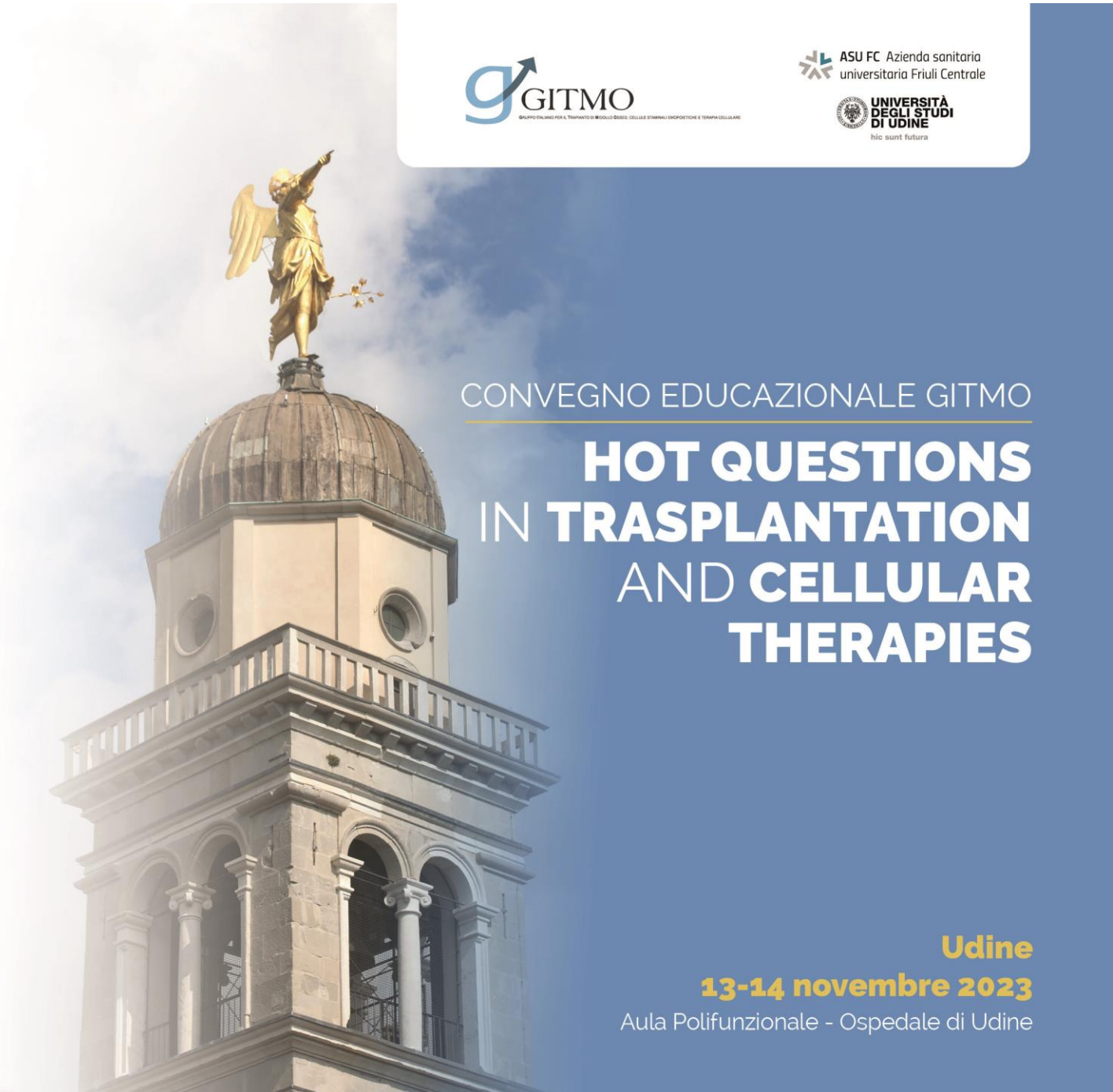
La terapia cellulare CAR-T è più efficace del trapianto autologo nella terapia di 2L dei DLBCL ricaduti precocemente?

Le ragioni del sì.

Francesco Zaja

UNIVERSITÀ DEGLI STUDI DI TRIESTE



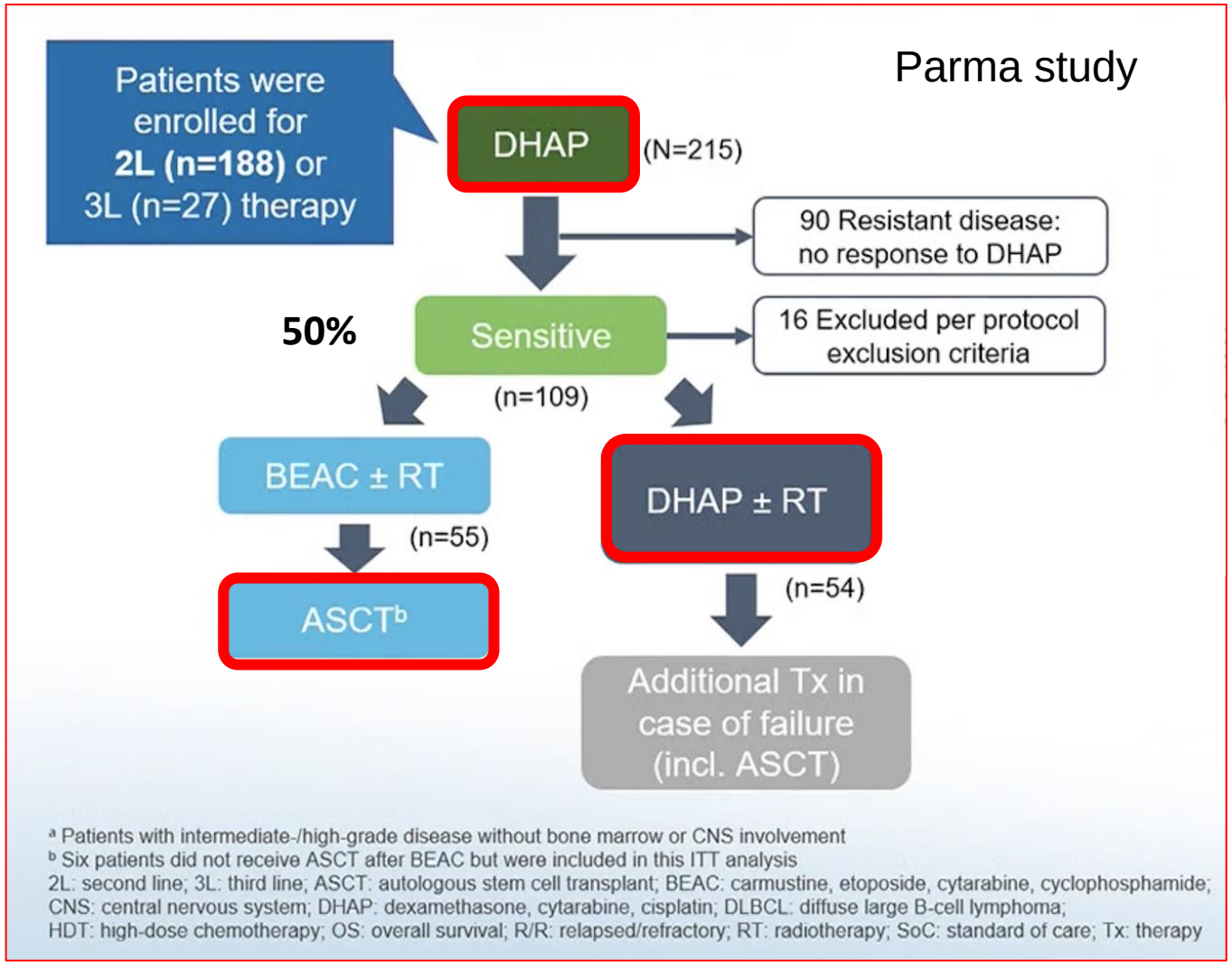
DISCLOSURES: overall

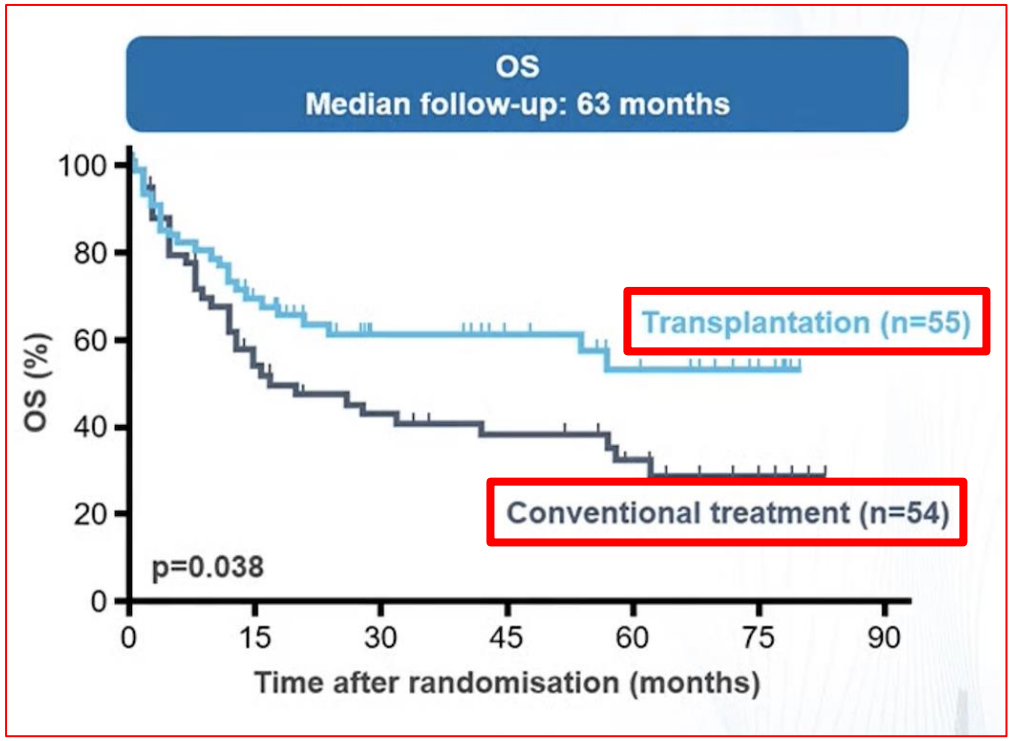
Consultancy: Novartis, Abbvie, Amgen, Sobi, Argenx, Grifols

Honoraria: Celgene, Janssen, Gilead, Novartis, Roche, Amgen, Abbvie, Grifols

Research funding: Abbvie, Novartis, Celgene, Janssen

La 2ª linea nei DLBCL in era pre-Rituximab: ASCT standard of care

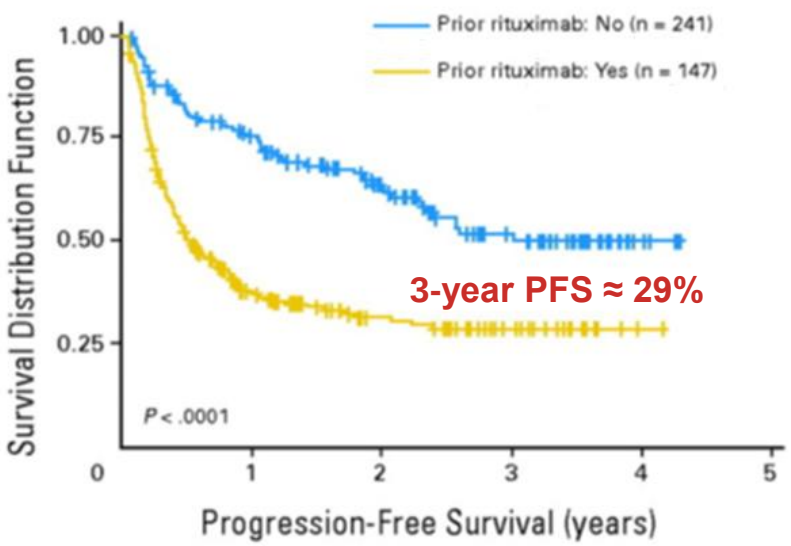




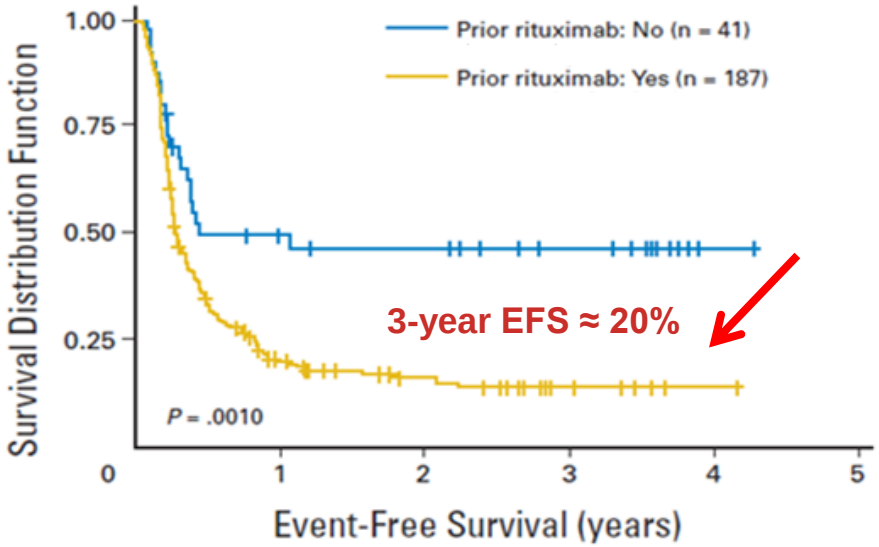
Philip T et al. NEJM 1995;333:1540-1545

Diminishing role of AutoSCT R/R patients in TE in the Rituximab era: CORAL study

HD chemo + autoSCT: all patients (intent to treat)



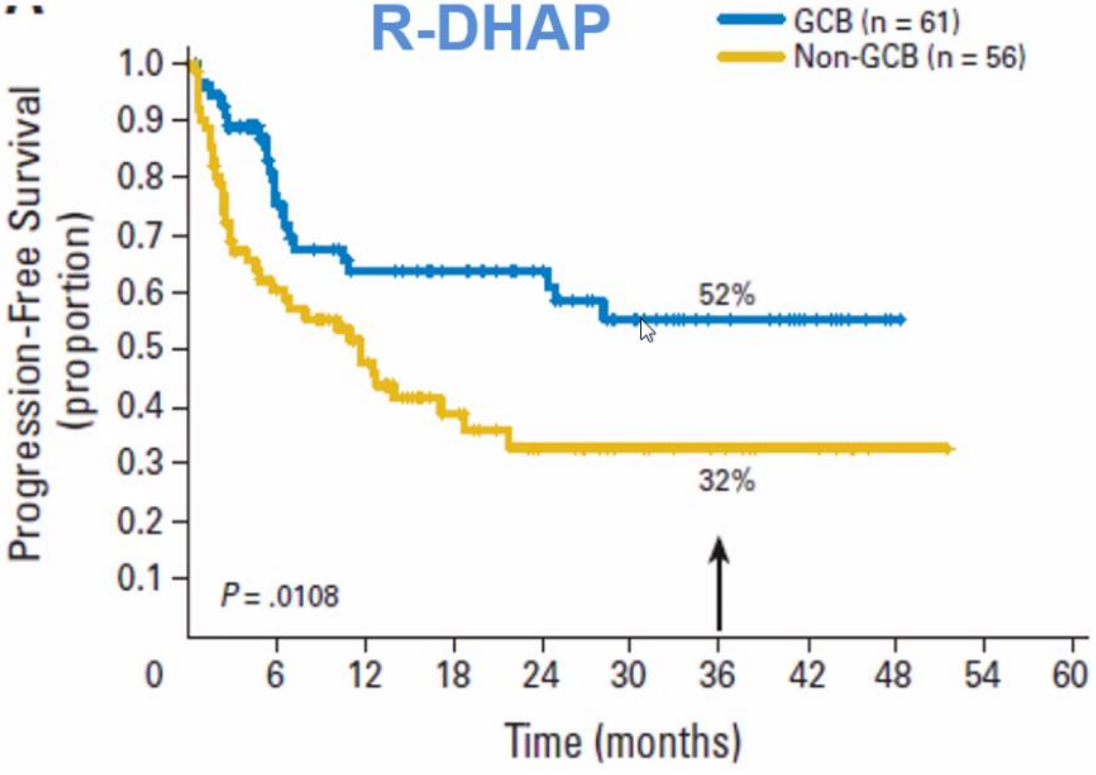
EFS for rituximab treatment + relapse <12 months after diagnosis

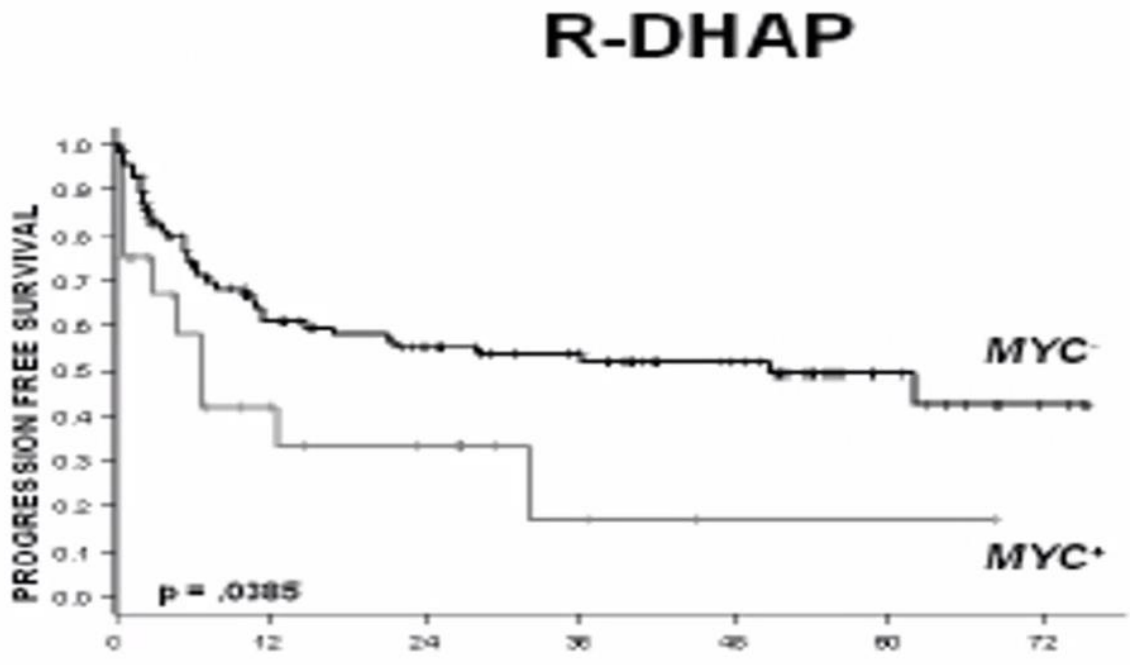


Gisselbrecht C., et al. J Clin Oncol. 2010;28:4184–90

Prognostic factors RR/DLBCL: Bio-CORAL trial experience

COO and MYC+ influence PFS at relapse according to second-line treatment for DLBCL





Thieblemont C et al, J Clin Oncol 2011

Pivotal Anti-CD19 CAR T-Cell Therapy Trials

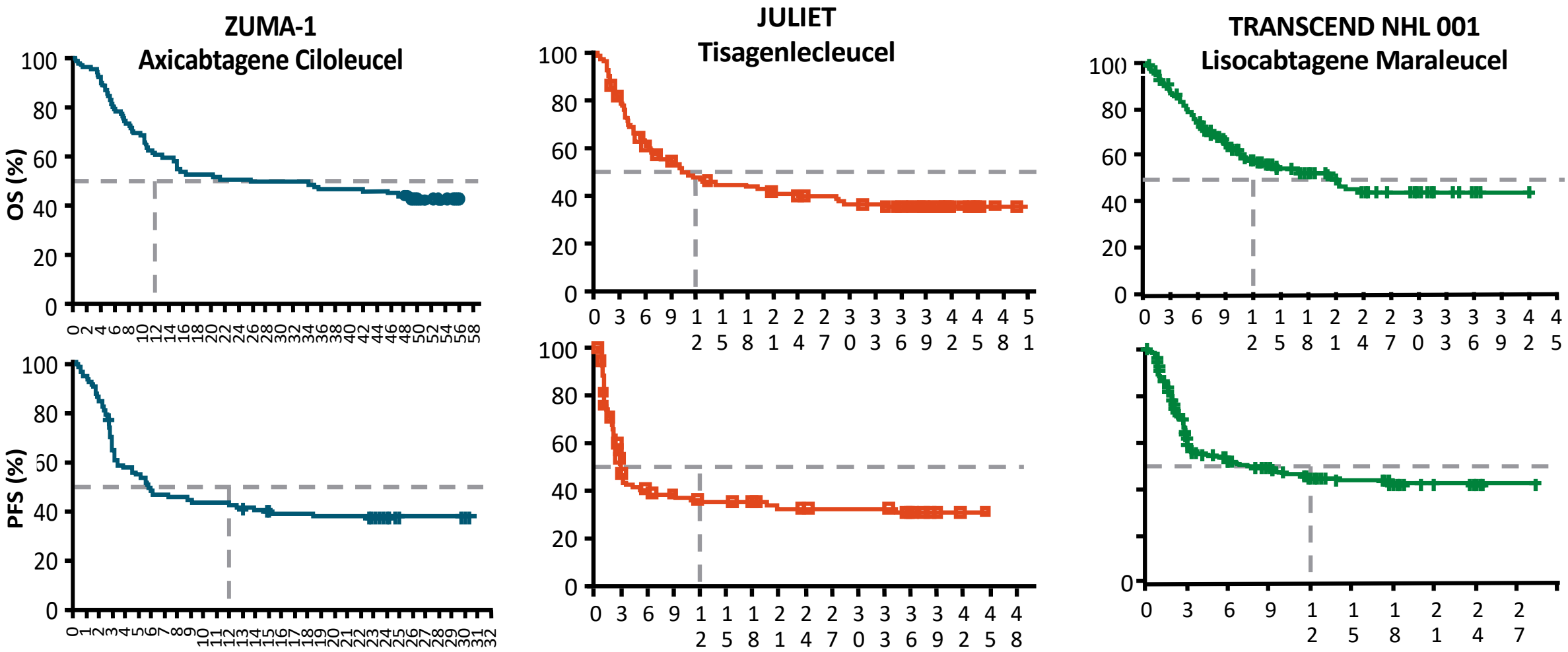
	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6 to 6.0 x 10^8/kg	50 to 150 x 10^6
Lymphodepletion	Flu/Cy 30/500 x 3 days	Flu/Cy 25/250 x 3 days, or bendamustine x 2 days	Flu/Cy 30/300 x 3 days

	ZUMA-1[1,2]	JULIET[3]	TRANSCEND NHL 001[4]
Study phase	II	II	I
Patient population	Adults with refractory DLBCL	Adults with R/R DLBCL	Adults with R/R DLBCL
Apheresed/treated, n	111/101	165/111	344/269^
Bridging therapy	None allowed in pivotal trial	92%	59%
ORR/CR, %	82/54%	52/40%	73/53%
Grade ≥ 3 CRS, %	13†	22*	2†
Grade ≥ 3 NT, %	28	12	10

^256 included in the efficacy-evaluable set.
*Per Penn scale. †Per Lee Scale.

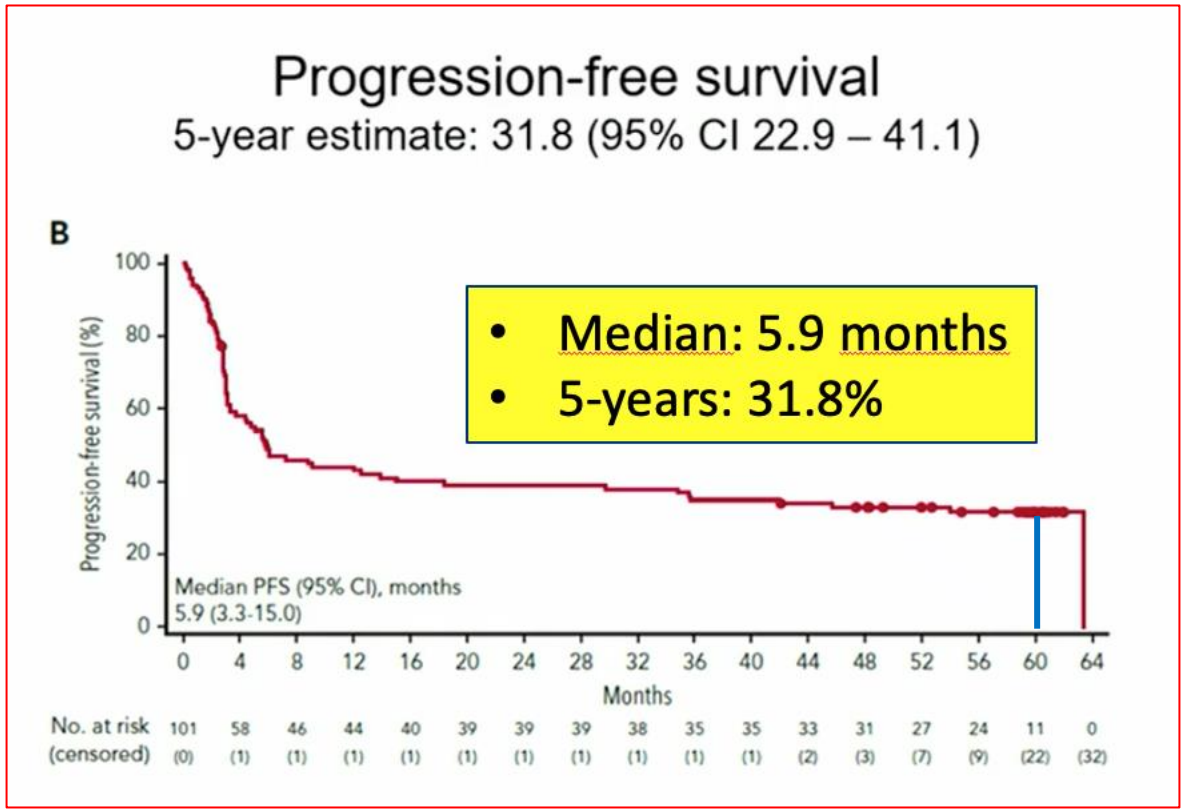
1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

Pivotal Anti-CD19 CAR T-Cell Therapy Trials

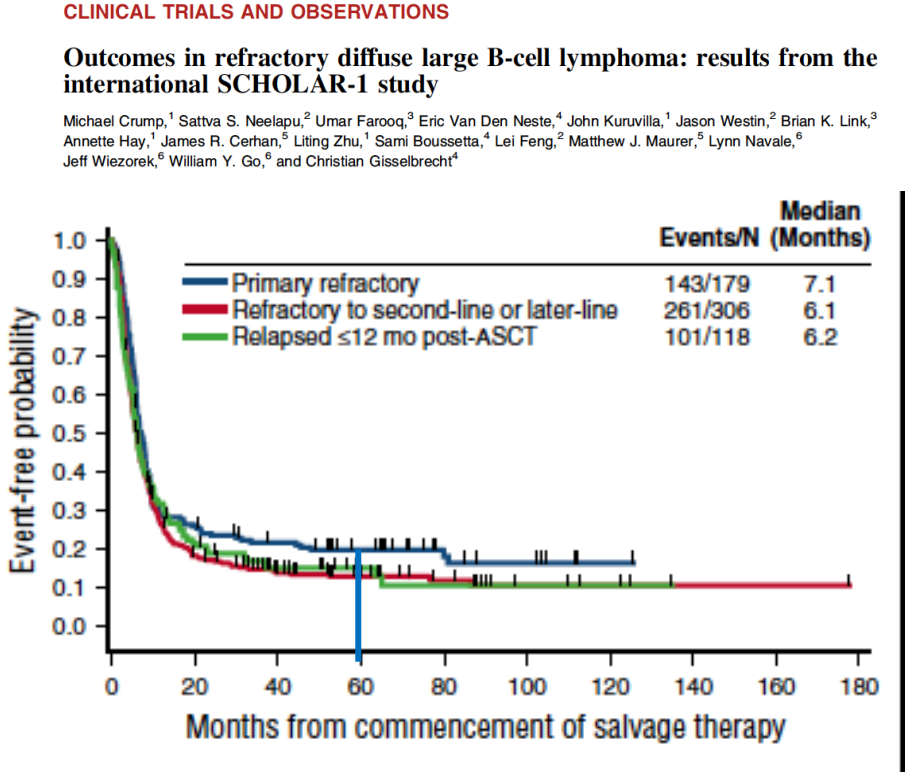


1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Schuster. NEJM. 2019;380:45. 4. Abramson. Lancet. 2020;396:839.

ZUMA-1 (Axi-Cel): 5-year follow-up



Neelapu SS et al, Blood 2023



CD19 CAR T versus ASCT in DLBCL patients at 1st treatment failure after R-CHOP (or equivalent)

Axi-cel	**ZUMA-7**
Liso-cel	**TRANSFORM**
Tisa-cel	**BELINDA**

NCT03391466; NCT03575351; NCT03570892

Differences exist:

- Inclusion criteria (histological subtypes, primary refractoriness definition…)
- **Bridging allowed before CAR T**
- Nb of chemo cycles in SOC arm
- **Product and LD therapy**
- Timing of response/events assessment
- Precise definition of events (EFS)
- Cross over planned / optional
- CAR T manufacturing time in SOC arm

Primary endpoint: Event Free Survival

The NEW ENGLAND JOURNAL of MEDICINE

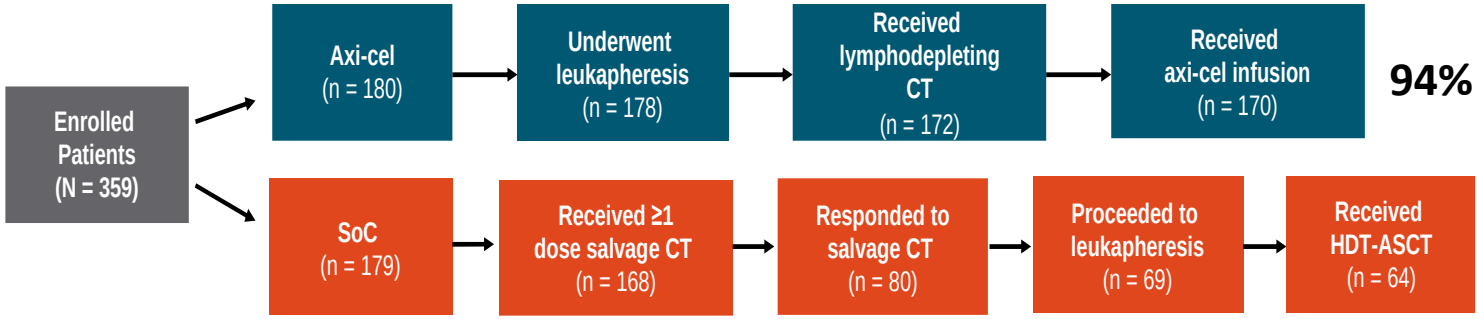
ORIGINAL ARTICLE

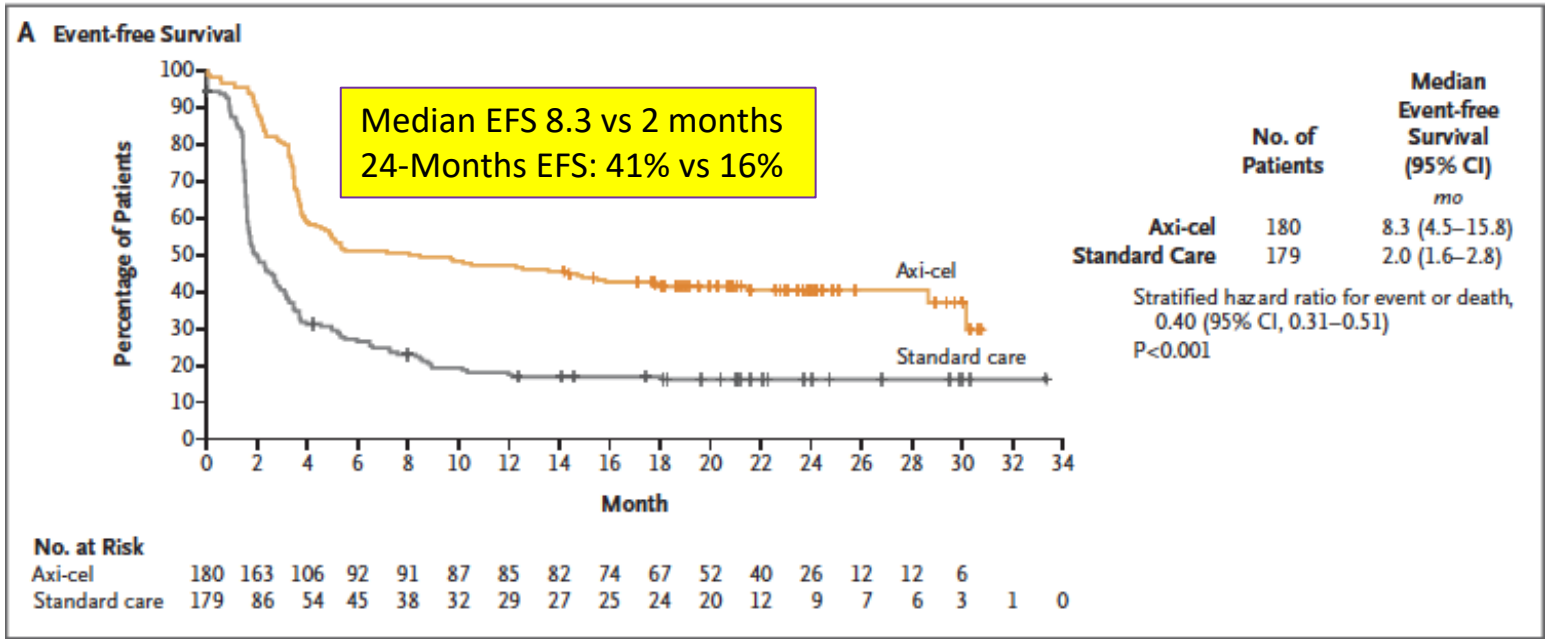
Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jacobson, M.-A. Perales, M.-J. Kersten, O.O. Oluwole, A. Ghobadi, A.P. Rapoport, J. McGuirk, J.M. Pagel, J. Muñoz, U. Farooq, T. van Meerten, P.M. Reagan, A. Sureda, I.W. Flinn, P. Vandenberghe, K.W. Song, M. Dickinson, M.C. Minnema, P.A. Riedell, L.A. Leslie, S. Chaganti, Y. Yang, S. Filosto, J. Shah, M. Schupp, C. To, P. Cheng, L.I. Gordon, and J.R. Westin, for All ZUMA-7 Investigators and Contributing Kite Members*

ZUMA-7:

Phase 3 Randomized Trial of Axi-cel vs. Standard-Of-Care





Locke FL, et al. NEJM 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

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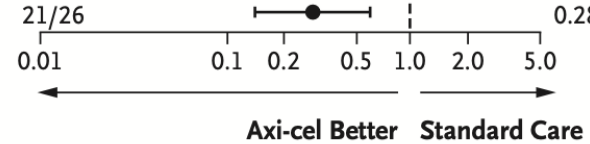
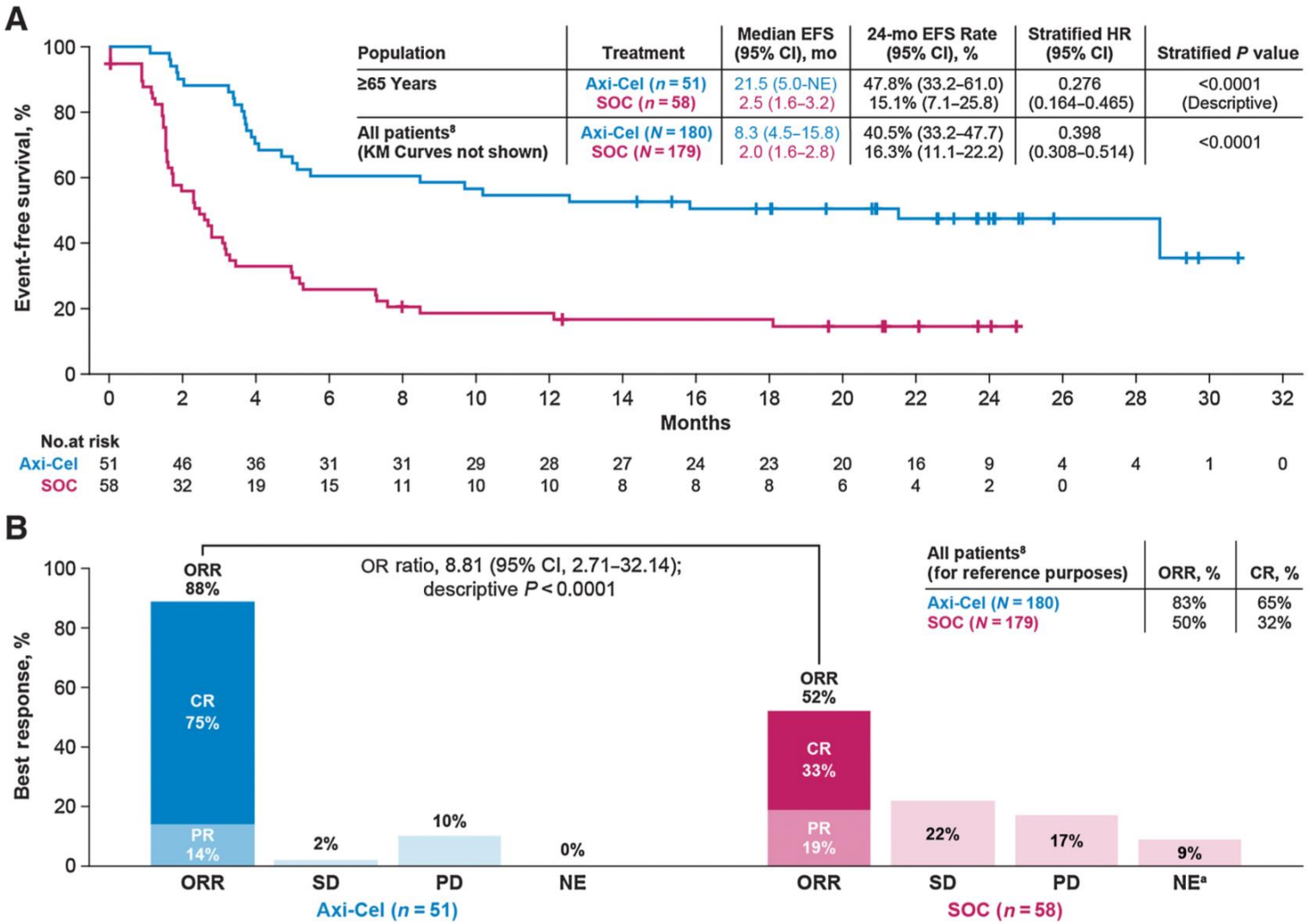
B Subgroup Analysis

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)



Safety and Efficacy of Axicabtagene Ciloleucel versus Standard of Care in Patients 65 Years of Age or Older with Relapsed/Refractory Large B-Cell Lymphoma



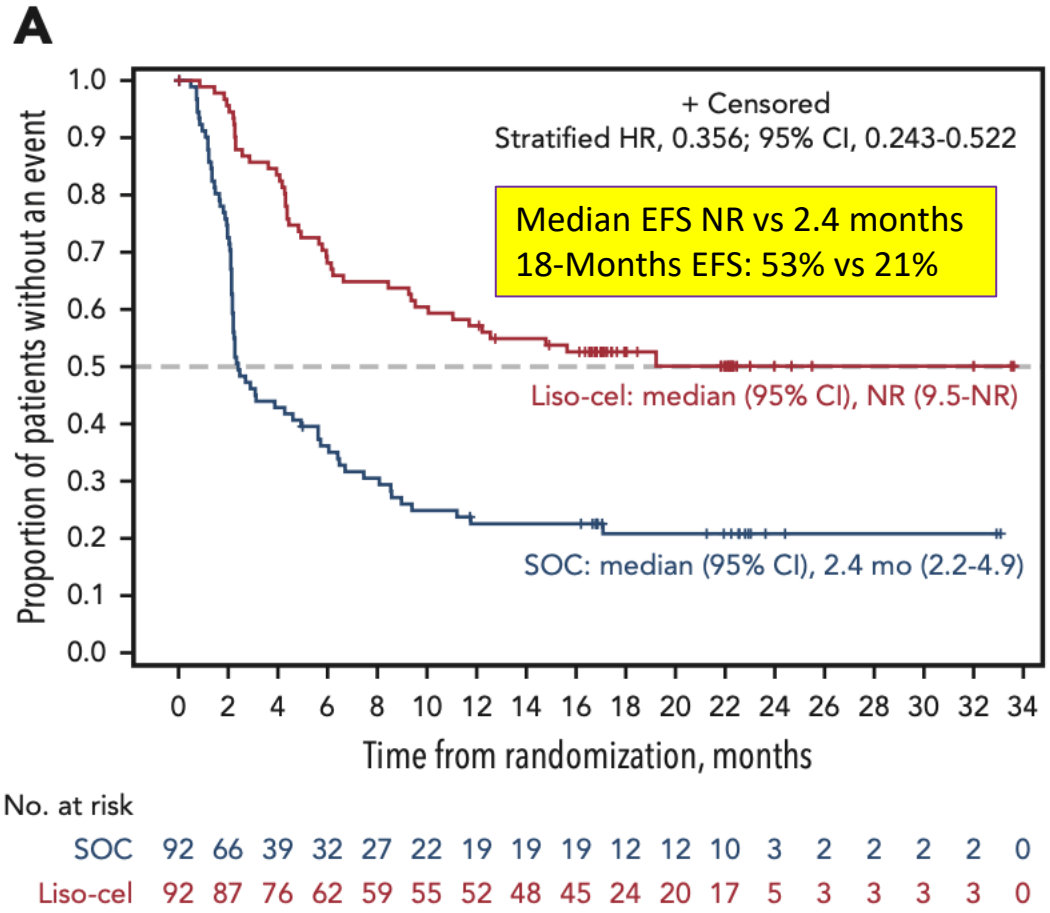
Westin et al 2023

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study

Jeremy S. Abramson,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami Ibrahimi,[7] Stephan Mielke,[8] Pim Mutsaers,[9] Francisco Hernandez-Ilizaliturri,[10] Koji Izutsu,[11] Franck Morschhauser,[12] Matthew Lunning,[13] Alessandro Crotta,[14] Sandrine Montheard,[14] Alessandro Previtali,[14] Ken Ogasawara,[15] and Manali Kamdar,[16] for the TRANSFORM Investigators

TRANSFORM:

Phase 3 Randomized Trial of Liso-cel vs. Standard-Of-Care



Abramson, et al. Blood 2023

The NEW ENGLAND JOURNAL of MEDICINE

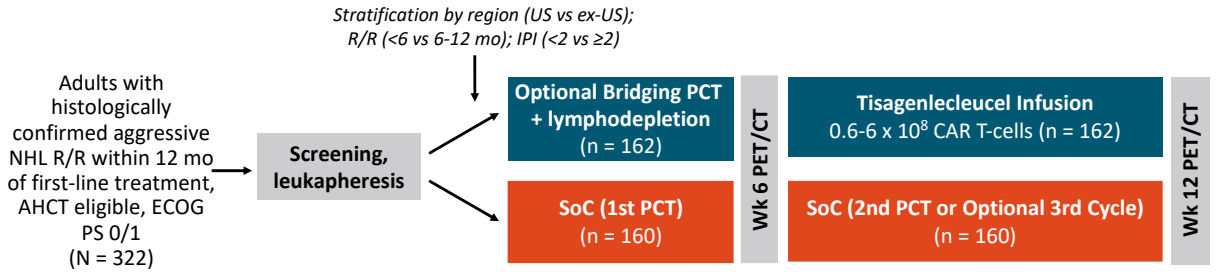
ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

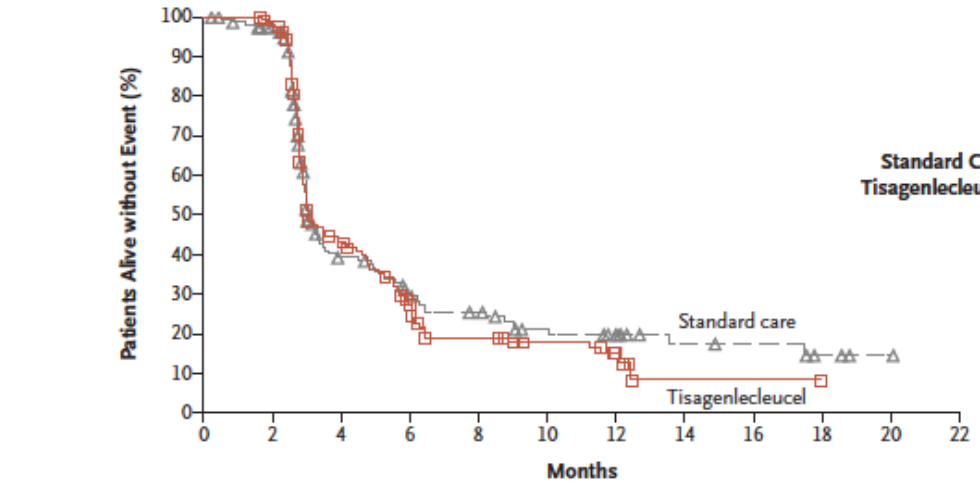
M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

BELINDA:

Phase 3 Randomized Trial of Tisa-cel vs. Standard-Of-Care



SoC arm received first PCT + AHCT for responders or second PCT for nonresponders, based on Wk 6 assessment. Crossover to tisagenlecleucel permitted for SoC at Wk 12 for nonresponders. Patients assessed at Wk 6 and 12, then 3-monthly to Mo 12, 6-monthly to Mo 24, and yearly to Mo 60.



	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

Bishop MR, et al. NEJM 2021

CAR T-cell therapy vs. SoC in 2L DLBCL - Safety

	ZUMA-7[1,2]		TRANSFORM[3]		BELINDA[4,5]	
	SoC	Axi-Cel	SoC	Liso-Cel	SoC	Tisa-Cel
N	168	170	91	92	160	162
Grade 3–5 AEs	83%	91%	87%	92%	84%	90%
Grade 3–5 haematological toxicity						
Anaemia	39%	30%	49%	49%	57%	33%
Thrombocytopenia	57%	15%	64%	49%	47%	32%
Neutropenia	41%	69%	51%	80%	39%	40%
Febrile neutropenia	27%	2%	24%	15%	25%	13%
Grade 3–5 infections	11%	14%	21%	15%	15%	17%
Prolonged cytopenias	19%	29%	3%	43%	N/A	N/A
CRS						
Grade 1–2	---	86%	---	48%	---	53.7%
Grade 3–5	---	6%	---	1%[b]	---	4.9%
Onset / Duration (median)	---	3 / 7 d	---	5 / 4 d	---	N/A
Neurological events						
Grade 1–2	19%	39%	---	7%	---	8.4%
Grade 3–5	1%	21%	---	4%	---	1.9%
Onset / Duration (median)	23 / 23 d	7 / 9 d	---	11 / 6 d	---	N/A
Toxic deaths (due to AEs)	**2 (1%)**	**7[a] (4%)**	2 (2%)	1 (1%)	**13 (8.1%)**	**10 (6.2%)**

Cross-study comparisons cannot be made due to differences in study designs, endpoint definitions and patient populations

[a] Only 1 related to CAR T; [b] No case Grades 4–5 AE: adverse event; CRS: cytokine release syndrome

1. Locke FL, *et al.* ASH 2021 (Abstract 2). 2. Locke FL, *et al. N Engl J Med* 2022. 3. Abramson R, et al. Blood 2022. 4. Bishop MR, *et al.* ASH 2021 (Abstract LBA6). 5. Bishop MR, *et al. N Engl J Med* 2022.

Caratteristiche pazienti	ZUMA-7 CAR-T arm	BELINDA CAR-T arm	TRANSFORM CAR-T arm
Pazienti	180	162	92
Età mediana	58	59.5	60
≥ 65 anni (%)	**28 (- anziani)**	33	39
PS ECOG 1 (%)	47	43	48
IPI ≥2 (%)	46	**65 (+ HR)**	39
Refractory (%)	74	66	73
	ZUMA-7 ASCT arm	**BELINDA ASCT arm**	**TRANSFORM ASCT arm**
Pazienti	179	160	92
Età mediana	60	58	58
≥ 65 anni (%)	32	29	27
PS ECOG 1 (%)	44	41	38
IPI ≥2 (%)	44	**58 (+ HR)**	40
Refractory (%)	73	67	74

Caratteristiche malattia	ZUMA-7 CAR-T arm	BELINDA CAR-T arm	TRANSFORM CAR-T arm
Pazienti	180	162	92
DLBCL (%) HGBCL (%) HGBCL including DHIT (%) Missing/other	70 0 17 13	62 4 20 14	58 / 24 18
GCB (%) ABC (%) Unclassified (%) Missing/NA (%)	61 9 (- ABC) 9 22	28 32 2 38	49 23 27 1
	ZUMA-7 ASCT arm	BELINDA ASCT arm	TRANSFORM ASCT arm
Pazienti	179	160	92
DLBCL (%) HGBCL (%) HGBCL including DHIT (%) Missing/other	67 1 14 19	70 5 12 13	53 / 23 24
GCB (%) ABC (%) Unclassified (%) Missing/NA (%)	55 5 (-ABC) 8 32	39 26 4 31	43 32 25 /

Study design	ZUMA-7 CAR-T arm	BELINDA CAR-T arm	TRANSFORM CAR-T arm
Inclusion criteria	• LBCL • refractory or relapsed within 12 months of 1L therapy • transplant-eligible	• LBCL • **PMBCL** • **FOL 3B** • refractory or relapsed within 12 months of 1L therapy • transplant-eligible	• LBCL • **PMBCL** • **FOL 3B** • refractory or relapsed within 12 months of 1L therapy • transplant-eligible
Primary endpoint	EFS **SD considered event at week 21**	EFS SD considered event at week 12 ***PET scan at 6 weeks*** *(that did not count as an event but might have affected clinical decision making)*	EFS SD considered event at week 9
Need for urgent therapy	**Excluded**	Included	Included
Bridging therapy	**Only steroids**	Allowed	Allowed
Control arm salvage therapy	**Only 1L allowed**	**Up to 2 lines allowed**	**Up to 2 lines allowed**

Differences in the 3 studies that may have impacted the outcomes

Study design	ZUMA-7 CAR-T arm	BELINDA CAR-T arm	TRANSFORM CAR-T arm
Definition of EFS	pro	**cons**	pro
Pathologic characteristics	More GCB	**More ABC**	More ABC and HGBCL
HR IPI distributon		**Higher IPI ≥2**	
Median time from randomization to infusion:	**29 days** (IQR, 27 to 34 days)		34 days (IQR, 31 to 36 days)
Median time from leukapheresis to infusion:		**52 days (IQR, 43 to 61 days)** US: 41 days Non-US: 57 days	36 days (IQR, 34 to 41 days)
Bridging therapy	Only steroids	1 cycle: 36% **>1 cycle: 48%**	1 cycle: 58% > 1cycle: 5%

Role of CD19 Chimeric Antigen Receptor T Cells in Second-Line Large B Cell Lymphoma: Lessons from Phase 3 Trials. An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy

Miguel-Angel Perales[1,2,*], Larry D. Anderson Jr[3], Tania Jain[4], Saad S. Kenderian[5], Olalekan O. Oluwole[6], Gunjan L. Shah[1,2], Jakub Svoboda[7], Mehdi Hamadani[8]

Trial	ZUMA-7		BELINDA		TRANSFORM	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
No. of patients	180	179	162	160	92	92
Patient disposition						
CAR T infusion, %	94	N/A	96	N/A	98	N/A
Bridging, %	36*	N/A	83	N/A	63	N/A
1 cycle	N/A	N/A	36	N/A	58	N/A
>1 cycle	N/A	N/A	48	N/A	5	N/A
Median days to infusion†	29	N/A	52	N/A	34	N/A
Auto-HCT, %	N/A	36	N/A	33	N/A	47
Crossover to CAR T cell therapy, %	N/A	56	N/A	51	N/A	55

Transplantation and Cellular Therapy 28 (2022) 546559

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Trial	ZUMA-7		BELINDA		TRANSFORM	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
No. of patients	180	179	162	160	92	92
Patient disposition						
CAR T infusion, %	94	N/A	96	N/A	98	N/A
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1 cycle	N/A	N/A	36	N/A	58	N/A
>1 cycle	N/A	N/A	48	N/A	5	N/A
Median days to infusion†	29	N/A	52	N/A	34	N/A
Auto-HCT, %	N/A	36	N/A	33	N/A	47
Crossover to CAR T cell therapy, %	N/A	56	N/A	51	N/A	55

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Trial	ZUMA-7		BELINDA		TRANSFORM	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
No. of patients	180	179	162	160	92	92
Patient disposition						
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1 cycle	N/A	N/A	36	N/A	58	N/A
>1 cycle	N/A	N/A	48	N/A	5	N/A
Median days to infusion†	29	N/A	52	N/A	34	N/A
Auto-HCT, %	N/A	36	N/A	33	N/A	47
Crossover to CAR T cell therapy, %	N/A	56	N/A	51	N/A	55

*only steroids

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Role of CD19 Chimeric Antigen Receptor T Cells in Second-Line Large B Cell Lymphoma: Lessons from Phase 3 Trials. An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy

Miguel-Angel Perales[1,2,*], Larry D. Anderson Jr[3], Tania Jain[4], Saad S. Kenderian[5], Olalekan O. Oluwole[6], Gunjan L. Shah[1,2], Jakub Svoboda[7], Mehdi Hamadani[8]

Trial	ZUMA-7		BELINDA		TRANSFORM	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
No. of patients	180	179	162	160	92	92
Patient disposition						
CAR T infusion, %	94	N/A	96	N/A	98	N/A
Bridging, %	36*	N/A	83	N/A	63	N/A
1 cycle	N/A	N/A	36	N/A	58	N/A
>1 cycle	N/A	N/A	48	N/A	5	N/A
Median days to infusion†	29	N/A	52	N/A	34	N/A
Auto-HCT, %	N/A	36	N/A	33	N/A	47
Crossover to CAR T cell therapy, %	N/A	56	N/A	51	N/A	55

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Possible bias of the Tisa cell arm of the BELINDA trial

Progressive disease on PET scan:

- Tisa-cel arm: 26% (impact of the long time before receiving Tisa-cel)
- > 1 cycle bridging therapy (48%)

In BELINDA, response rates (ORR and CR) with Tisa-cel resulted lower than expected

- BELINDA: ORR: 46%; CR: 28%
- JULIET: ORR: 52%; CR 40%

Comparing apples and oranges: The ZUMA-7, TRANSFORM and BELINDA trials

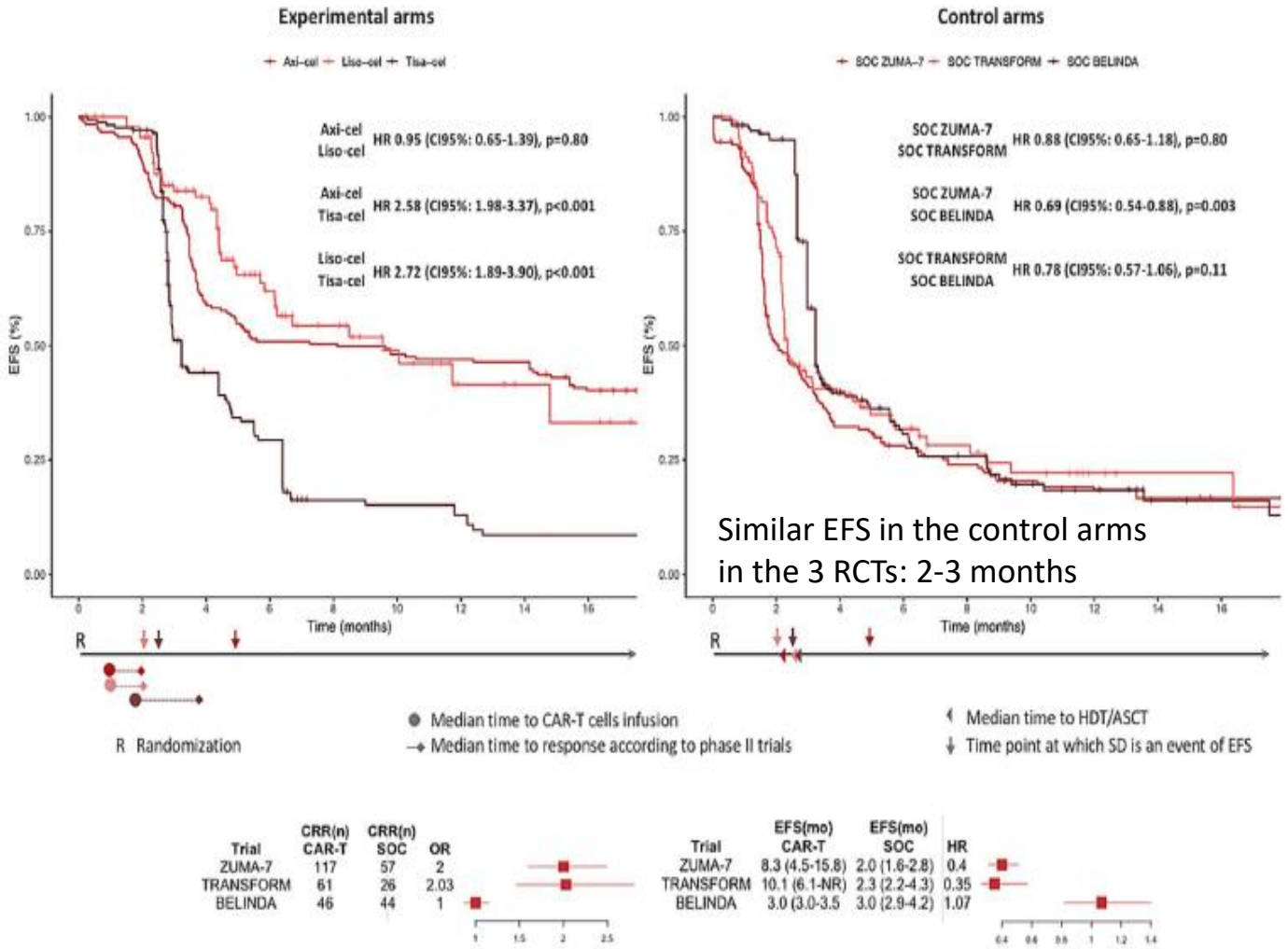
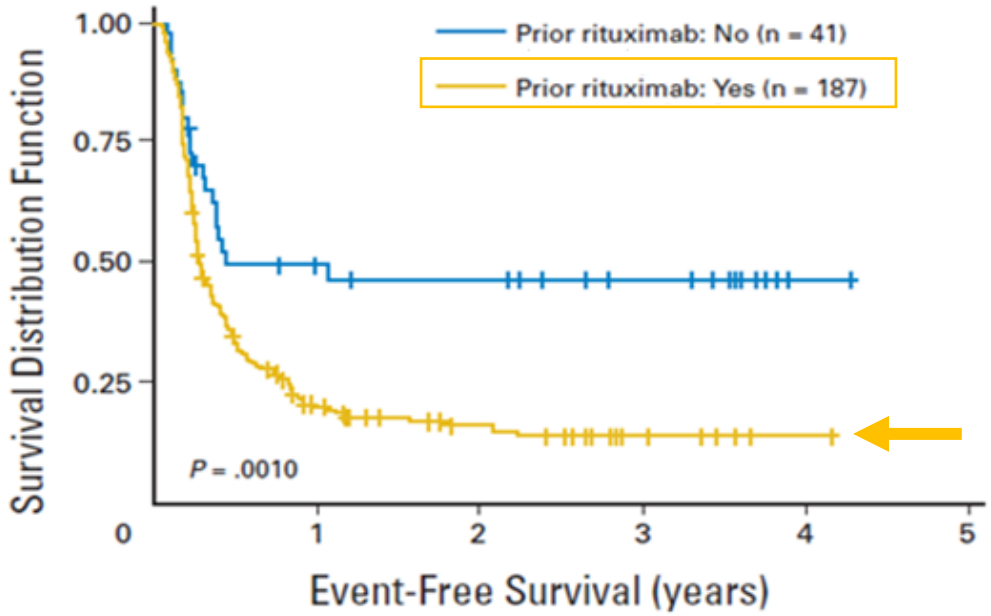


FIGURE 1 Reconstructed Event-Free Survival (EFS) curves and Forest plots showing EFS hazard ratio (HR) and complete response rate (CRR) odds ratio in the three trials. EFS: event-free survival, high dose therapy (HDT)/ASCT: HDT/autologous stem cell transplant (ASCT), SD: stable disease, HR: hazard ratio, CI: confidence interval, CRR: complete response rate, OR: odds ratio

CORAL strudy: EFS for rituximab treatment + relapse <12 months after diagnosis



Bommier C, et al. Hematol Oncol 2022; Gisselbrecht C. JCO 2010

How to approach patients who started salvage therapy and have a response ?

- high-dose therapy and auto-HCT consolidation is curative for approximately 45% of patients with DLBCL despite achieving only a PR after salvage therapy.
- no alternative consolidation strategy (including CAR T cell therapy) has been proven superior to auto-HCT consolidation in patients with DLBCL
- cost considerations may favor auto- HCT
- although CAR T cell therapy can salvage patients who relapse after auto-HCT, the reverse sequence often is not feasible

Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission

- CIBMTR registry database
- adult patients with DLBCL who received either an auto-HCT (266 patients; 2013-2019) or CAR-T treatment with axi-cel (145 patients; 2018-2019) while in a PR by CT-PET
- Median lines of therapy before auto-HCT vs CAR-T: 2 (1-6) vs 3 (2-11) ($p < 0.001$)
- > 2 lines of therapy before auto-HCT vs CAR-T: 33% vs 67% ($p < 0.001$)

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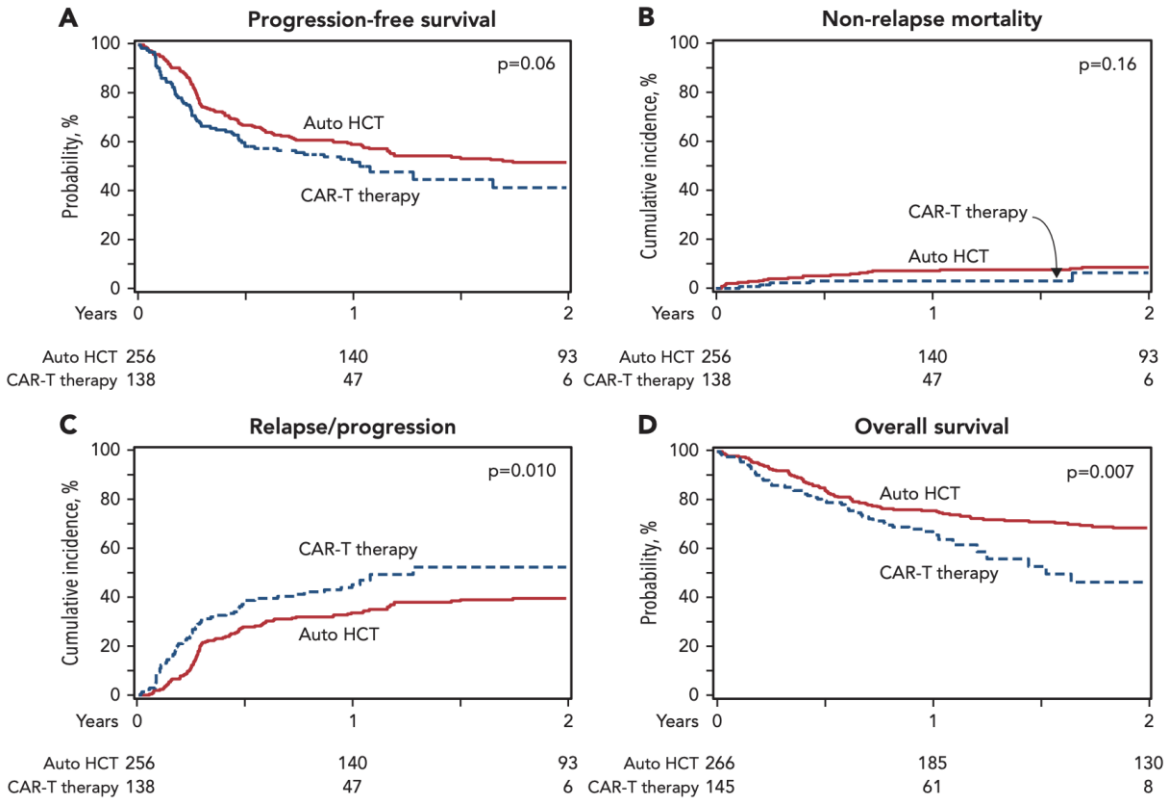
KEY POINTS

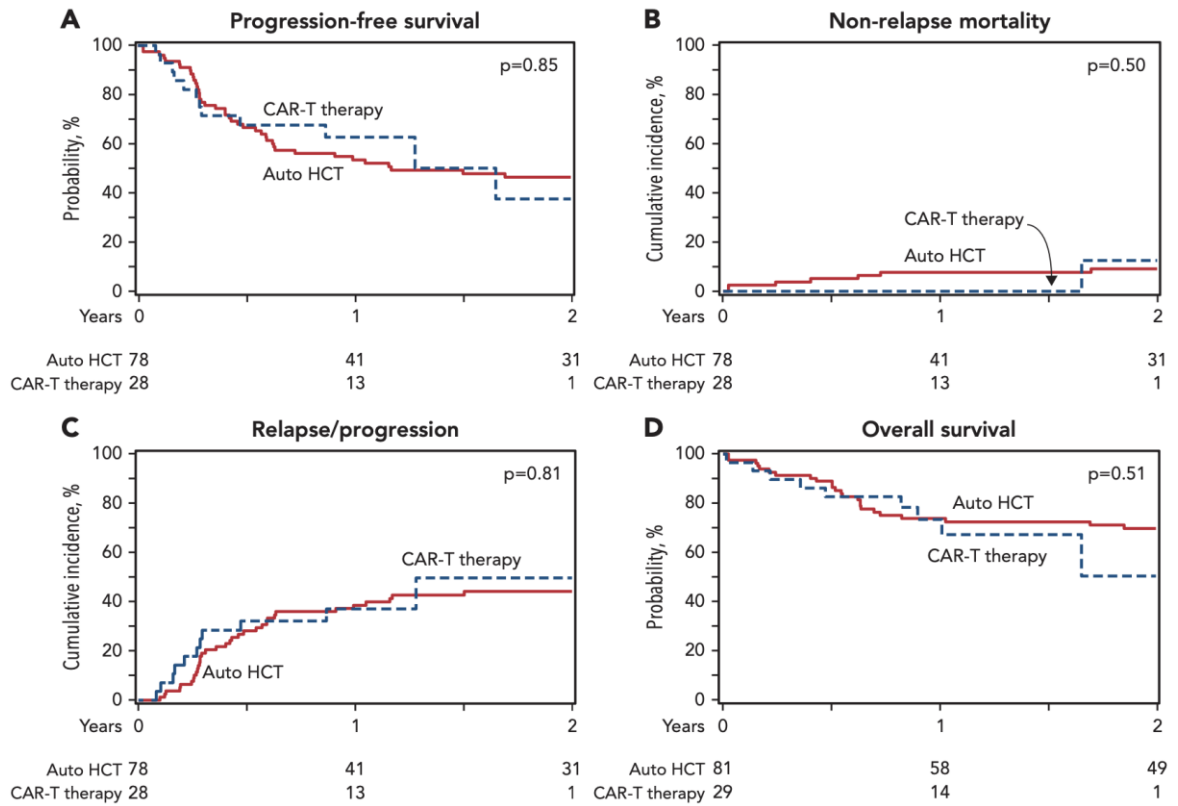
- In patients with DLBCL in PR postsalvage, auto-HCT and CAR-T gave 2-year progression-free survival (PFS) of 52% vs 42% and OS of 69% vs 47%.
- In patients with ≤2 prior lines of therapy, there was no difference in PFS or OS between the 2 groups.

Auto-HCT vs CAR-T in patients with DLBCL in PR

All patients



Patients with ≤ 2 prior lines of therapy



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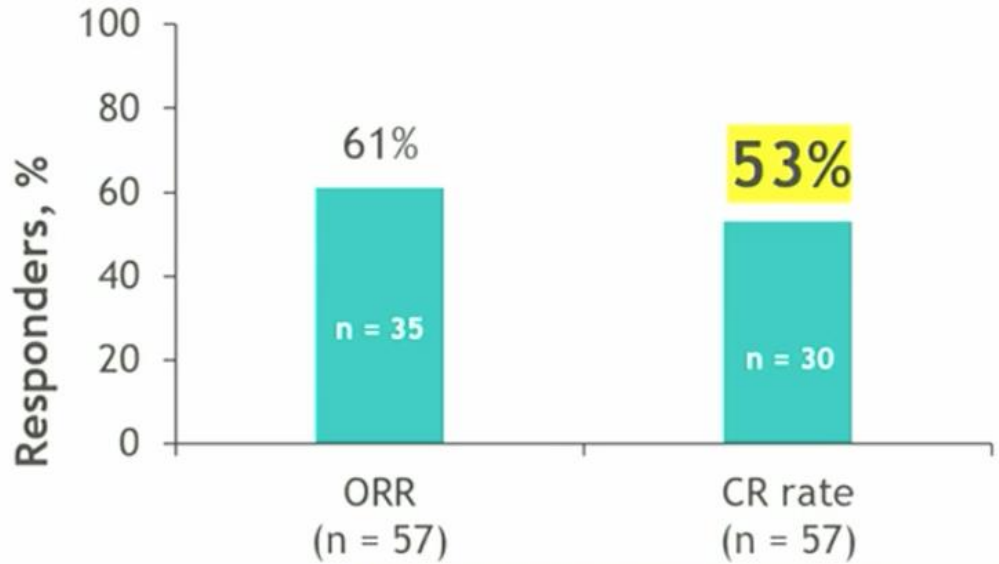
TRANSFORM: Efficacy outcomes in the crossover subgroup

Of 92 patients in the SOC group, 61 (66%) were approved for crossover to receive liso-cel

- 58 received CAR+ T cells (57 received liso-cel, 1 received nonconforming product)
- Median time from crossover approval to liso-cel infusion was 15 days (range, 8–95)



	Crossover subgroup (n = 57)[a]
Median (range) follow-up, months[b]	12.0 (1.4–28.1)
Median (95% CI) EFS, months[c]	5.9 (3.1–15.1)
Median (95% CI) PFS, months[c]	5.9 (3.2–26.5)
Median (95% CI) OS, months[c]	15.8 (11.8–NR)

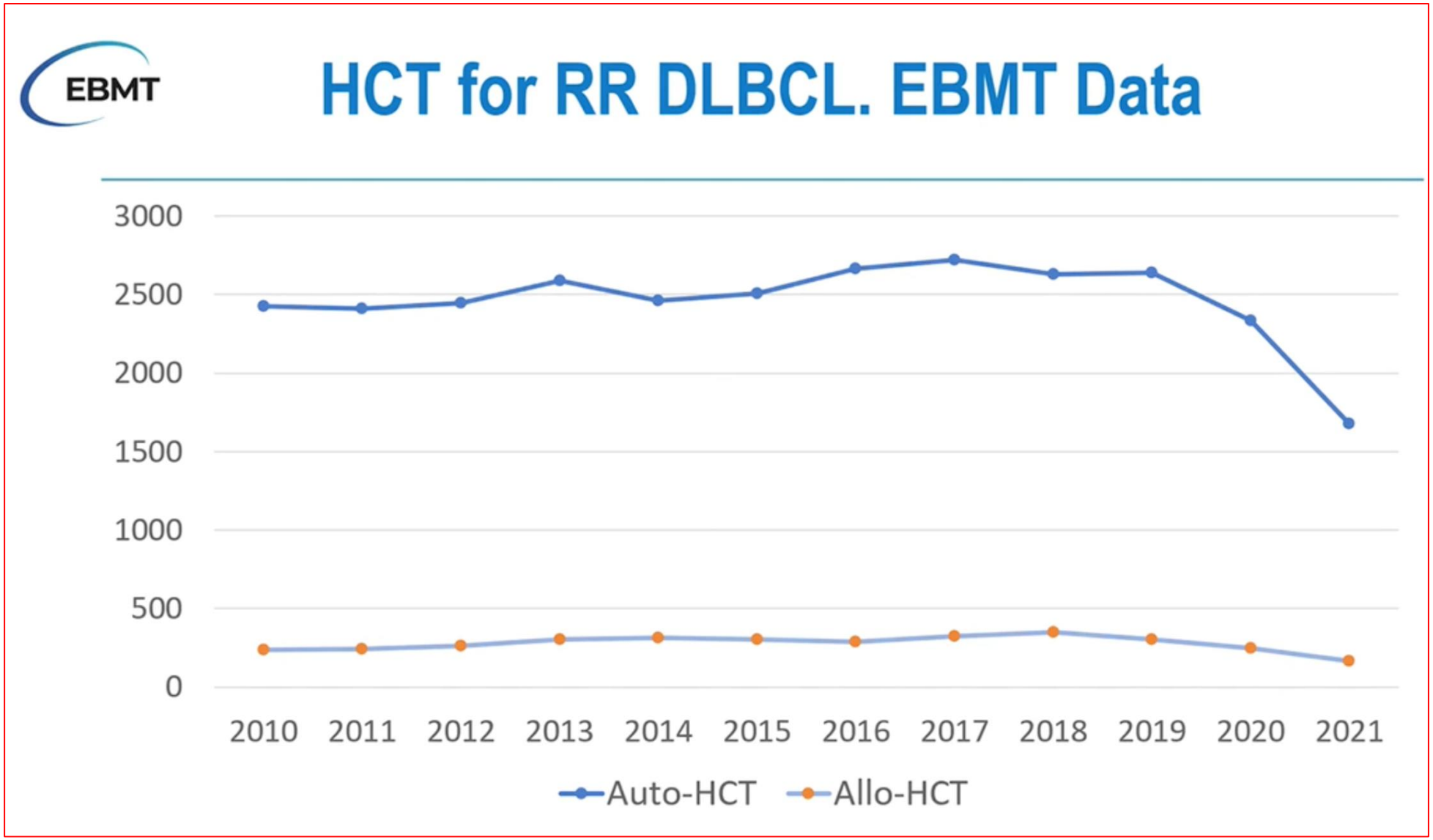
All endpoints were evaluated from the time of liso-cel infusion.

Compared to 74% CR rate in 2nd line (exp arm)

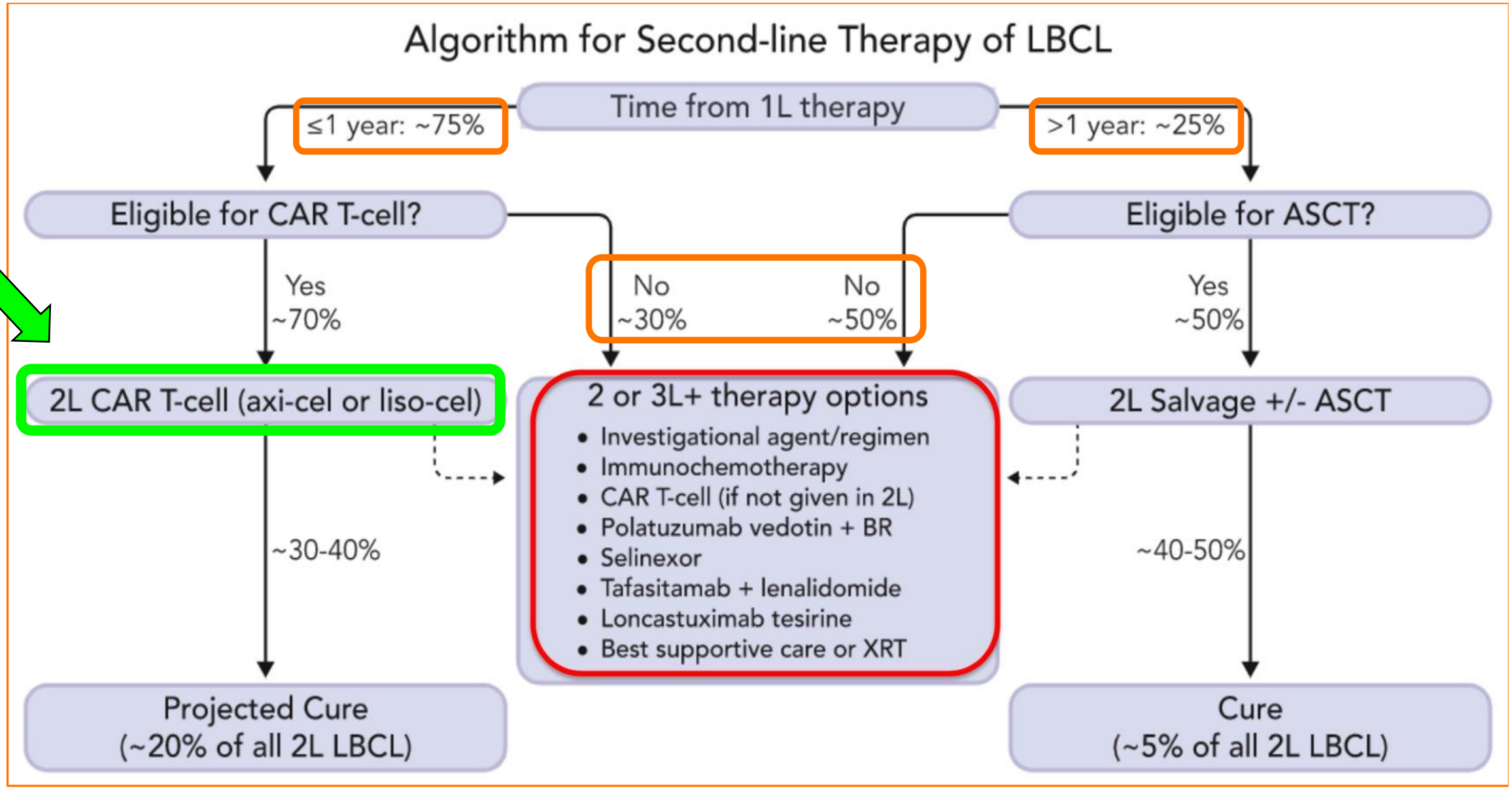
[a]Three patients approved for crossover who did not receive liso-cel and 1 patient who received nonconforming product were not included in the efficacy analyses; [b]Calculated for the 58 patients randomized to the SOC group who were approved for crossover and received CAR+ T cells; [c]Median estimates of time to event were Kaplan-Meier product-limit estimates.

Abramson JS, et al. ASH 2022 [Abstract #655]

La 2ª linea nei DLBCL: ruolo del ASCT ?



Data from EBMT Registry



Westin J, Blood 2022

Conclusioni

- La terapia di 2L nei pazienti giovani/fit viene data con **significato curativo**
- Nei pazienti con **DLBLC refrattari o ricaduti entro 12 mesi** dalla terapia di 1L e ritenuti **eleggibili al trapianto**, il trattamento di salvataggio con Axi-cel e Liso-Cel si è dimostrato globalmente superiore al trapianto autologo
- Le curve di EFS del braccio di controllo nei 3 studi sono risultate sovrapponibili; questo dato riflette lo scarso beneficio derivante dalla CIT di salvataggio
- Il trattamento di salvataggio con **Tisa-Cel** non si è dimostrato superiore al trapianto autologo; alcuni motivi legati al **disegno dello studio** possono almeno in parte essere responsabili del mancato raggiungimento dell'obiettivo
- Il reale impatto delle CAR-T vs autologo **nei pazienti responsivi alla terapia di salvataggio** rimane ancora da definire

Gazzetta Ufficiale del 11/11/2023

«Yescarta» e' indicato per il trattamento di pazienti adulti con linfoma diffuso a grandi cellule B (diffuse large B-cell lymphoma, DLBCL) e linfoma a cellule B ad alto grado (high-grade B cell lymphoma, HGBL) refrattario alla chemioimmunoterapia di prima linea o recidivante entro dodici mesi dal completamento della chemioimmunoterapia di prima linea».

Attribuzione del requisito dell'innovazione terapeutica.

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