (sicker patients), additional chemo cycles for standard group, longer time (52d) to get CAR-T (and 25.9% pre-infusion PD), different agent, less lymphodepletion, event definitions

CAR-T will be SOC for those with PD < 1 year

- for practical reasons seems likely there will still be 2nd line chemo for many patients

AutoSCT remains SOC for those with later relapses

Conclusions

Polatuzumab + R-CHP a new option for patients with newly diagnosed DLBCL (IPI 2-5)

CAR-T option for second line DLBCL therapy in patients with relatively chemo-refractory disease (response < 12 mo)

Bispecifics of interest in recurrent DLBCL (and other subtypes)