



SINTOMA'25

8 A 10 DE MAIO

HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA



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Educação
e Pesquisa



Is there a golden moment to indicate CAR-T cell therapy? Holding and bridging strategies

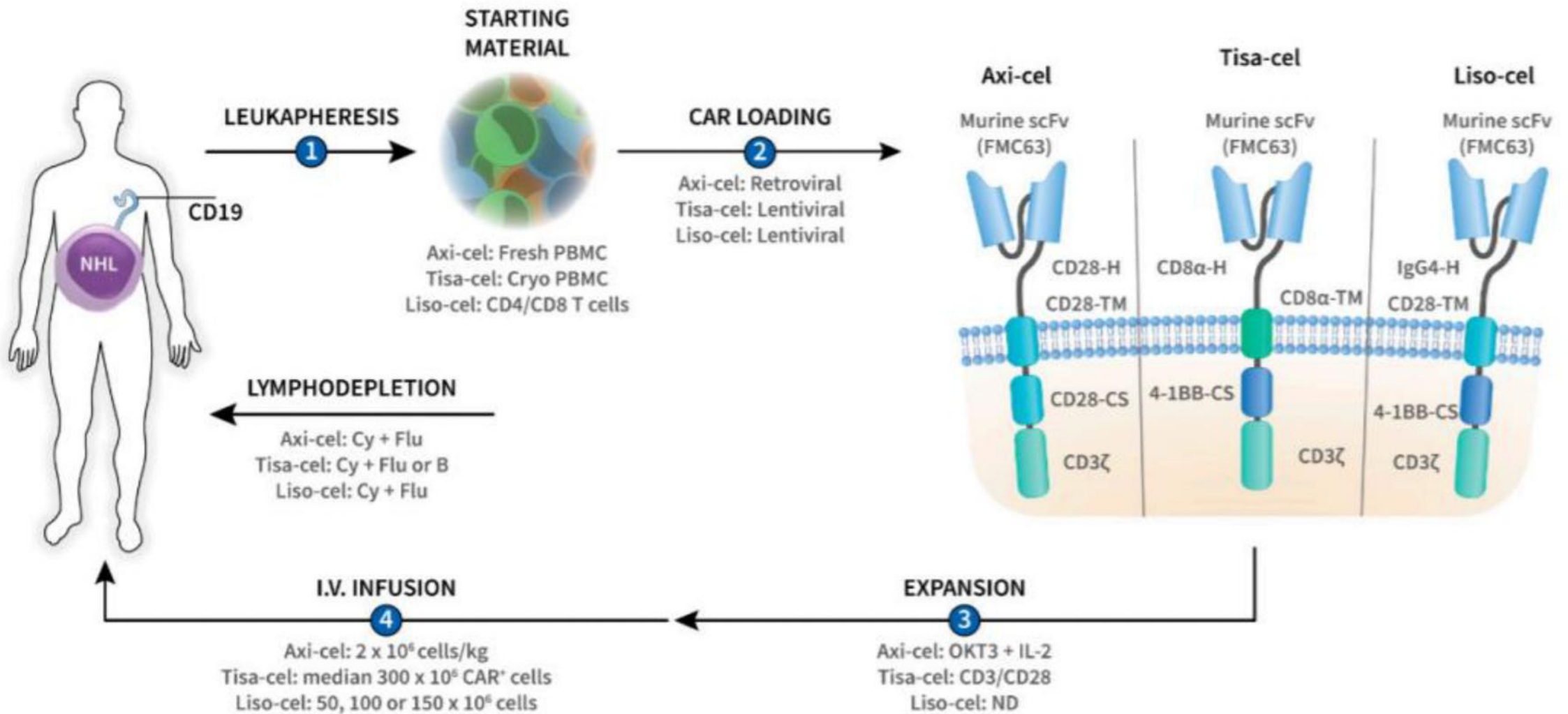
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MD Anderson Cancer Center

Research funding and/or consulting fees:

AbbVie Inc, Allogene Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, a member of the Roche Group, Genmab US Inc, Incyte Corporation, Janssen Biotech Inc, Kite, A Gilead Company, MorphoSys, Novartis, Nurix Therapeutics Inc, Pfizer Inc

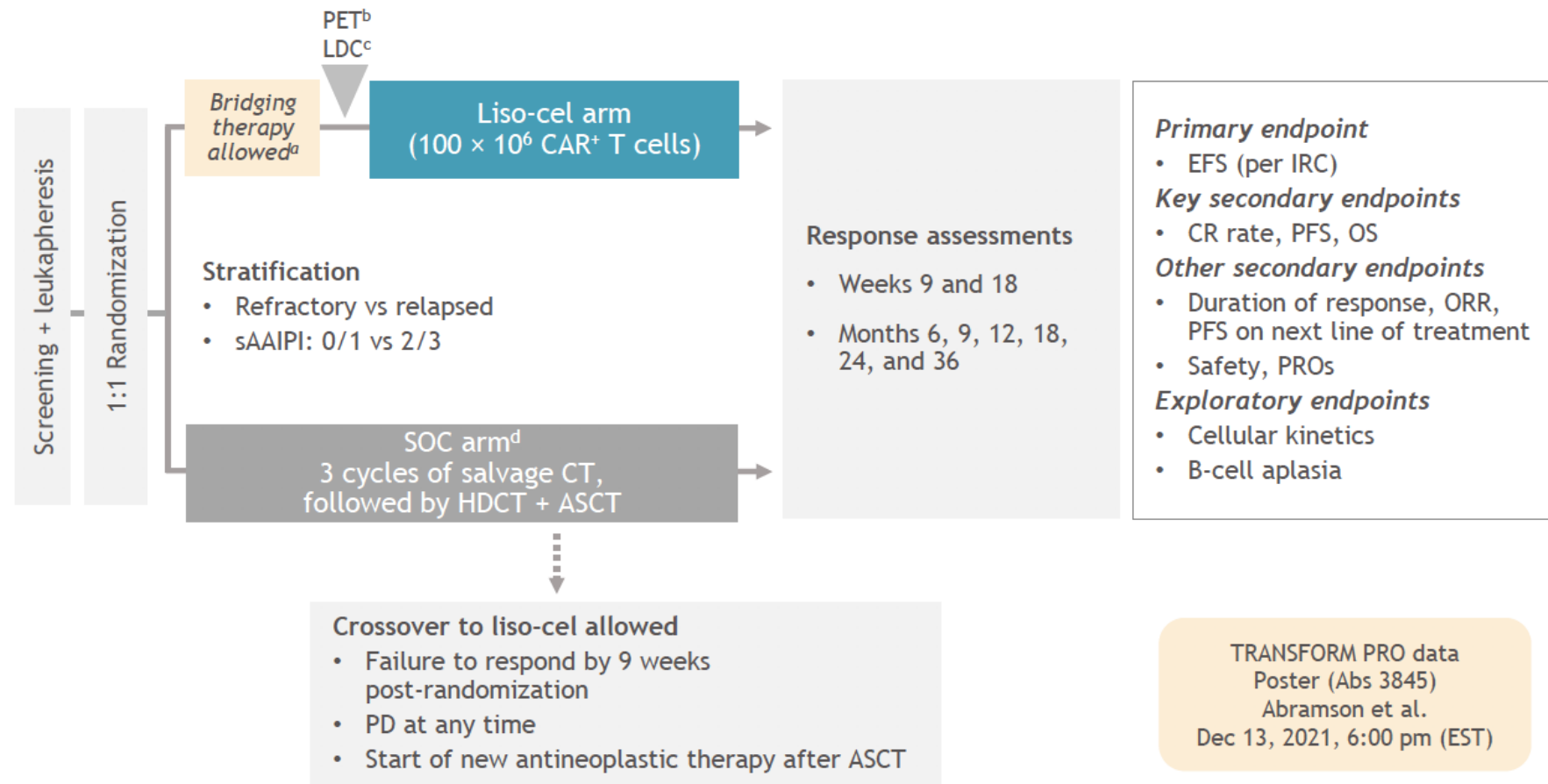
Auto CD19 CAR T-cell Products



TRANSFORM study design

Key eligibility

- Age 18–75 years
- Aggressive NHL
 - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed \leq 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS \leq 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count



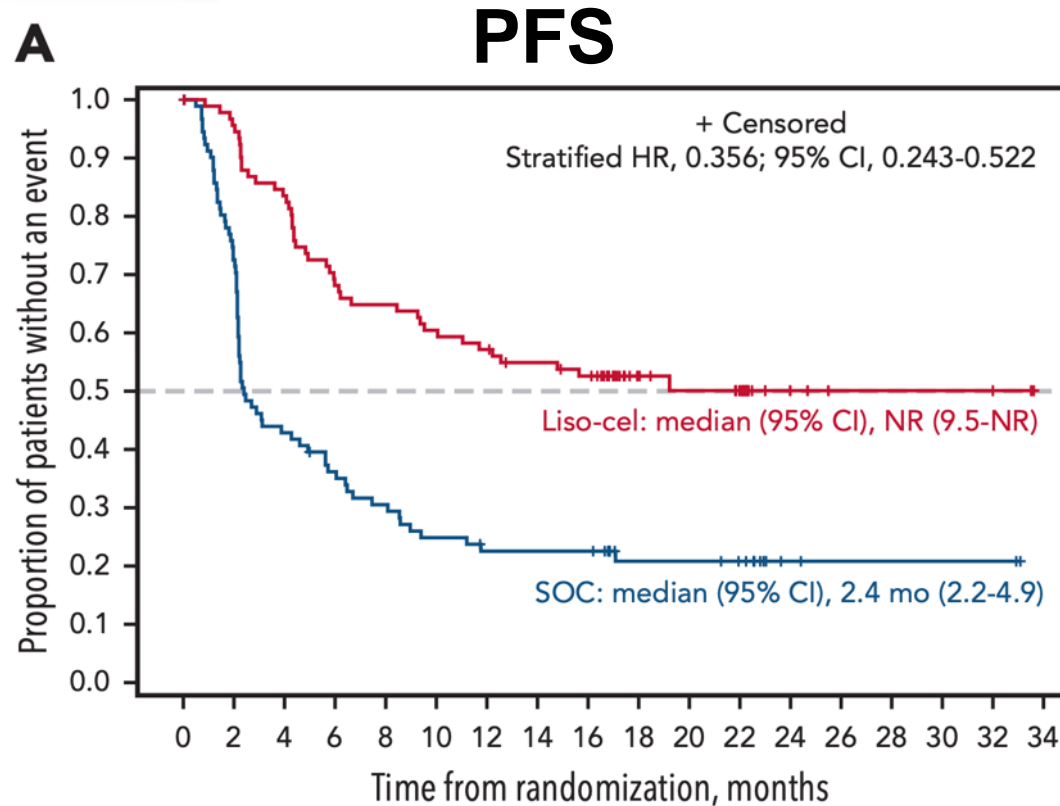
- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

^aPatients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; ^bOnly for patients who received bridging therapy;

^cLymphodepletion with fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² for 3 days; ^dSOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.

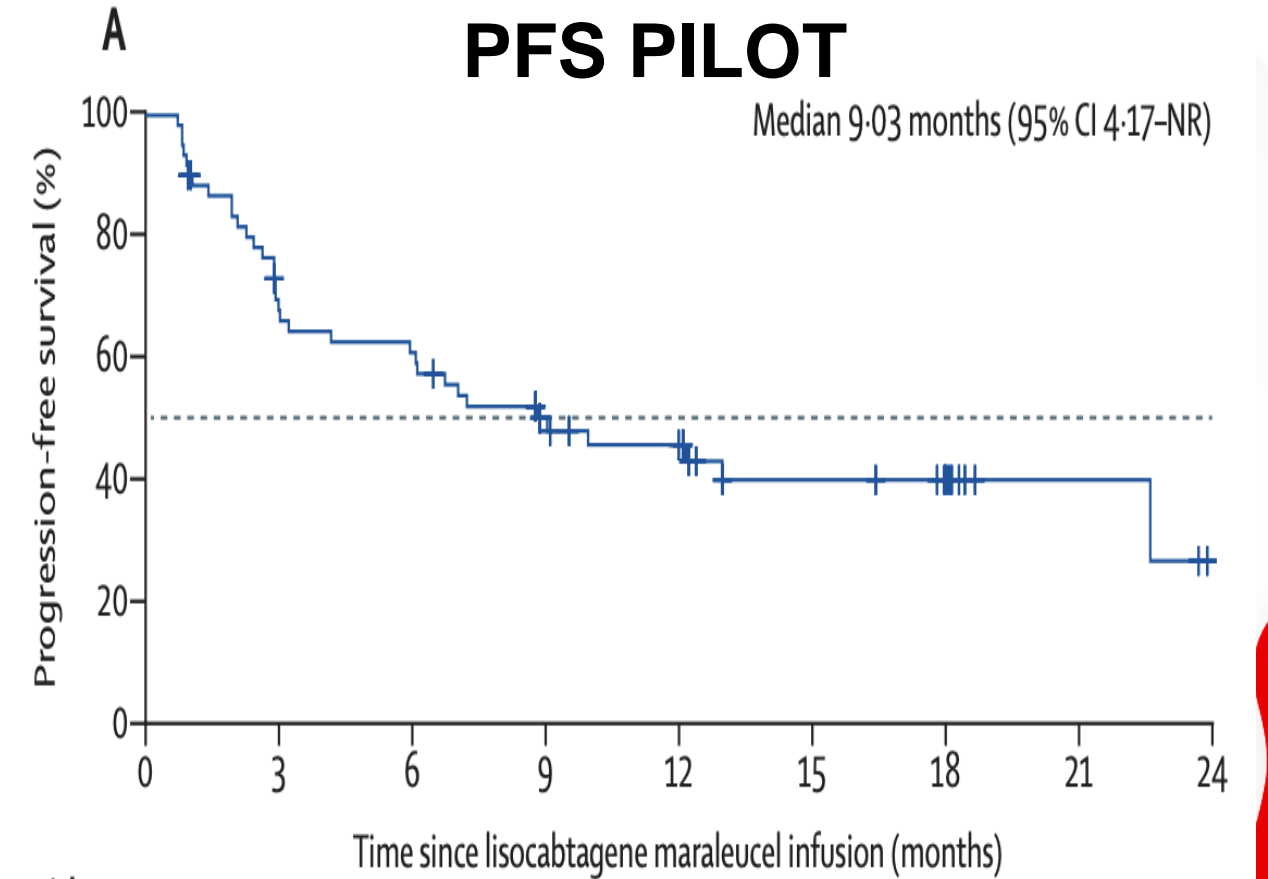
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Transform: Liso-cel is superior to SOC



No. at risk

SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	0



at risk

Total	61 (0)	39 (3)	35 (3)	24 (8)	19 (11)	12 (16)	9 (19)	3 (25)	0 (27)
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PILOT Eligibility

At least 1:

Age \geq 70y

ECOG 2

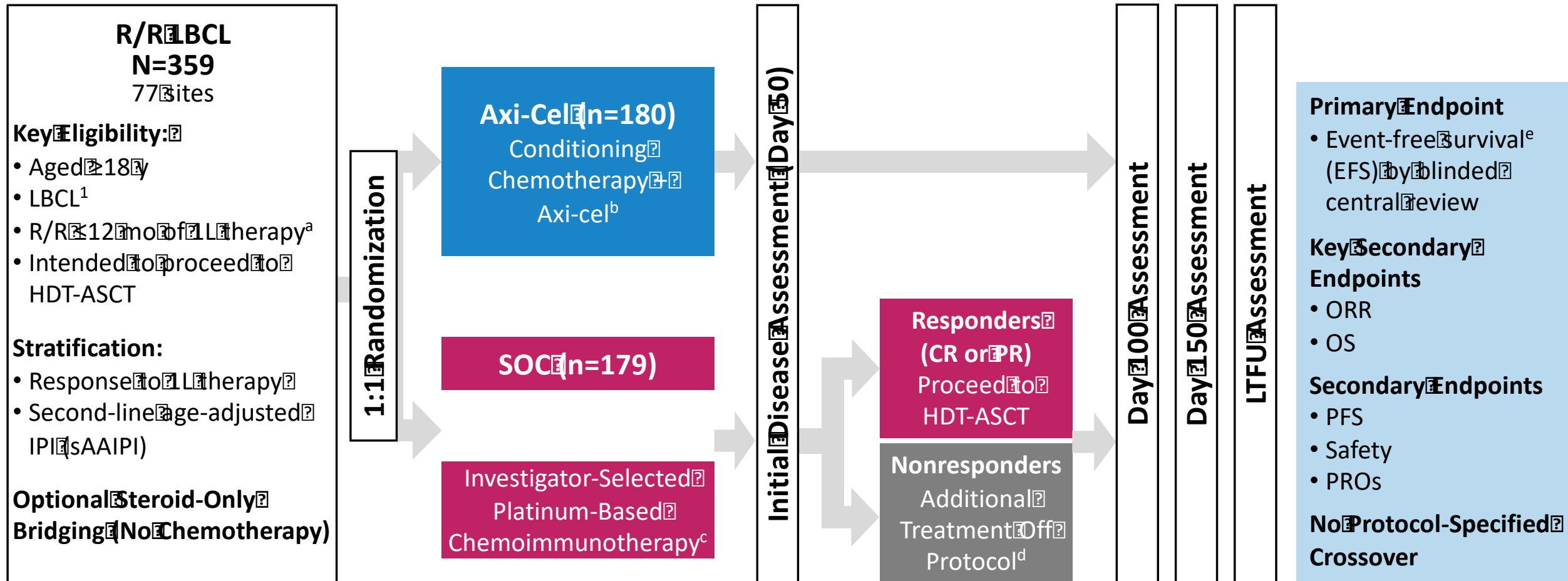
DLCO \leq 60%

EF \leq 50%

CrCl \leq 60mL/min

AST/ALT 2x ULN

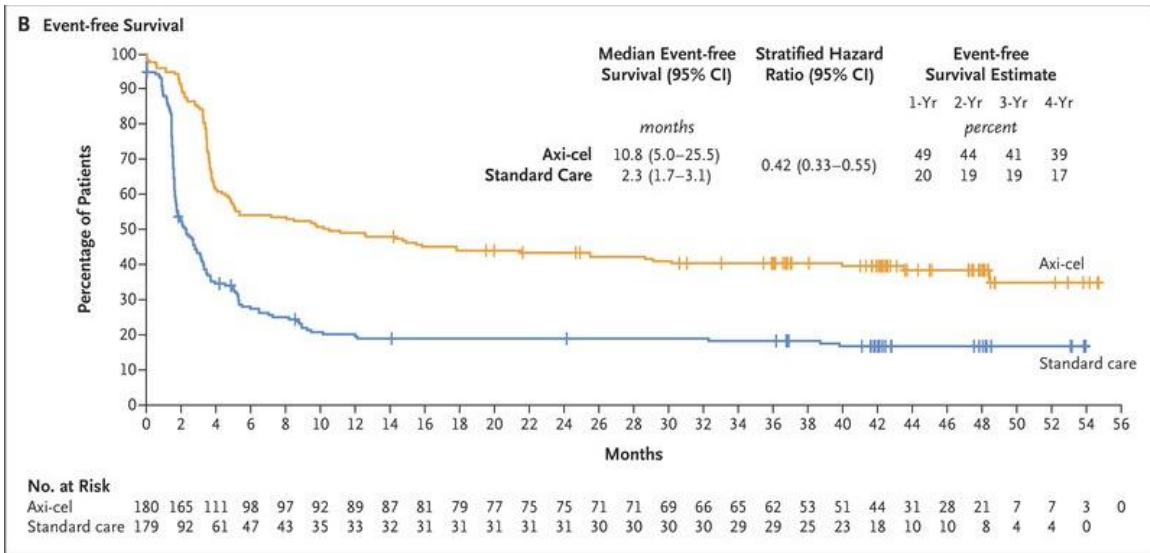
ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



^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. Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 3, 4, and 5 days before receiving single Axi-cel infusion (target intravenous dose, 2×10^6 CAR⁺ cells/kg).
^b Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. 56% of patients received subsequent cellular immunotherapy. 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. Cheson BD, et al. *Clin Oncol*. 2014;32:3059-3068.

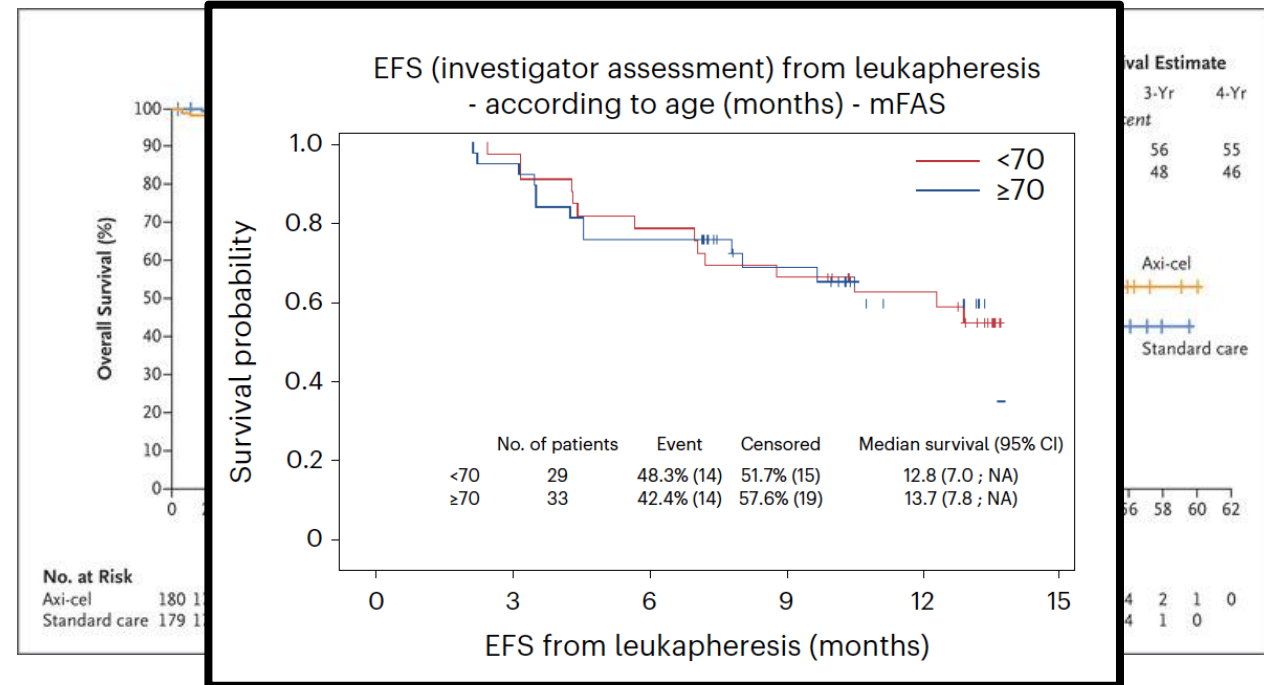
ZUMA7: Axi-cel is superior to SOC

EFS



ALYCANTE

EFS



Westin et al, NEJM 2023

Houot et al, Nat Med 2023

ALYCANTE Eligibility

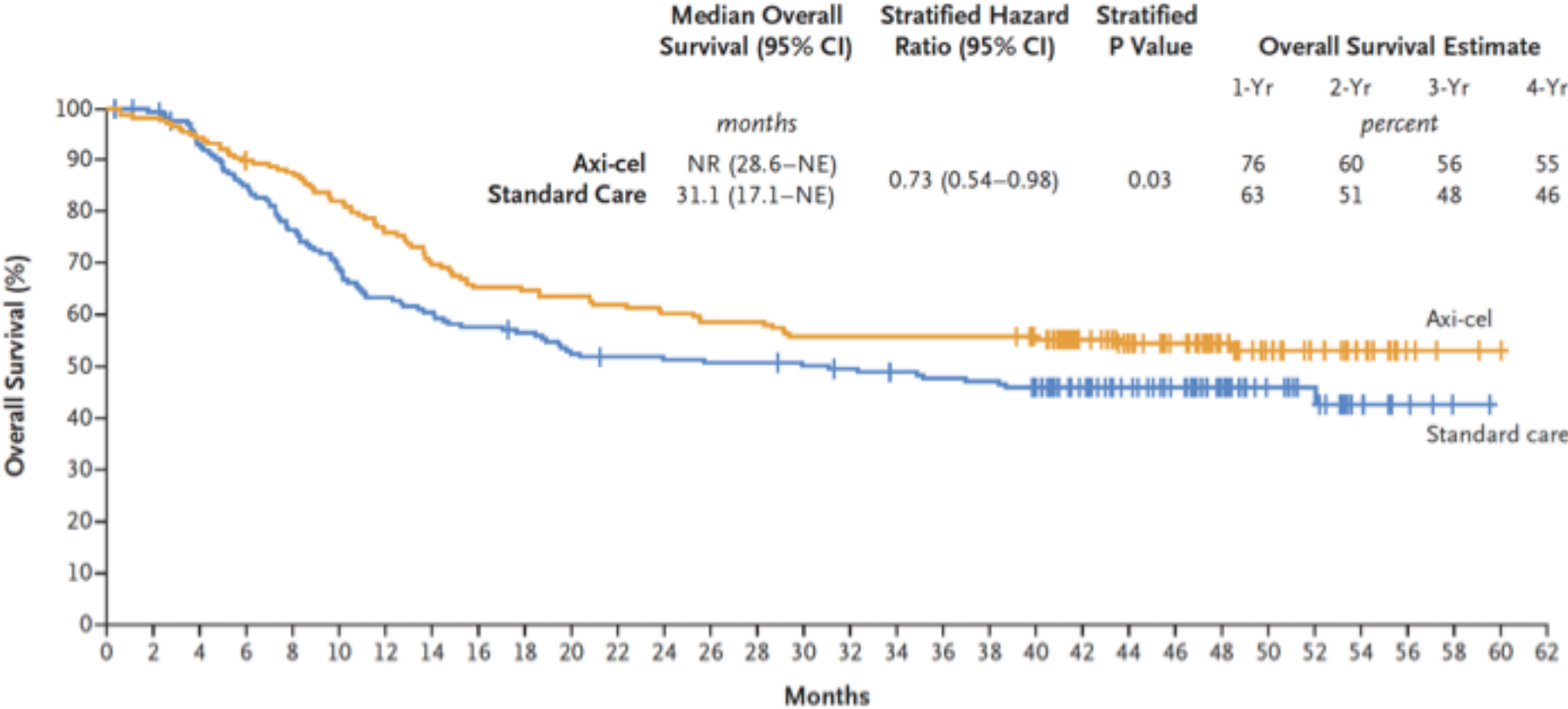
Age \geq 65y

HCT-CI \geq 3

Prior ASCT

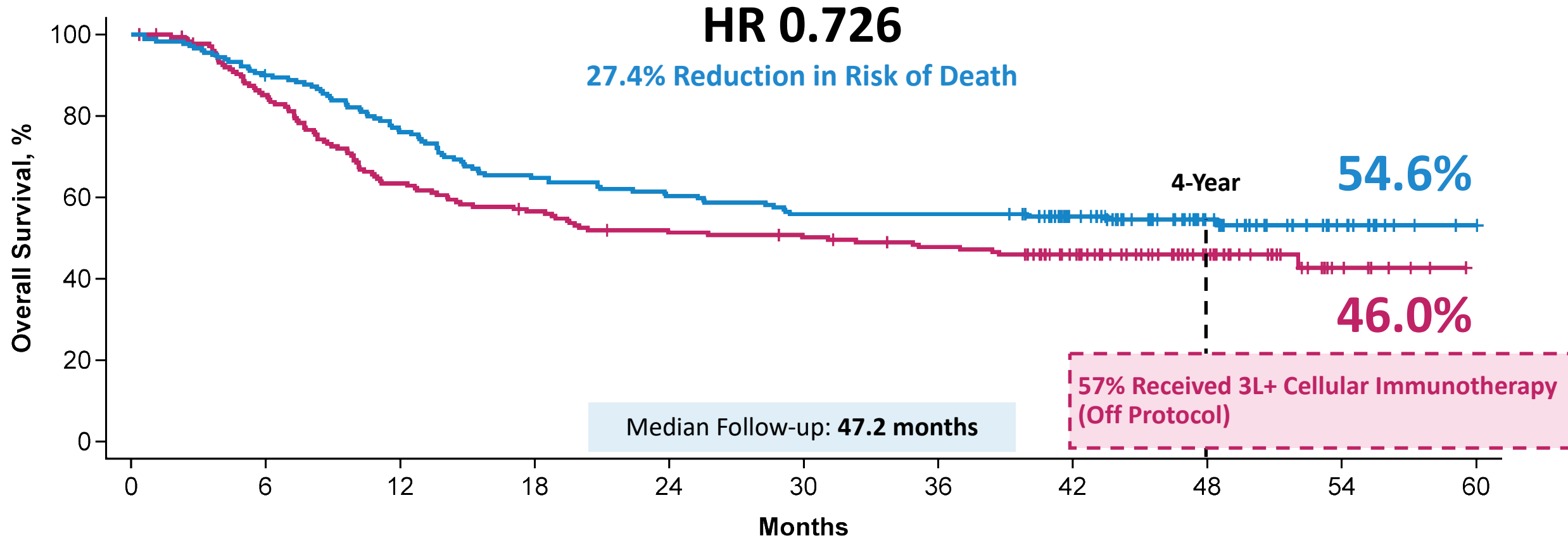
- 1. ECOG performance status of 0, 1 or 2.**
- 2. Absolute neutrophil count $\geq 1.0 \times 10^9 \text{ l}^{-1}$.**
- 3. Absolute lymphocyte count $\geq 0.1 \times 10^9 \text{ l}^{-1}$.**
- 4. Platelet count $\geq 75 \times 10^9 \text{ l}^{-1}$.**
- 5. Creatinine clearance $\geq 40 \text{ ml min}^{-1}$.**
- 6. Left ventricular ejection fraction $\geq 45\%$.**

Axi-cel improves overall survival compared to chemotherapy and AutoSCT



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	58	60	62
Axi-cel	180	177	170	161	157	147	136	125	117	116	114	111	108	105	105	100	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	

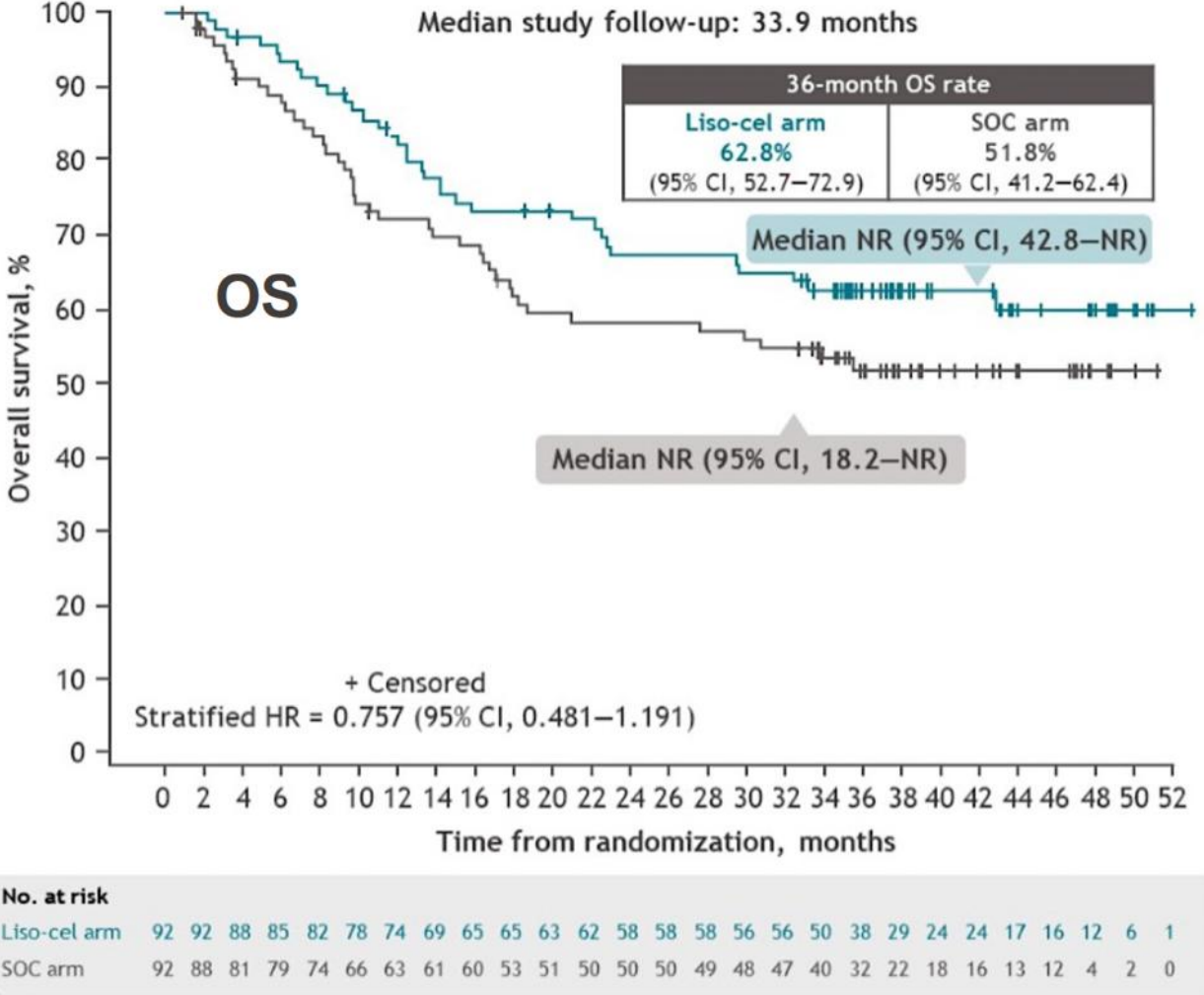
Axi-Cel Improved Overall Survival Versus Standard of Care



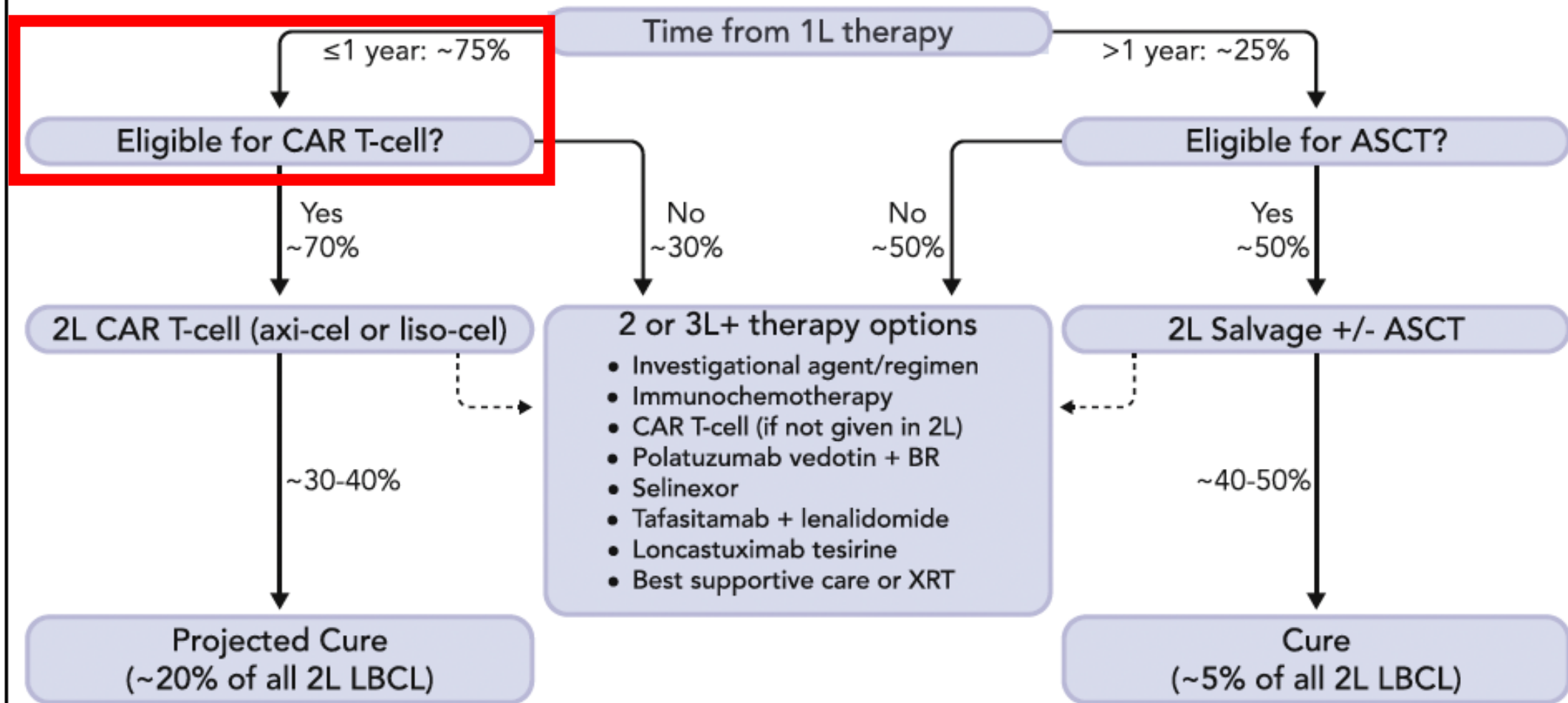
- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC^{a,b}

^a Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *J Clin Oncol.* 2017;35:544-551). ^b <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *J Clin Oncol.* 2010;28:4184-4190). 3L, third line; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.


Liso-cel trends toward overall survival improvement compared to chemotherapy and AutoSCT



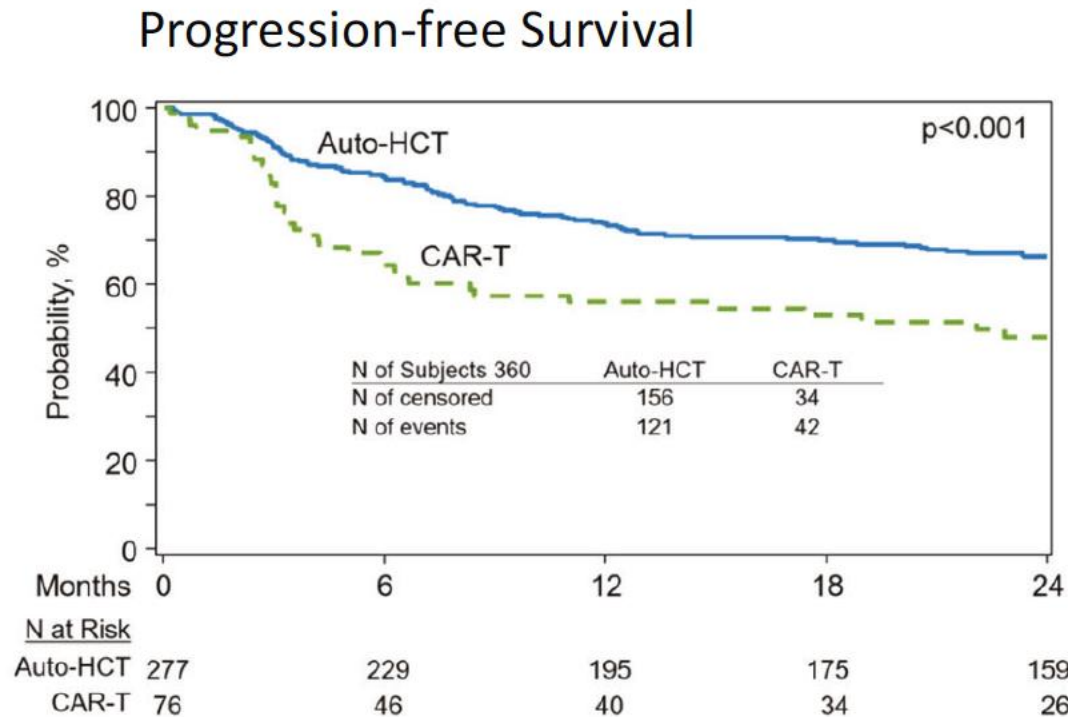
Algorithm for Second-line Therapy of LBCL



AutoSCT is inferior

- 2L standard is CAR T-cell, either axi-cel or liso-cel
 - Trying chemotherapy first and proceed to AutoSCT or CAR T-cell is the control arm of Zuma7 and Transform = worsened overall survival
 - What about in patients with CR to chemo?
 - What about when CAR T-cell is not available easily?
- 

R/R LBCL in CR: Auto vs CAR T-cell



Overall Survival

	Auto-HCT	CAR T-cell
Prior Lines of Therapy	2	3
KPS >90% (performance status)	57%	39%
Refractory to 1L	20%	29%
Treatment failure <12m	58%	72%
Product		Tisa: 53% Axi-cel: 45% Liso-cel 1%

Months	0	6	12	18	24
N at Risk					
Auto-HCT	281	256	233	211	196
CAR-T	77	64	54	43	33

the outcome of patients with relapsed LBCL who receive an auto-HCT while in CR is superior to those who receive CAR-T therapy, both in CR and PFS. This analysis is not practice informing: cannot predict CR

- 2L does better than 3L

Patients in earlier lines of therapy have better outcomes

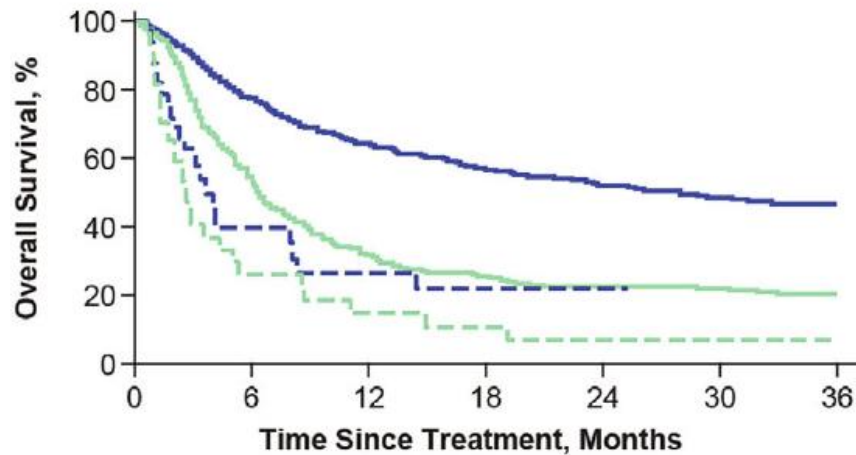
This thing all things devours:
Birds, beasts, trees, flowers;
Gnaws iron, bites steel;
Grinds hard stones to meal;
Slays king, ruins town,
And beats high mountain down

J.R.R Tolkien, The Hobbit,
Gollum's riddle about time

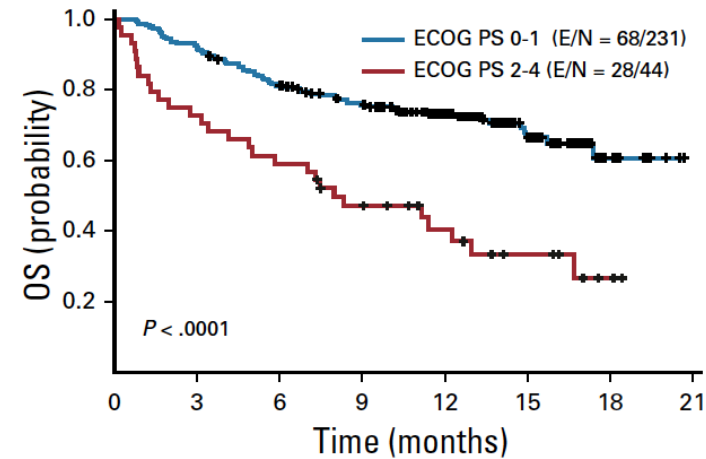
	Phase	CHR	MCyR	CCyR	MMR	Median OS (mo)	OS at 12 months
Blast crisis							
	Imatinib	I	11%	5%	0%	—	—
	Imatinib	I/II	23%	3%	8%	—	22%
	Imatinib	II	15%	16%	7%	—	32%
	Dasatinib ^a	II	27%	36%	26%	—	50%
	Nilotinib ^a	I	6%	18%	6%	—	—
Accelerated-phase relapse							
	Imatinib	II	53%	24%	17%	—	NR
	Dasatinib ^a	II	39%	33%	24%	—	74% ^b
Previously treated chronic phase							
	Imatinib	I	77%	31%	13%	—	—
	Imatinib	III	82%	55%	39.6% ^c	—	>97%
	Dasatinib ^a	II	91%	59%	49%	—	>96%
Newly diagnosed chronic phase							
	Imatinib	III	95%	85%	73.8% ^c	—	NR
	Imatinib	III	—	—	66% ^d	28% ^d	NR
	Imatinib	III	—	—	65% ^d	22% ^d	NR
	Dasatinib	III	—	—	77% ^d	46% ^d	NR
	Nilotinib	III	—	—	79% ^d	44% ^d	NR

Patients with poor PS have worse

	Median OS (95% CI), mo	HR (95% CI)
— Axi-Cel, ECOG PS<2 (N=526)	25.5 (19.3-32.6)	0.27 (0.20-0.35)
— CIT, ECOG PS<2 (N=296)	5.7 (5.2-6.4)	
- - Axi-Cel, ECOG PS=2 (n=33)	25.7 (19.4-32.6)	0.72 (0.41-1.29)
- - CIT, ECOG PS=2 (n=27)	5.7 (5.1-6.4)	



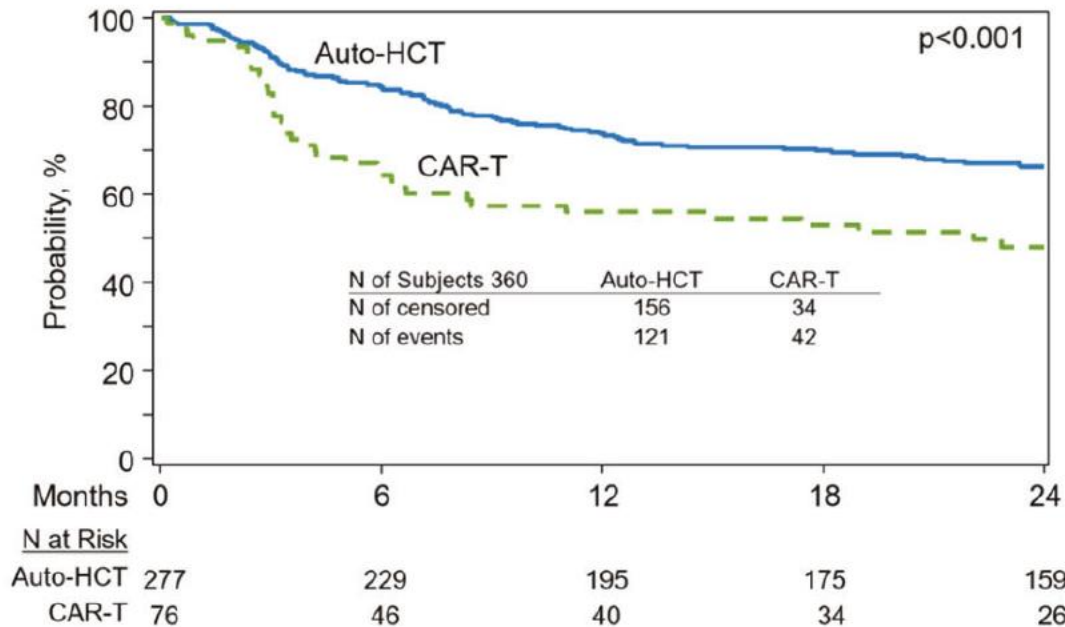
	No. at risk						
	0	6	12	18	24	30	36
Axi-Cel, ECOG PS<2	526	788	301	229	168	160	54
CIT, ECOG PS<2	296	158	90	72	59	56	50
Axi-Cel, ECOG PS=2	33	12	8	5	1	0	0
CIT, ECOG PS=2	27	7	4	3	1	1	1



	No. at risk							
	0	3	6	9	12	15	18	21
ECOG PS 0-1	231	212	184	162	113	47	10	0
ECOG PS 2-4	44	32	26	19	12	7	2	0

R/R LBCL in CR: Auto vs CAR T-cell

Progression-free Survival



	Auto-HCT	CAR T-cell
Prior Lines of Therapy	2	3
KPS >90% (performance status)	57%	39%
Refractory to 1L	20%	29%
Treatment failure <12m	58%	72%
Product		Tisa: 53% Axi-cel: 45% Liso-cel 1%

This analysis is not practice informing:

- Cannot predict CR
- 2L does better than 3L

	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
Received bridging corticosteroids (%)	36	—	—	—	—	—
Received bridging chemotherapy (%)	0	—	83	—	63	—
Received >1 SOC chemotherapy regimen (%)	—	0	—	54	—	0
Received intended CAR T cell (%)	94	—	96	—	97.8	—
Median time to CAR T-cell infusion in days, (interquartile range* or range†)	29 (27-34)*	—	52 (31-135)†	—	NR	—
Received intended ASCT (%)	—	36	—	32.5	—	45.6
Crossover pn protocol (%)	—	—	—	51	—	51
Received cellular therapy off protocol (%)	—	56	—	—	—	—
Follow up, median in months	24.9		10		6.2	
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
PFS, median in months	14.7	3.7	NR	NR	14.8	5.7
PFS HR (95% CI)	0.49 (0.37-0.65)		NR		0.406 (0.21-0.66)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

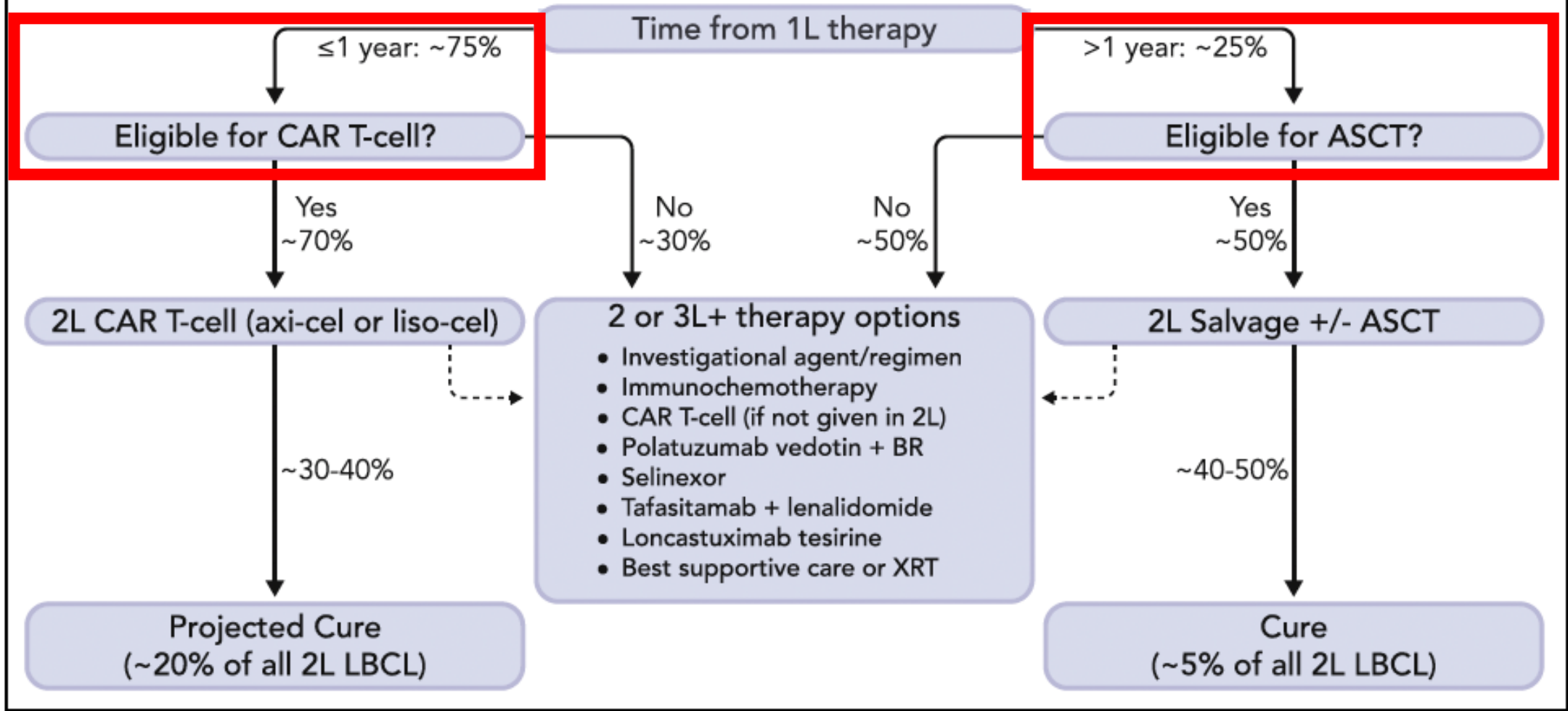
	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
Received bridging corticosteroids (%)	36	—	—	—	—	—
Received bridging chemotherapy (%)	0	—	83	—	63	—
Median time to CAR T-cell infusion in days, (interquartile range* or range†)	29 (27-34)*	—	52 (31-135)†	—	NR	—

1. Platinum chemotherapy in early relapse DLBCL: CR rate is 28-39%
2. Using bridging therapy is ok
3. Time to infusion is important

AutoSCT is sub-optimal, but useful

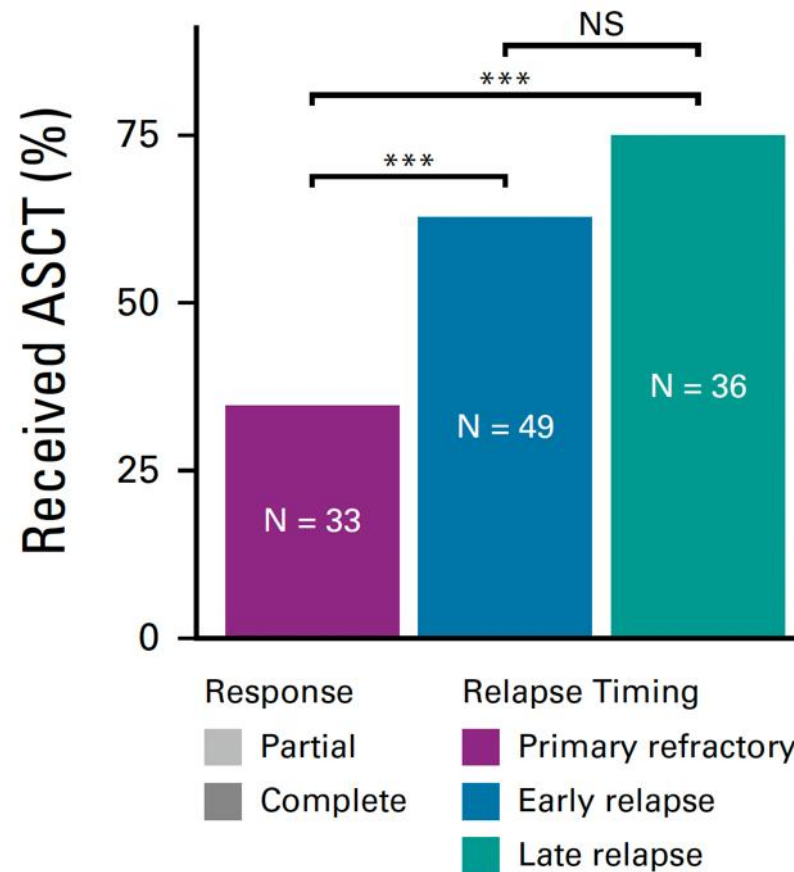
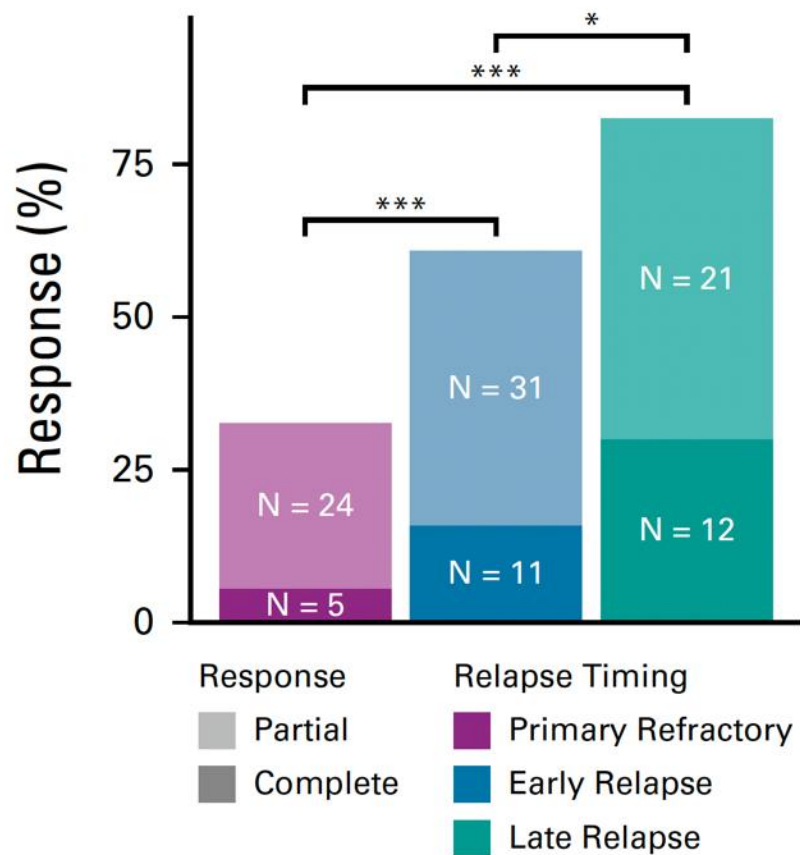
- 2L is CAR T-cell, either axi-cel or liso-cel
- Trying chemotherapy first and going AutoSCT is the control arm of Zuma7 and Transform = worsened overall survival
- Chemotherapy CRR: 32% (Zuma7) and 39% (Transform)
- In many places, CAR T-cell therapy is available but logistics take +++ time or cost is prohibitive
 - If bridging therapy = a CR, AutoSCT is reasonable if apheresis/manufacturing not started

Algorithm for Second-line Therapy of LBCL



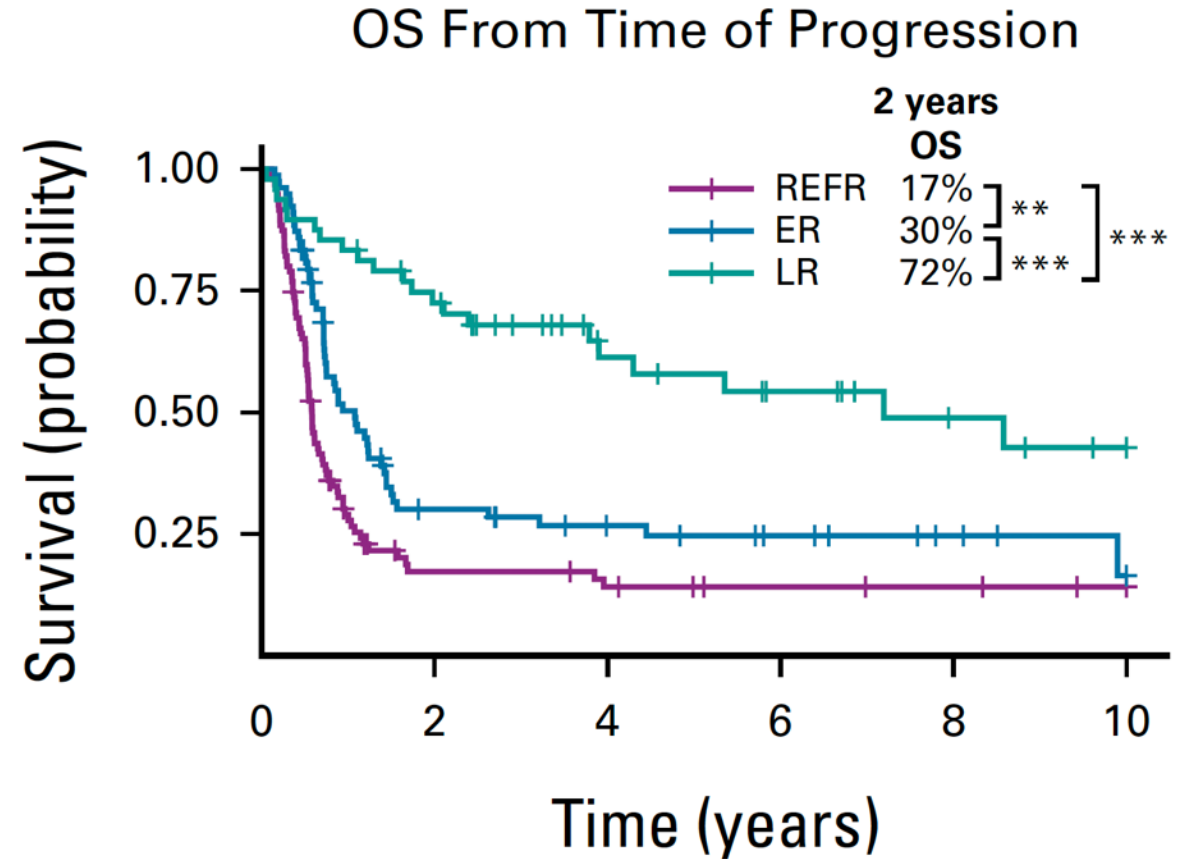
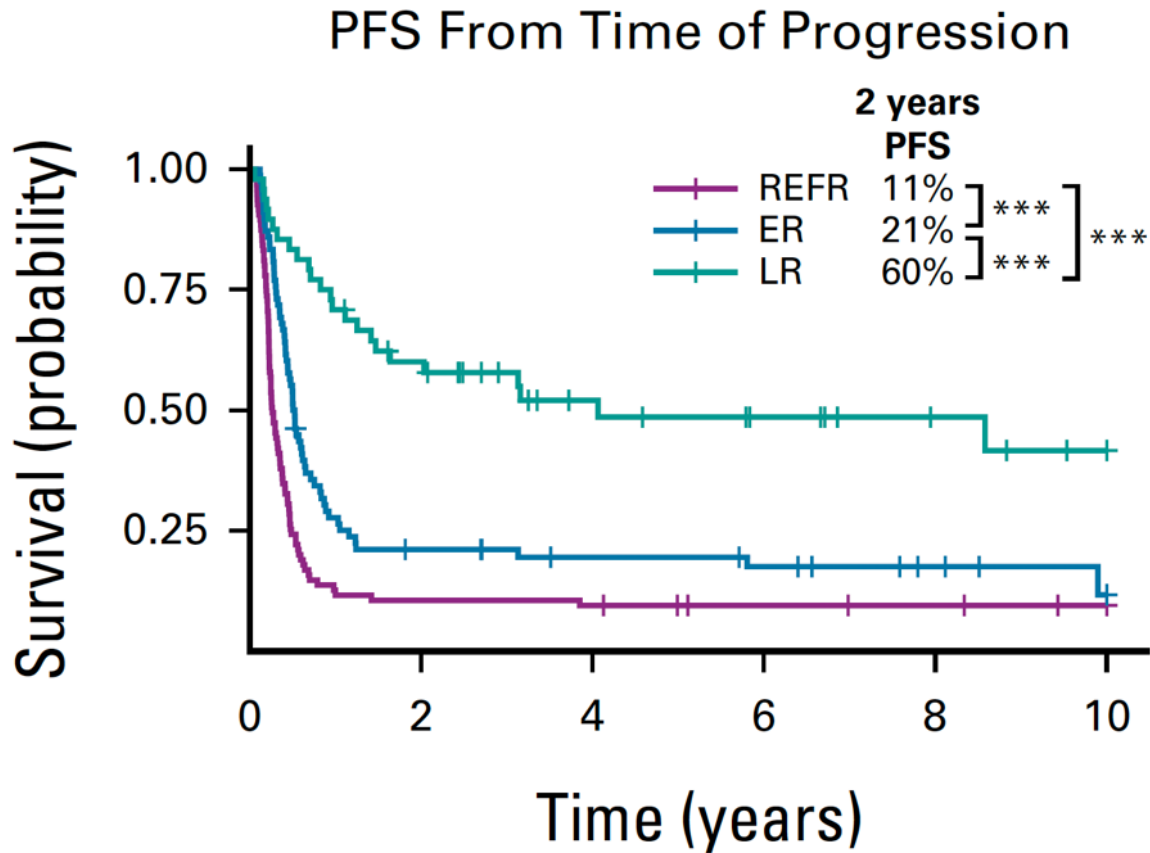
What about late relapsing patients?

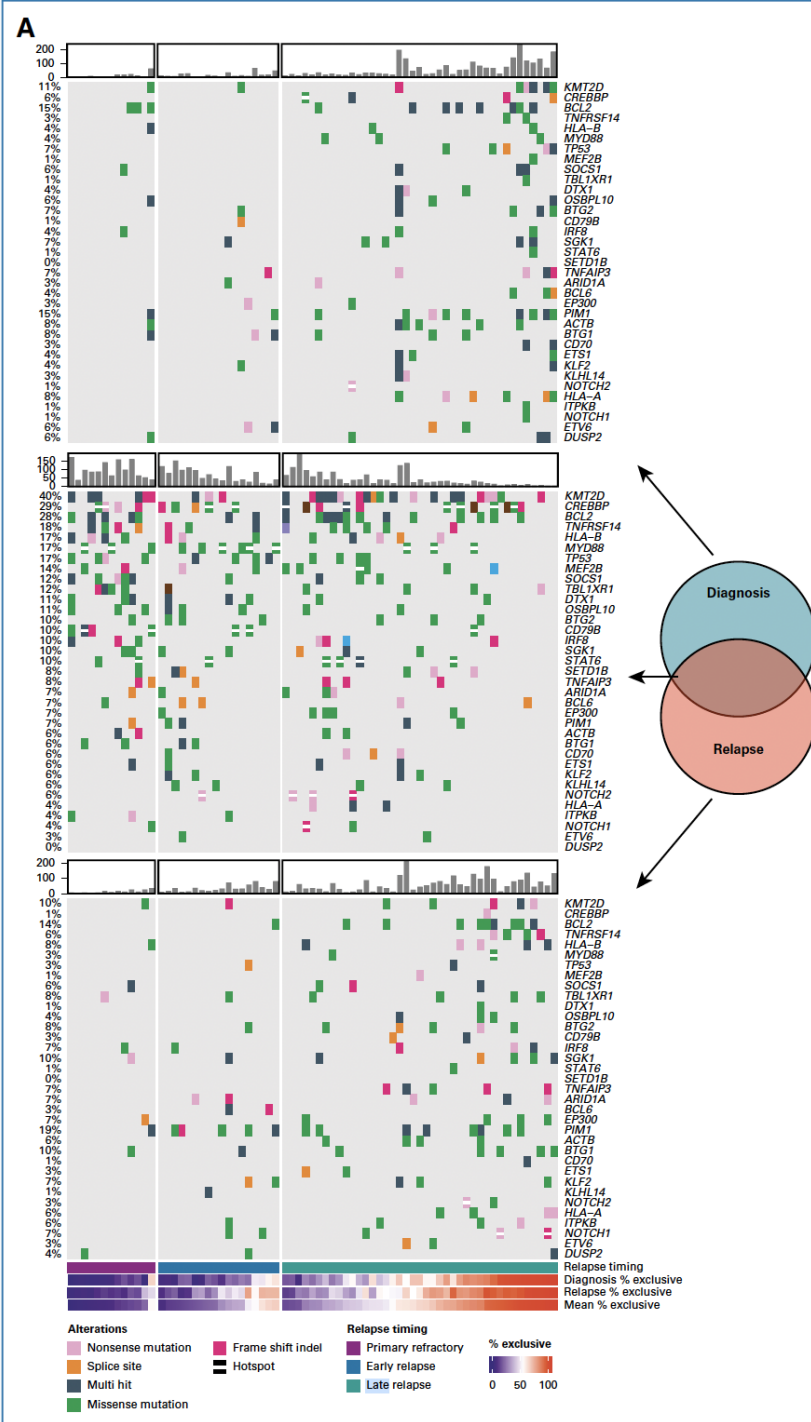
Early relapse: 9-24m
Late relapse: >24m



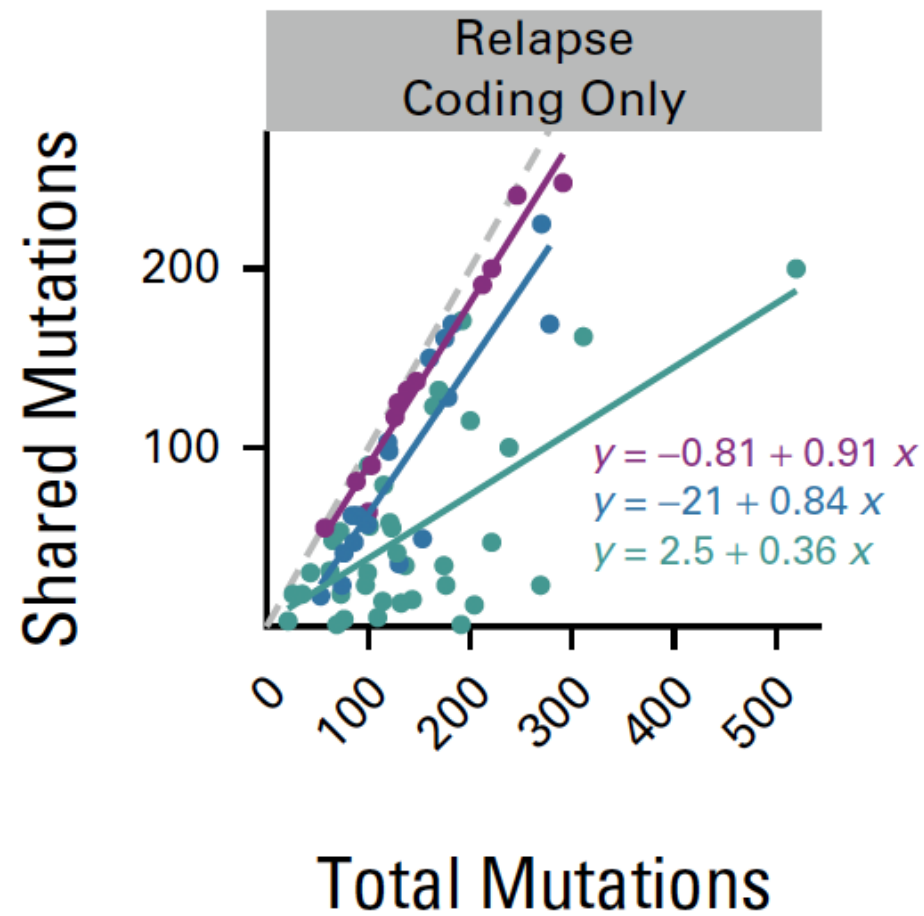
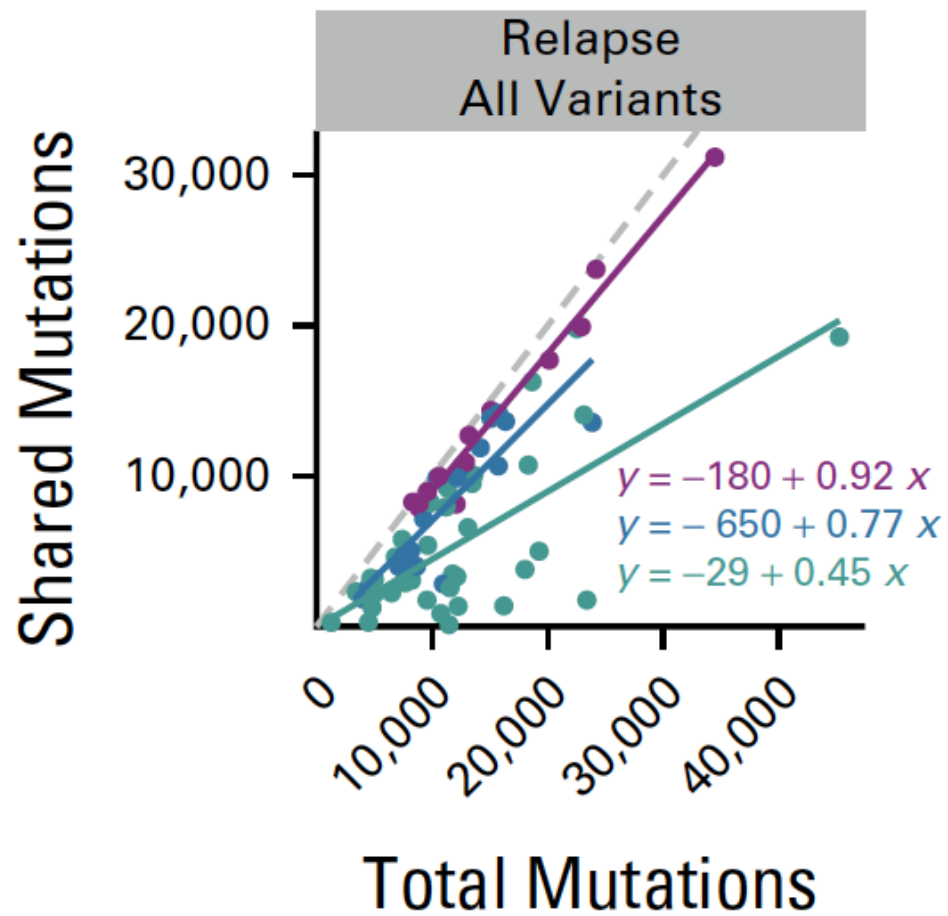
What about late relapsing patients?

Early relapse: 9-24m
Late relapse: >24m



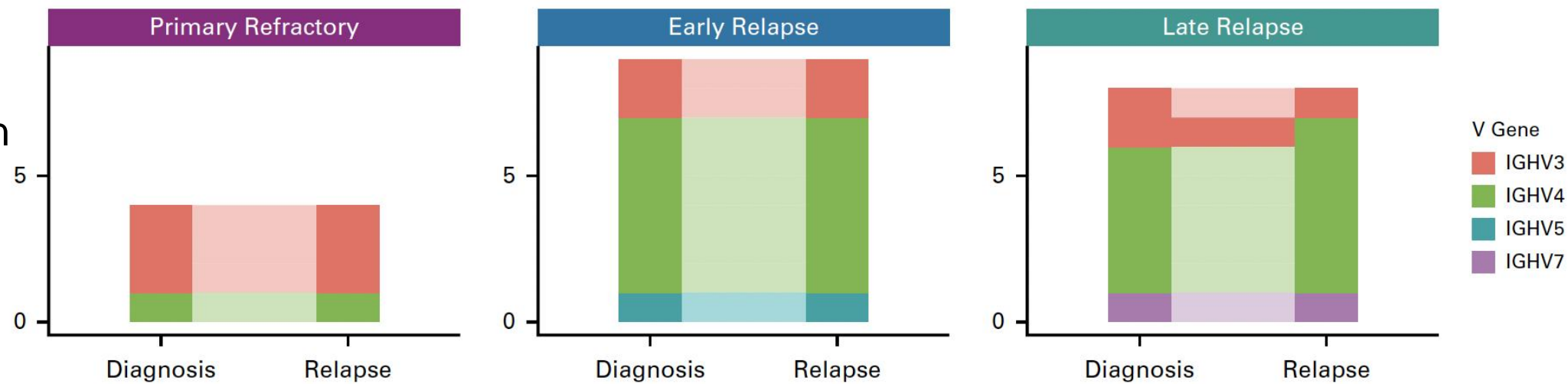


Many unshared mutation between initial diagnosis and relapse

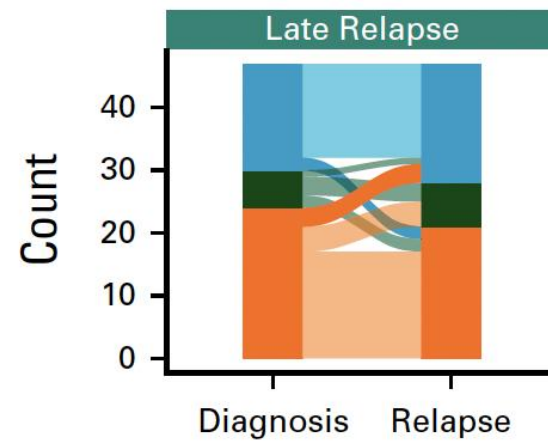
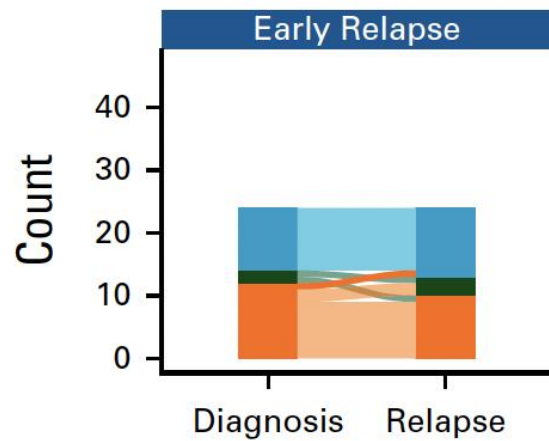
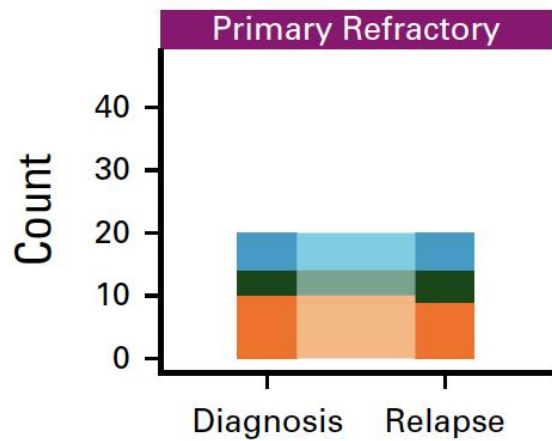


—●— Primary refractory
 —●— Early relapse
 —●— Late relapse

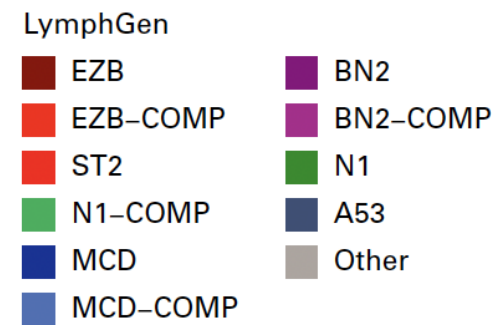
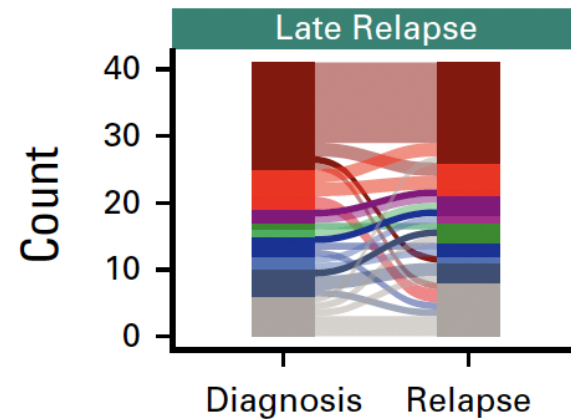
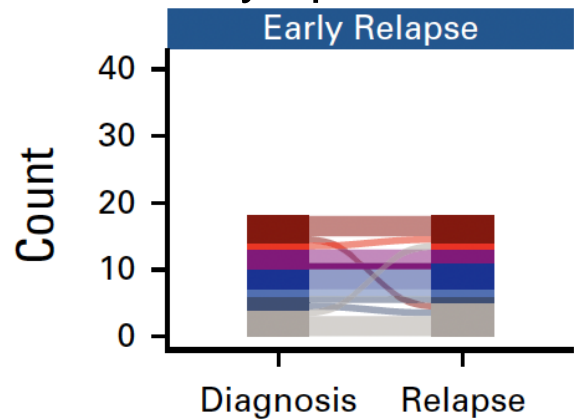
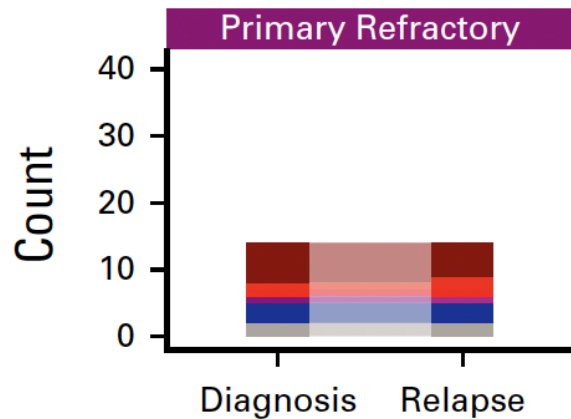
Light Chain

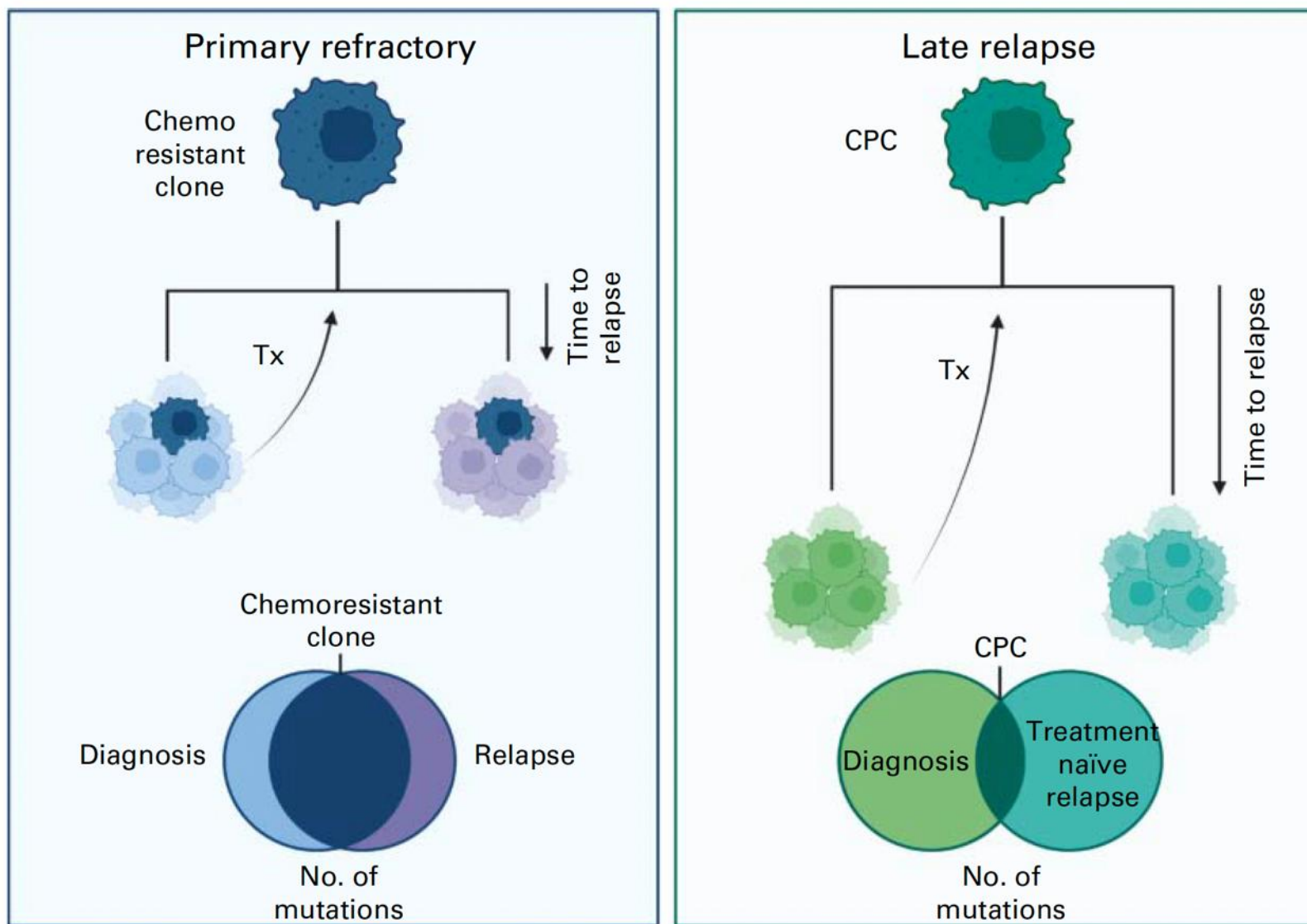


Cell of Origin



LymphGen





4454 Retreatment with R-CHOP-like Therapy Is Active with Durable Responses in Patients with Late Relapse of Diffuse Large B-Cell Lymphoma

Program: Oral and Poster Abstracts

Session: 626. Aggressive Lymphomas: Clinical and Epidemiological: Poster III

Hematology Disease Topics & Pathways:

Research, Lymphomas, Non-Hodgkin lymphoma, Clinical Research, Health outcomes research, B Cell lymphoma, Diseases, Therapy sequence, Aggressive lymphoma, Treatment Considerations, Lymphoid Malignancies

Monday, December 9, 2024, 6:00 PM-8:00 PM

Eduardo Edelman Saul, MD¹, Bryan Valcarcel, MD, MPH², Amy A. Ayers, MPH^{3}, Mansoor Noorani, MD^{3*}, Dai Chihara, MD, PhD³, Fateeha Furqan, MBBS³, Sairah Ahmed, MD³, Swaminathan P Iyer, MD^{3*}, Sattva S. Neelapu, MD³, Luis E. Fayad, MD³, F. B. Hagemeister, MD³, Chijioke Nze, MD, MPH³, Preetesh Jain, MD, MBBS, PhD, DM³, Michael Wang, MD³, Paolo Strati, MD³, Ayushi Chauhan, MD³, Francisco Vega, MD, PhD⁴, Christopher R. Flowers, MD, MS³ and Jason R. Westin, MD³*

If “relapse” is >3y from initial therapy, could you try 1L again?

	First-Line therapies	N	%	Second-Line therapies	N	%
R-CHOP-like retreatment						
	R-CHOP	12	54.5	R-CHOP	3	13.6
	R-EPOCH	5	22.7	R-CHOP followed by R-CEOP	5	22.7
	R-CEOP	1	4.5	R-CHOP + novel agent	1	4.5
	R-CVP	1	4.5	R-EPOCH	4	18.2
	R-cytosan/gemzar/vincristine	1	4.5	R-EPOCH followed by R-CEOP	1	4.5
	R-CHOP+bortezomib	1	4.5	R-EPOCH followed by R-miniCHOP	1	4.5
				Pola-R-CHP followed by R-CEOP	1	4.5
				R-CEOP	4	18.2
				R-CEOP+ibrutinib+lenalidomide (*3L)	1	4.5
				R-CVP	1	4.5
HD-ICT +or- ASCT						
	R-CHOP	61	77.2	R-ICE-like	31	39.2
	miniR-CHOP	3	3.8	R-GemOx	8	10.1
	R-EPOCH	13	16.5	Tafasitamab + Lenalidomide	8	10.1
	R-CHOP+ibrutinib	2	2.5	R-DHAP	7	8.9
				R-GDP	7	8.9
				Other regimens	18	22.8

Results

- R-CHOP-like retreatment group
 - 22 patients received 2L or 3L R-CHOP-like therapy
 - Median age 69.8 years
 - 45% female
 - 41% MYC/BCL2 double-expressor (DE) and 9.1% double-hit (DH)
 - 72.7% stage III-IV
 - 50% IPI 3-5
 - Median cumulative anthracycline dose was 315.9 mg/m²
 - Median time to relapse (TTR) was 87.28 months
 - 27.3% received CAR-T therapy as 3L

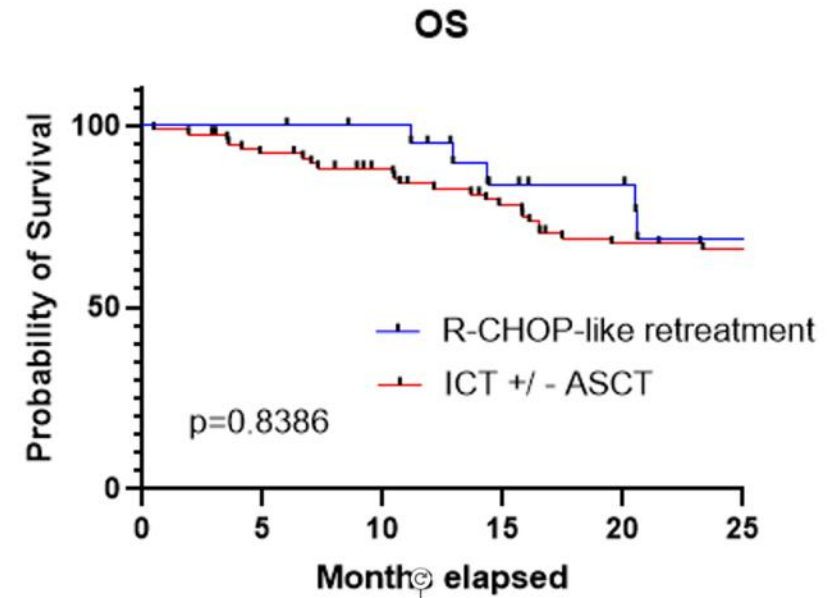
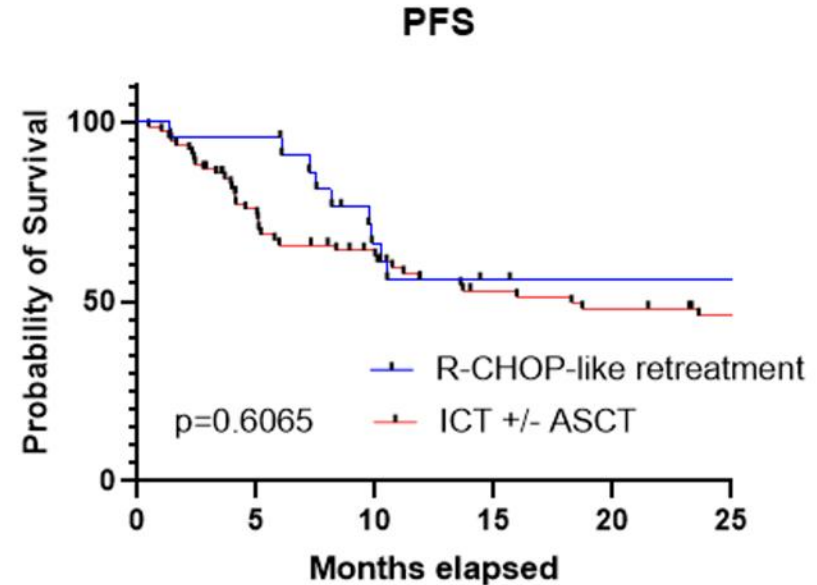
If “relapse” is >3y... could you try 1L again?

R-CHOP-like retreatment vs. HD-ICT
+/- ASCT:

- CR rate: 90.9% vs. 70.9%
- 2-year PFS 56% vs. 46.2%
- 2-year OS 68.6% vs. 65.8%

R-CHOP-like retreatment vs. HD-ICT+/-ASCT:

- Diastolic dysfunction grade 1 in 2 (9%) vs. 5 (6.3%) patients
 - Systolic dysfunction 0% vs. 6.3%
- Treatment-related (t-) CCUS/MDS/AML 0% vs. 10%



My approach to very late 'relapse'

If fit, 2 cycles of RCHOP-like therapy

- If CR, change to RCEOP to complete planned course
- If <CR, move to CAR T-cell therapy

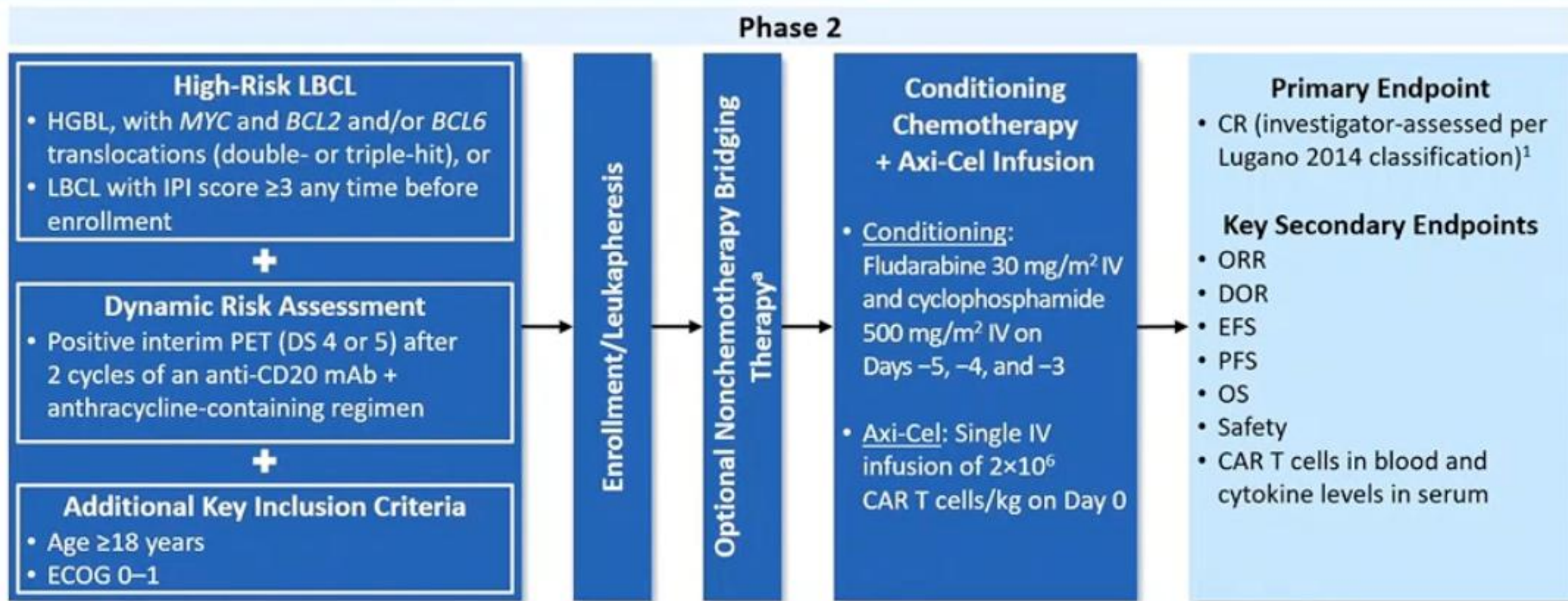
When is the golden moment for CAR T-cell?

When chemotherapy is unlikely to work

Early relapse or refractory

Suboptimal response to 2L chemotherapy (consider restage after 1 cycle)

ZUMA-12 Study Design

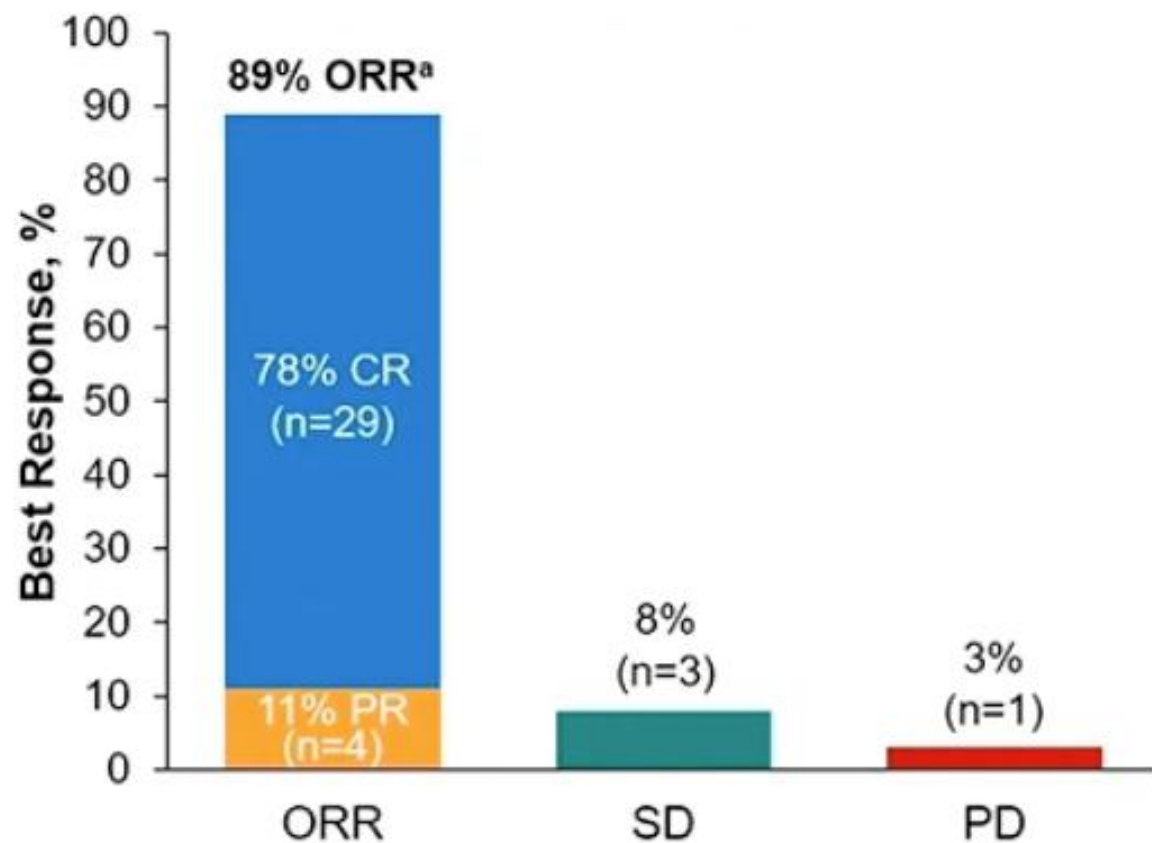


^a Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

ORR Was 89% (95% CI, 75–97) and CR Rate Was 78% (95% CI, 62–90) Among Efficacy-Evaluable Patients



	Efficacy Evaluable N=37 ^b
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%) ^c	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

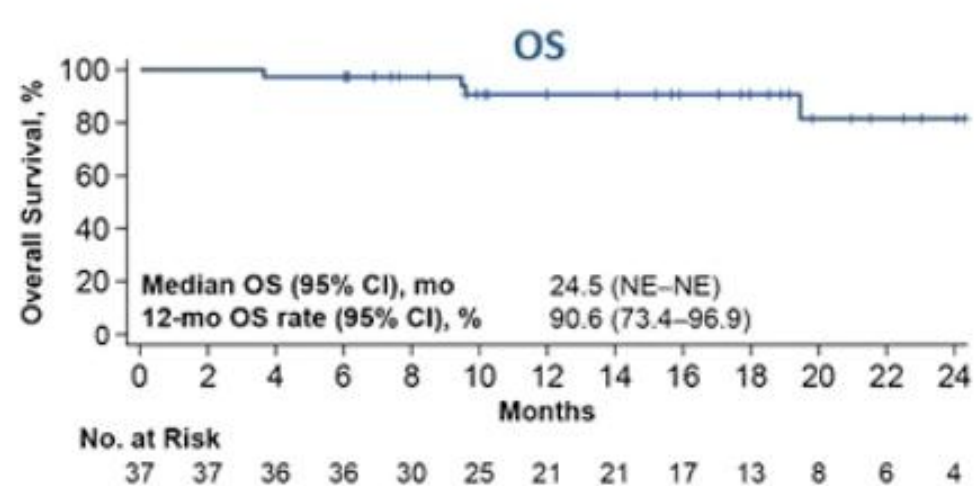
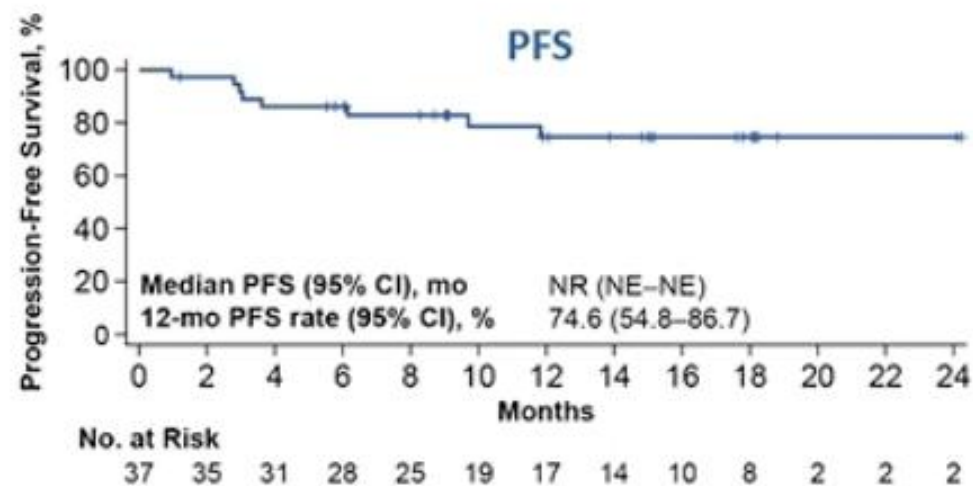
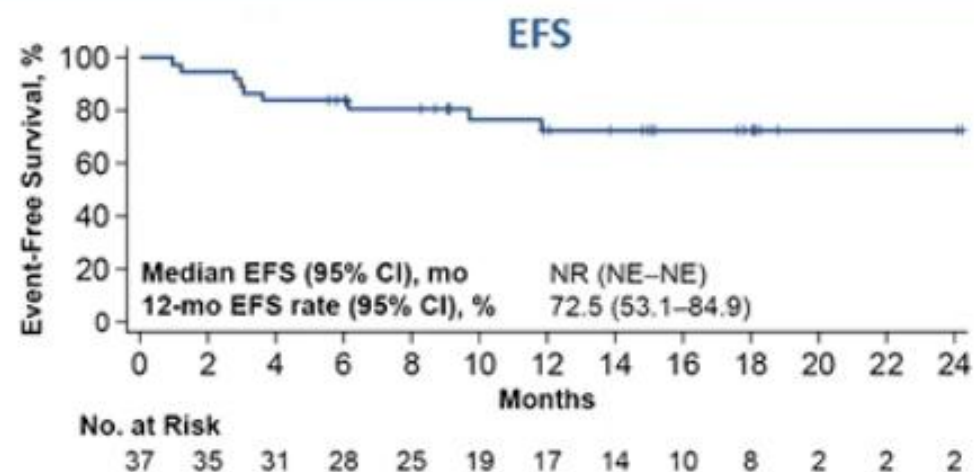
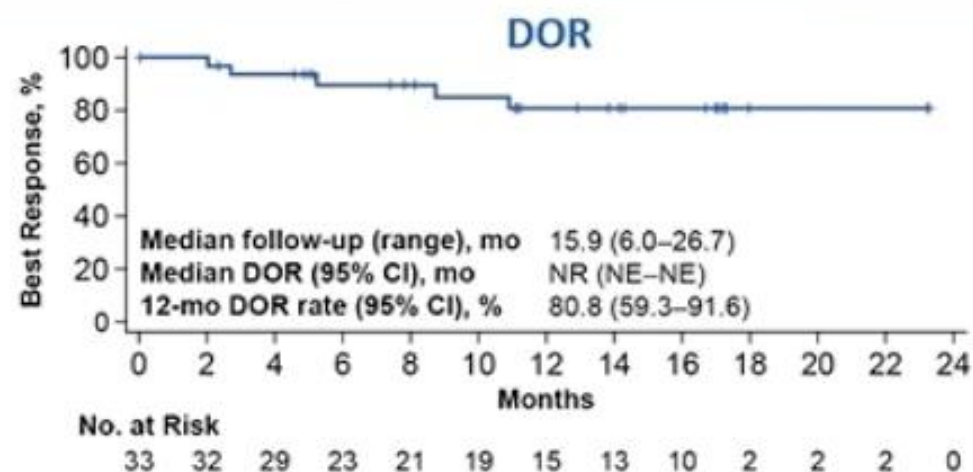
- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

^a Response assessments are based on best overall response. ^b Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10⁶ CAR T cells/kg.

^c All 7 patients converted to a CR by Month 6 postinfusion.

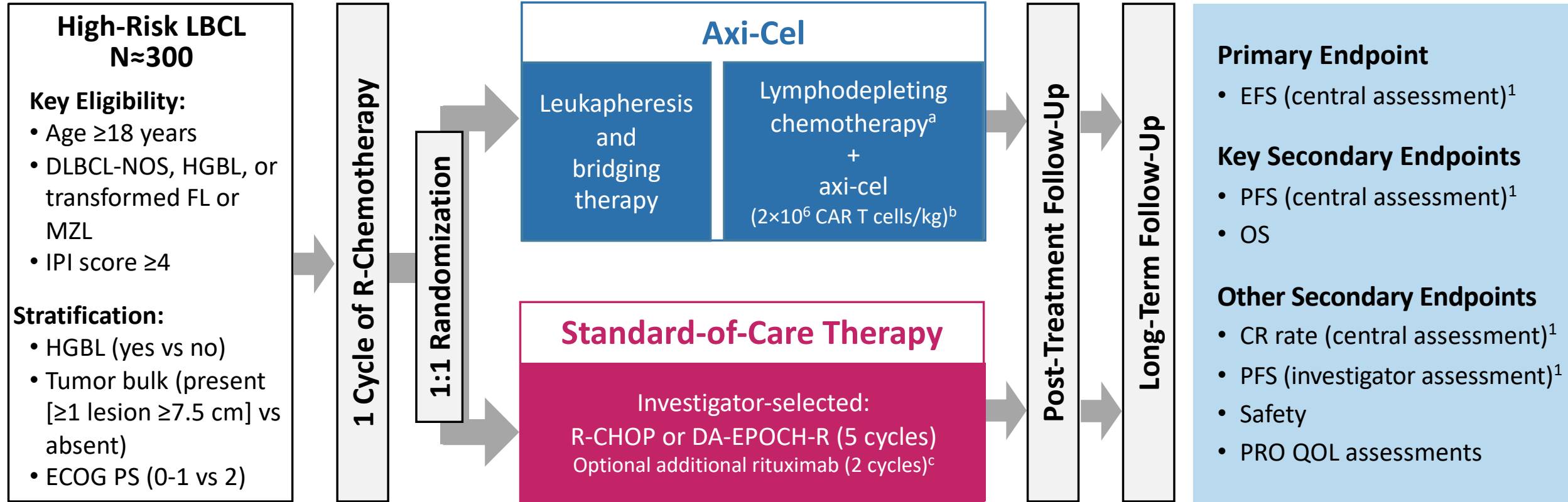
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival^a



^a Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥ 3 who received $\geq 1 \times 10^6$ CAR T cells/kg. DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

ZUMA-23 Phase 3 Study Design

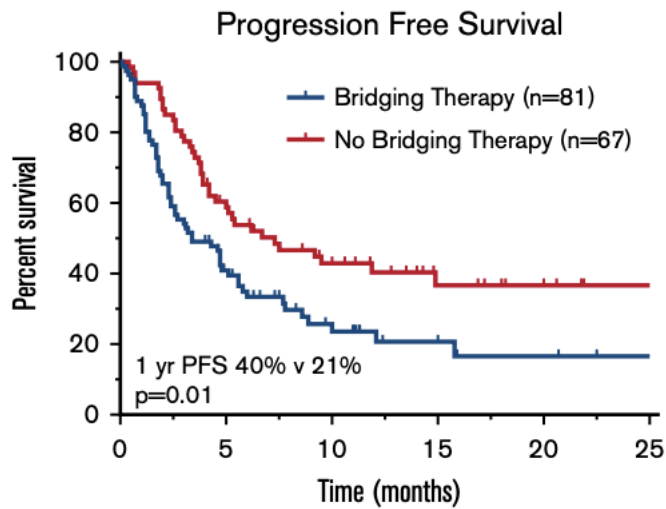


1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

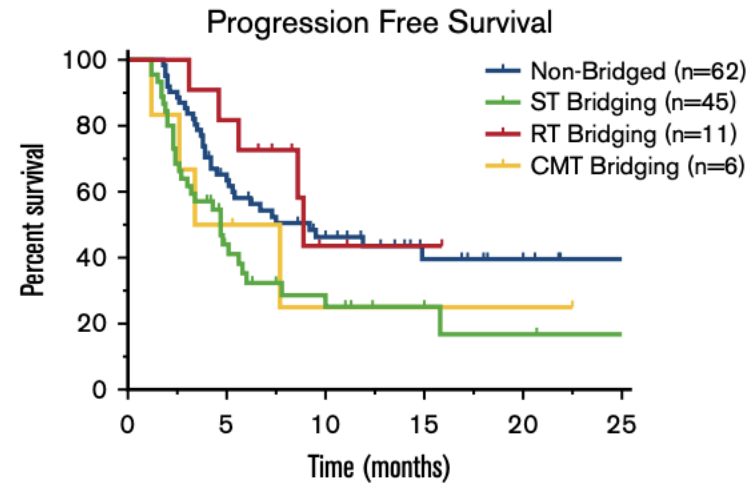
^a Lymphodepleting chemotherapy will consist of cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day), received Days -5 through -3 before receiving axi-cel. ^b Prophylactic corticosteroids may be administered after axi-cel infusion per investigator discretion. ^c If standard of care per local clinical practice, patients may also receive 2 additional cycles of rituximab monotherapy. Axi-cel, axicabtagene ciloleucel; CR, complete response; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R-chemotherapy, rituximab plus chemotherapy; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; QOL, quality of life.

I want to try to get my patient to CAR but disease is progressing too rapidly...

Use whatever tools you have



	0	5	10	15	20	25
No Bridging	67	37	22	10	5	2
Bridging	81	29	12	6	4	1



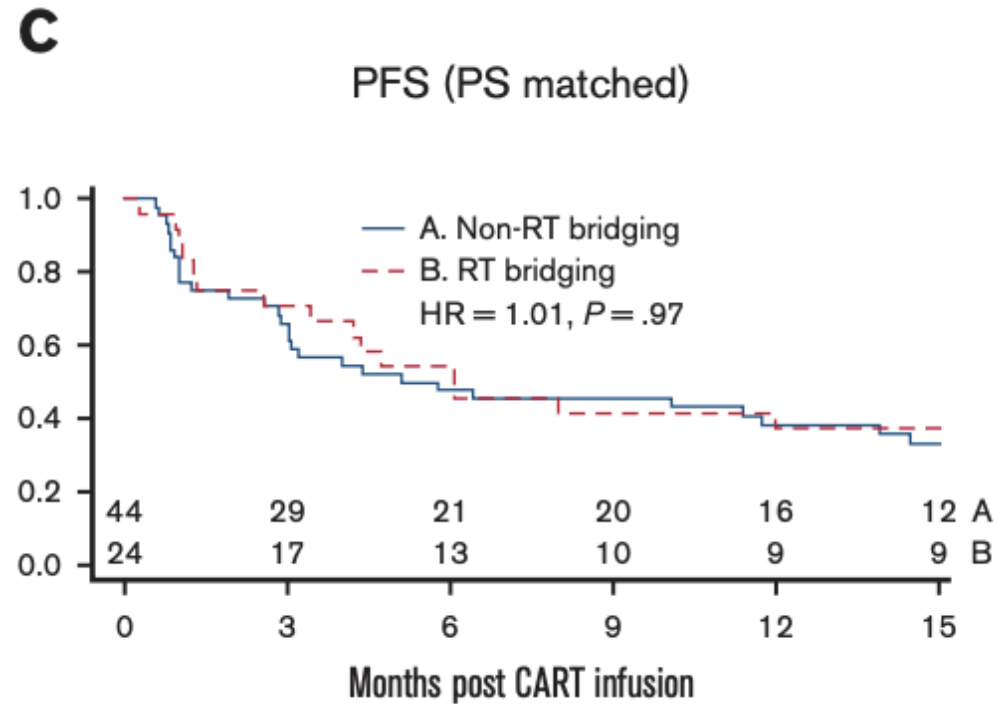
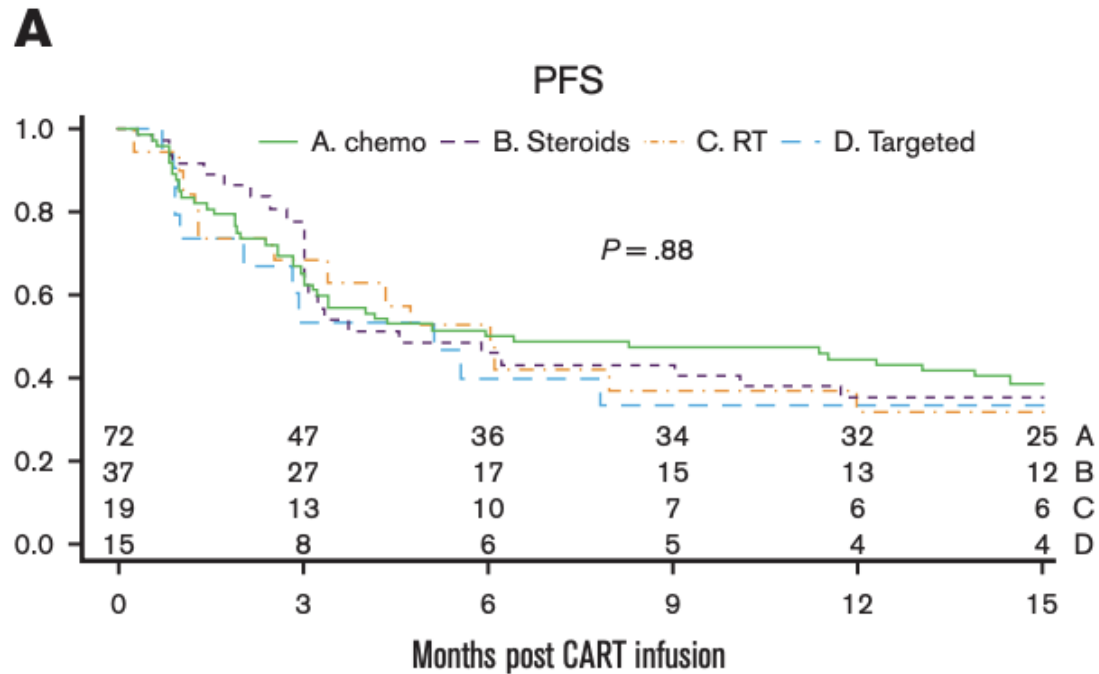
	0	5	10	15	20	25
No Bridging	62	37	22	11	5	1
ST Bridging	45	16	8	4	3	1
RT Bridging	11	10	3	2	0	0
CMT Bridging	6	4	2	2	1	0

No bridging vs ST p=0.01
 No bridging vs RT p=0.52
 No bridging vs CMT p=0.36
ST vs RT p=0.05
 ST vs CMT p=0.78
 RT vs CMT p=0.17

Pinnix et al, Blood Advances 2020

I want to try to get my patient to CAR but disease is progressing too rapidly...

Use whatever tools you have



Jain et al, Blood Advances 2024

Conclusion:

The golden moment to use CAR T-cell is

- second line
- third line
- maybe first line in IPI 4-5?

Bridging and holding therapies?

- Polatuzumab
- Radiation
- Steroids
- Chemotherapy



Thank you!
Obrigado!

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