GIORNATE EMATOLOGICHE VICENTINE

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DLBCL in seconda linea: ASCT vs CAR-T

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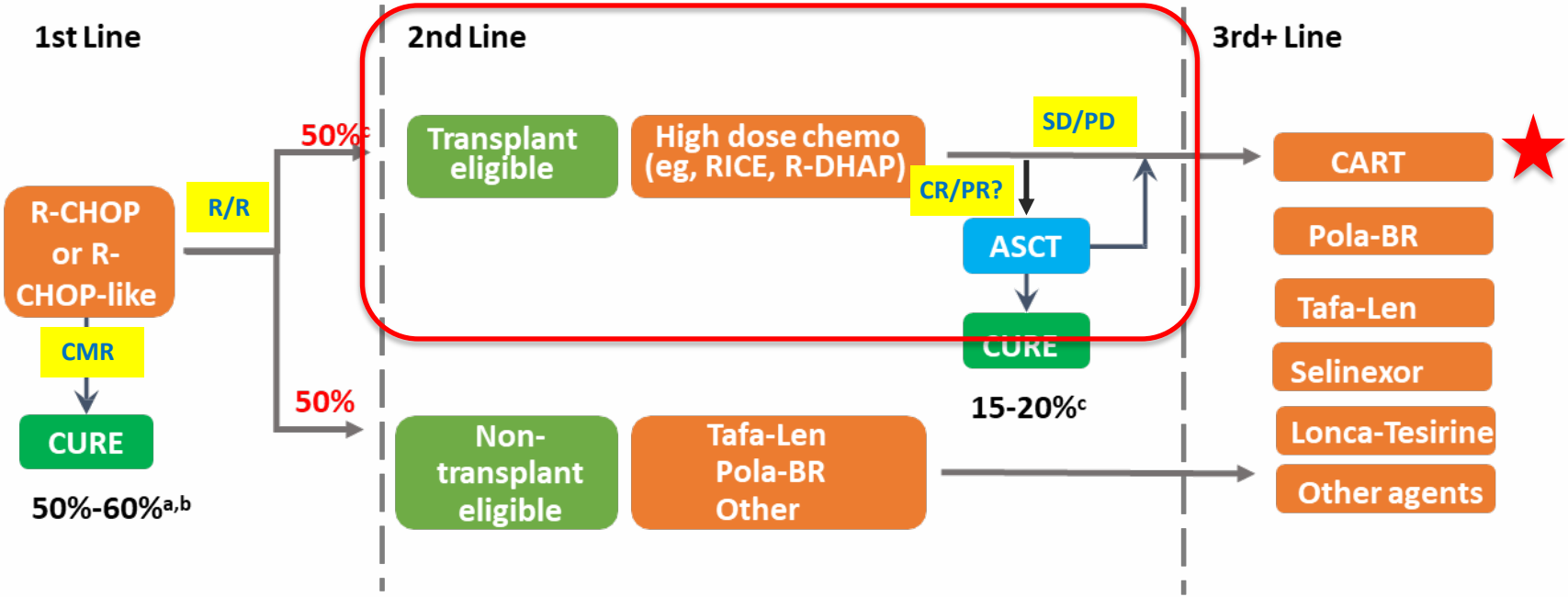
Disclosures of Alice Di Rocco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X		
Incyte							
Janssen					X	X	
Takeda			X			X	
Novartis	X				X	X	
Gilead			X		X	X	
Abbvie			X				
Eli-Lilly					X		
BMS						X	

Pattern of Care in DLBCL up to 2023



ASCT

The success of ASCT has always depended on the chemosensitivity of tumors

50% of R/R DLBCL patients are ineligible to HDT-ASCT

VS

CAR-T

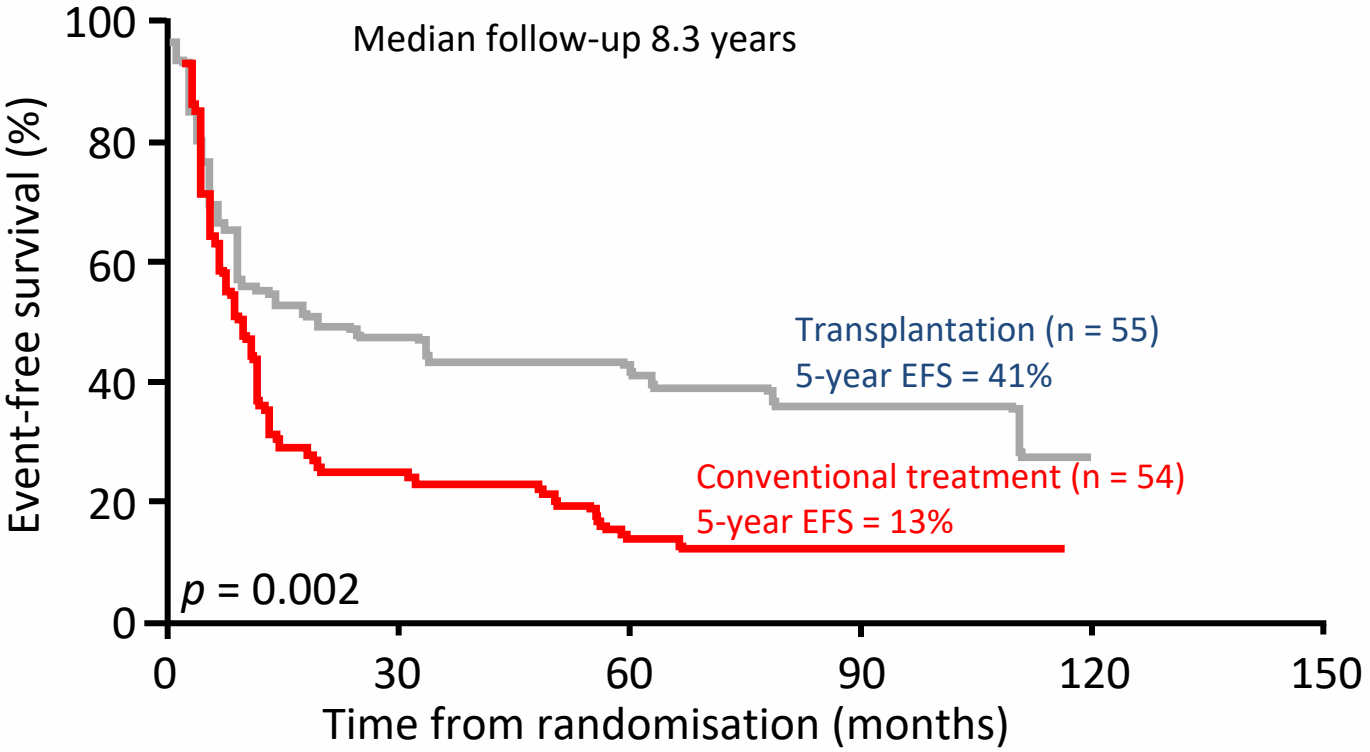
All three commercial CAR T-cell products for DLBCL induced unprecedented complete remission rates (30% to 50% of CR) in patients with predominantly chemorefractory DLBCL

Effective and safe even in ASCT ineligible patients

Who is the non responder patient?
How do we consider partial response?

PARMA study: relapsed DLBCL

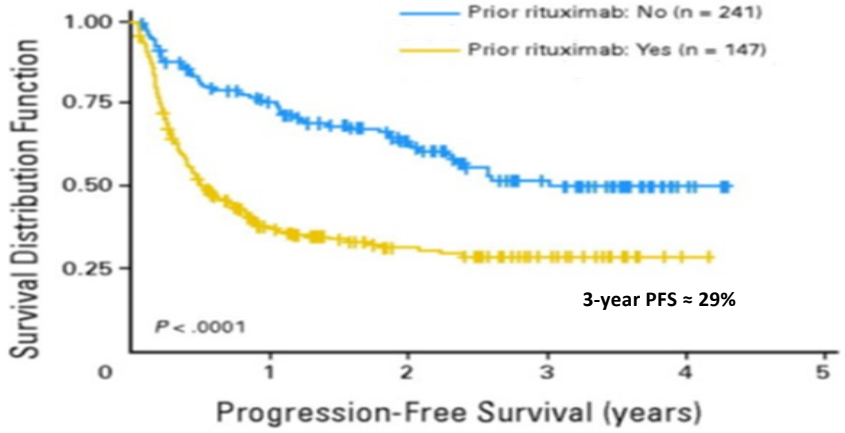
Improved EFS with transplantation



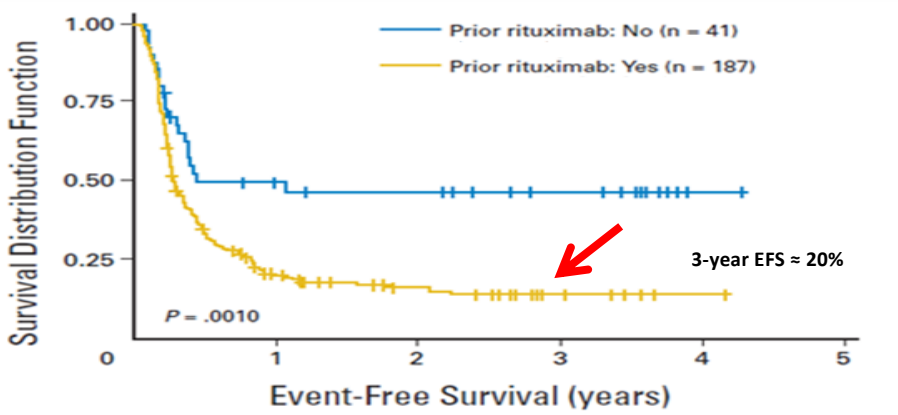
Philip T, et al. N Engl J Med 1995; 333:1540–1545.

Diminishing Role of AutoSCT in the Rituximab Era: CORAL study

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



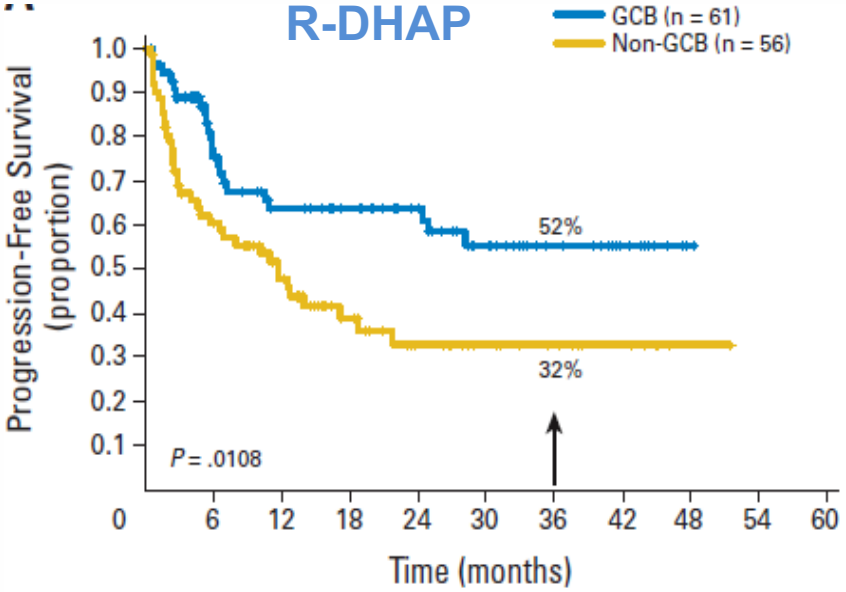
EFS for rituximab treatment + relapse <12 months after diagnosis

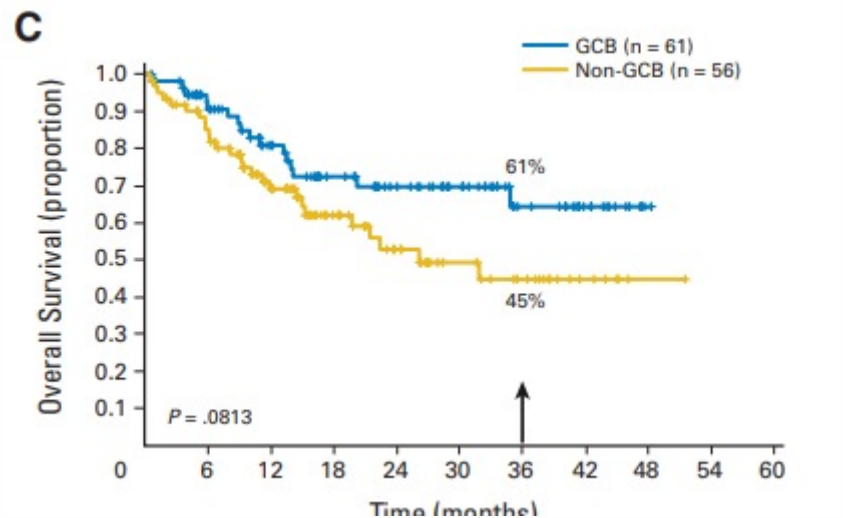


Gisselbrecht C, *et al.* J.Clin Oncol 2010

Prognostic factors RR/DLBCL: Bio-CORAL trial experience

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





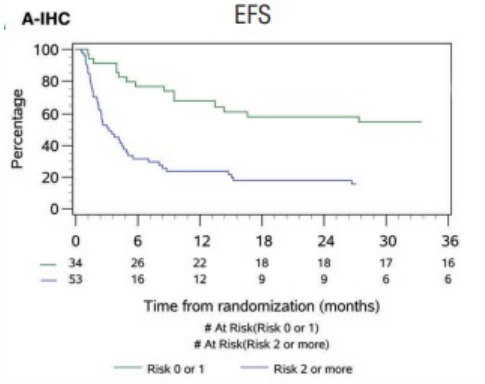
Thieblemont C et al, J Clin Oncol 2011

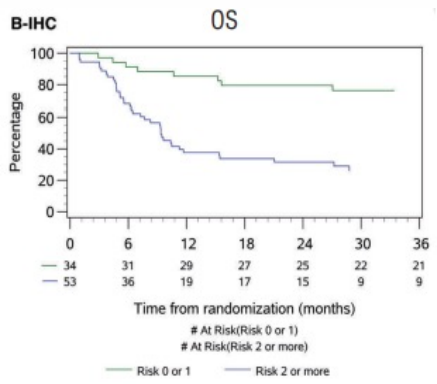
A bioclinical prognostic model using MYC and BCL2 predicts outcome in relapsed/refractory diffuse large B-cell lymphoma

Factors	IHC HR	IHC 95%CI	IHC P	Digital GEP HR	Digital GEP 95%CI	Digital GEP P	FISH HR	FISH 95%CI	FISH P
OS									
BCL2 Expression	1.935	1.016, 3.685	0.046	3.526	1.945, 6.392	<0.0001	1.090	0.529, 2.243	0.82
MYC Expression	2.636	1.469, 4.730	0.001	2.755	1.487, 5.104	0.001	2.364	0.856, 6.528	0.10
SD/PD to Initial Therapy	3.195	1.730, 5.882	0.0002	2.899	1.605, 5.236	0.0004	2.604	1.176, 5.747	0.02
Elevated LDH at Salvage Therapy	3.484	1.818, 6.667	0.0002	2.545	1.441, 4.505	0.001	2.786	1.256, 6.173	0.01
EFS									
BCL2 Expression	1.872	1.085, 3.231	0.024	3.336	1.878, 5.925	<0.0001	1.065	0.565, 2.006	0.85
MYC Expression	2.081	1.232, 3.517	0.006	1.763	1.008, 3.086	0.047	1.710	0.699, 4.182	0.24
SD/PD to Initial Therapy	2.519	1.416, 4.484	0.002	2.299	1.330, 3.984	0.003	1.802	0.883, 3.676	0.11
Elevated LDH at Salvage Therapy	1.900	1.133, 3.175	0.015	1.976	1.163, 3.356	0.012	1.724	0.932, 3.247	0.08

Bioclinical score that predicted ORR, EFS and OS

Low risk (0-1) vs High risk (2-4)



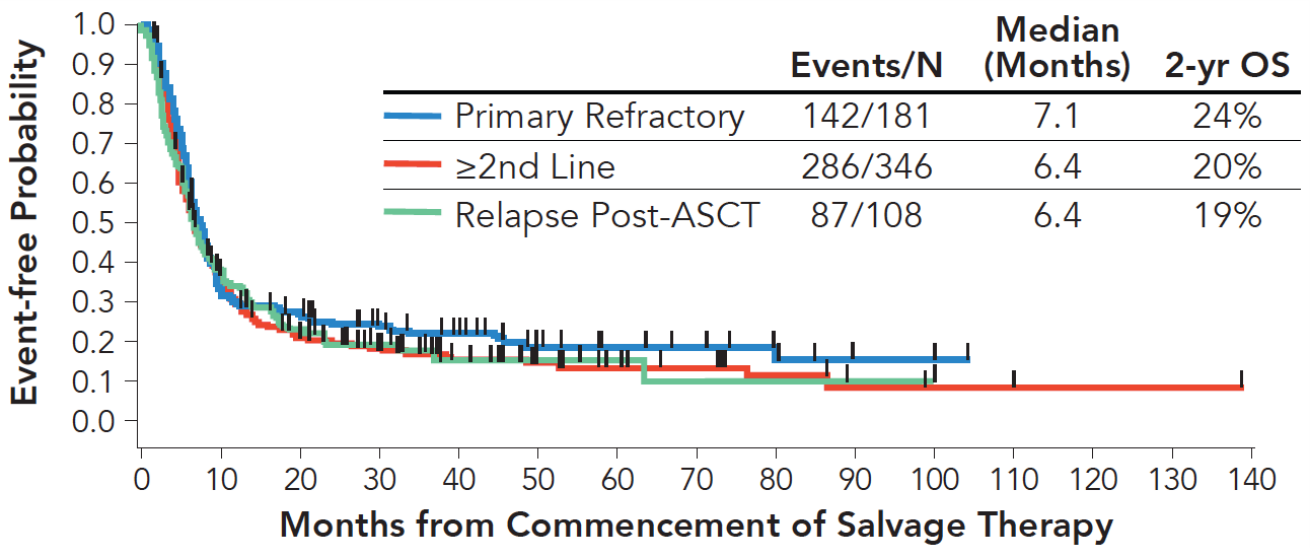


Bosch M et al. Haematologica 2018 Volume 103(2):288-296

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]



	Events/N	Median (Months)	2-yr OS
Primary Refractory	142/181	7.1	24%
≥2nd Line	286/346	6.4	20%
Relapse Post-ASCT	87/108	6.4	19%

ORR= 26%
CR-rate= 7%

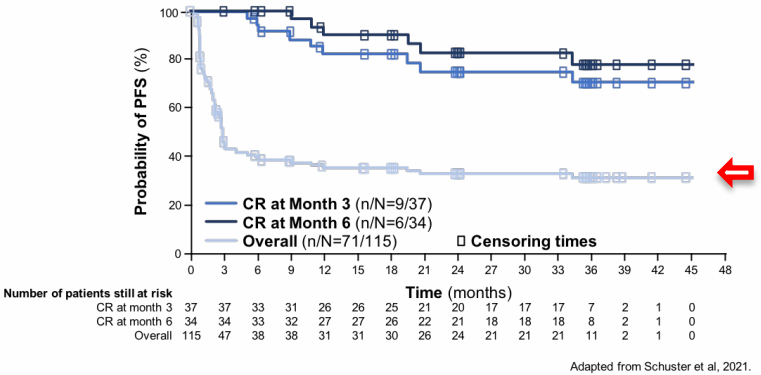
Median OS 6.3 months

Outcomes in the modern era for relapsed refractory DLBCL are poor

Crump M.et al. Blood. 2017;130:1800–8.

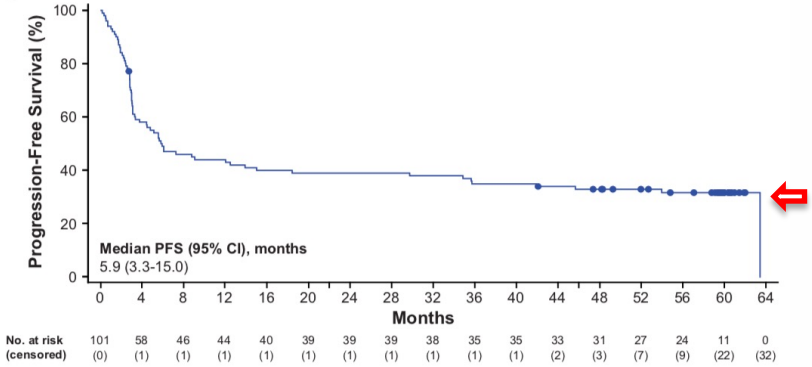
CART produced durable remissions patients with r/r DLBCL

Tisa-cel PFS from JULIET

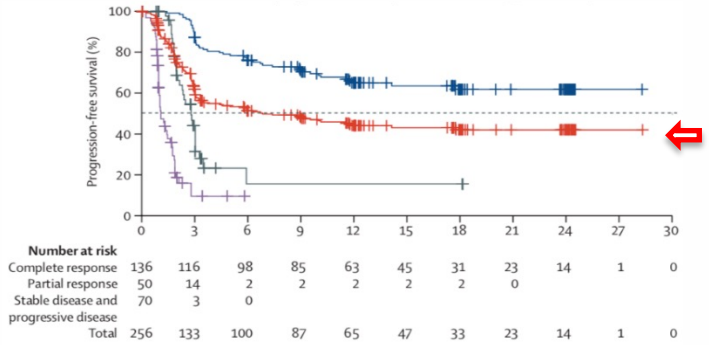


Adapted from Schuster et al, 2021.

Axi-cel, PFS from ZUMA-1

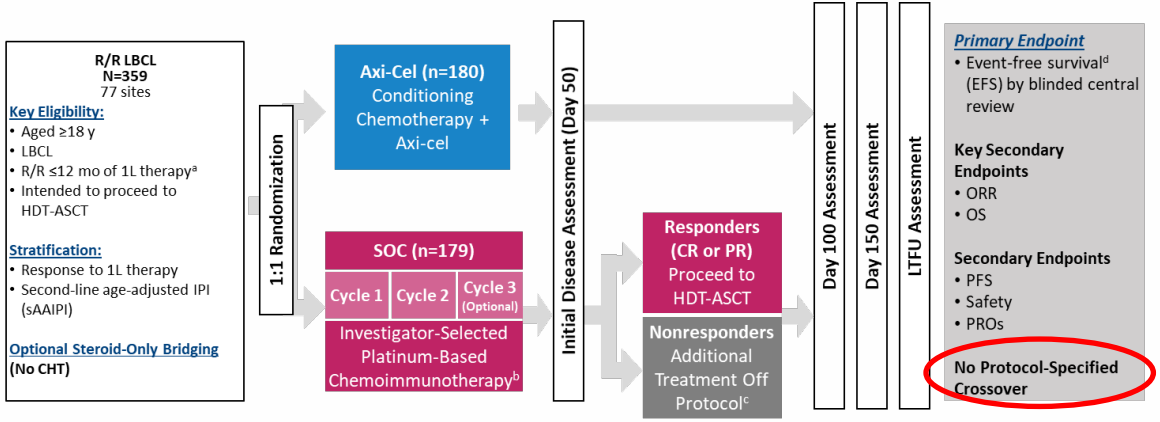


Liso-Cel PFS from TRASCEND

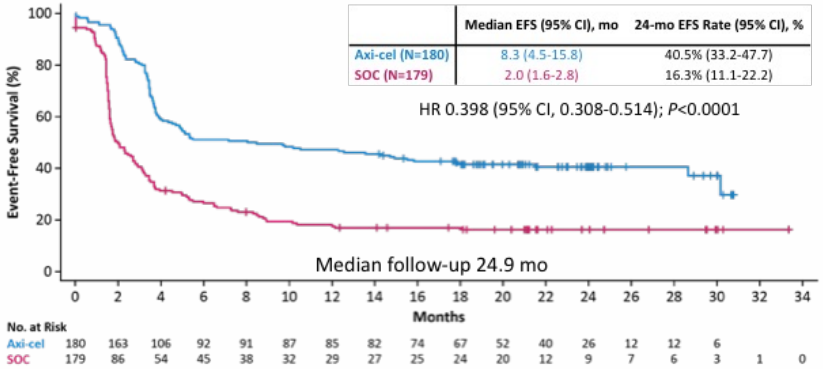


CAR T-cell as Second Line Treatment – ZUMA 7

ZUMA-7: Axicel vs SOC



Response n (%)	Axicel (n=180)	SoC (n=179)	
ORR	150 (83)	90 (50)	
CR	117 (65)	58 (32)	
Survival, mo	**Axicel (n=180)**	**SoC (n=179)**	**HR**
Median PFS	14.7	3.7	0.49
Median OS	NR	35.1	0.73



- ZUMA-7 met its primary endpoint, demonstrating statistically significant improvement in efficacy with axi-cel versus second-line SOC in R/R LBCL (4x median EFS, 2.5x 2-years EFS)
- Nearly 3× the number of patients in the axi-cel arm received definitive therapy versus the SOC arm

Locke F.L. et al, New Engl J Med; 2022: 386;7

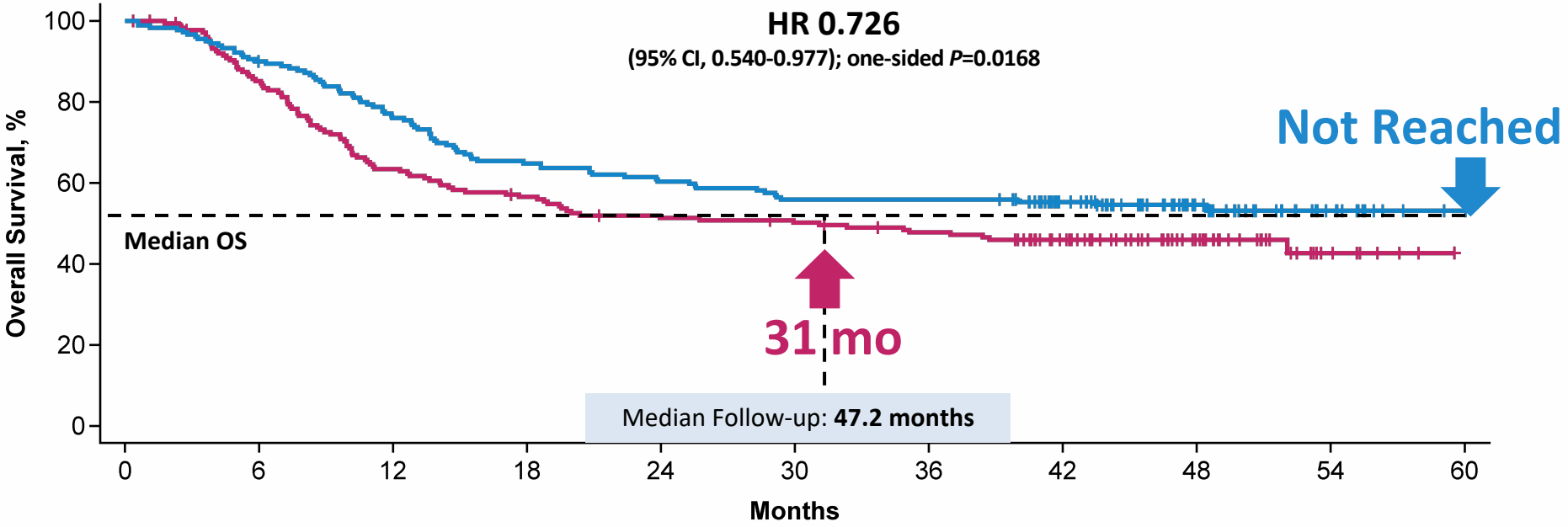
Baseline Characteristics Were Generally Balanced Between Axi-Cel and Standard of Care

Characteristic	Axi-Cel n=180	SOC n=179	Overall N=359
Median age (range), years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2-3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-hit lymphomas)	32 (18)[b]	25 (14)	57 (16)[b]
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[c]	101 (56)	94 (53)	195 (54)

Westin et al ASCO 2023 Late-Breaking Abstract 107

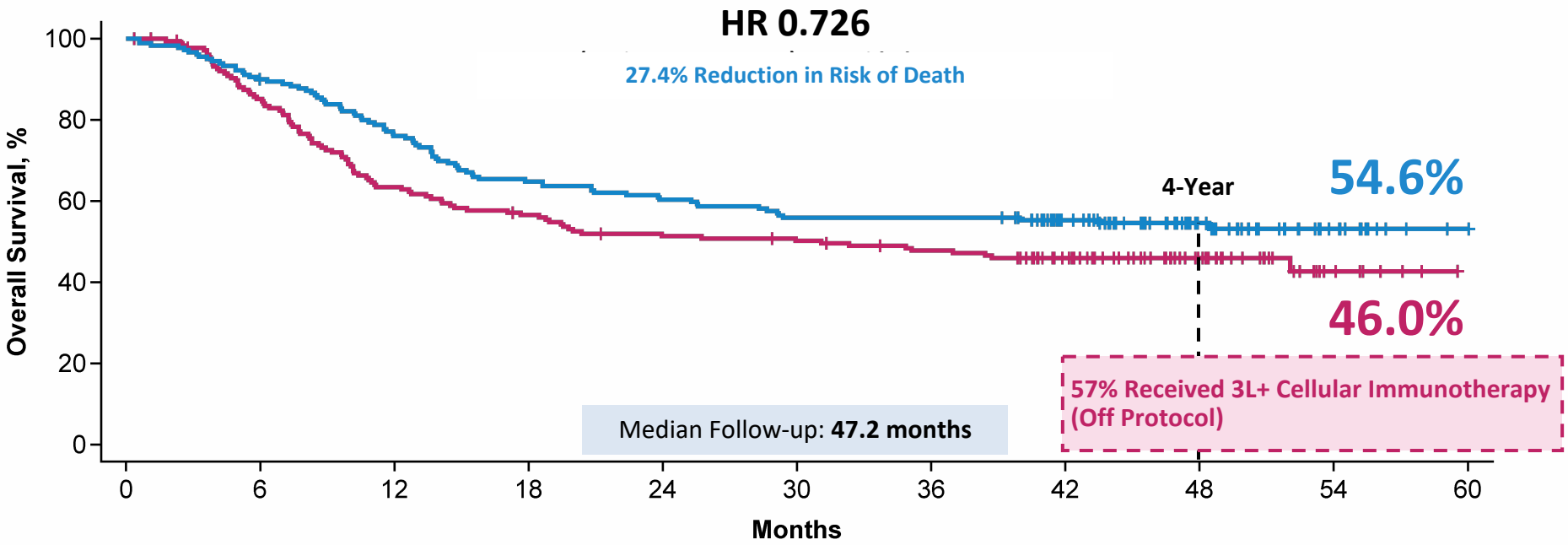
Locke FL et al. New Eng J Med 2022; 386:640-54

Axi-Cel Improved Overall Survival Versus Standard of Care



- Historical SOC trials had lower OS rates in early R/R LBCL, including median OS of ~10 months in ORCHARRD[a]

Axi-Cel Improved Overall Survival Versus Standard of Care



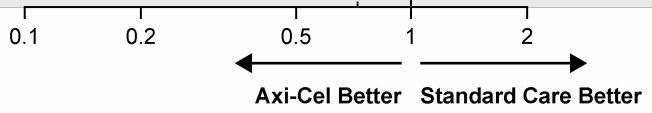
- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[a,b]

Westin et al ASCO 2023 Late-Breaking Abstract 107

Westin JR , et al. ASCO. 2023;

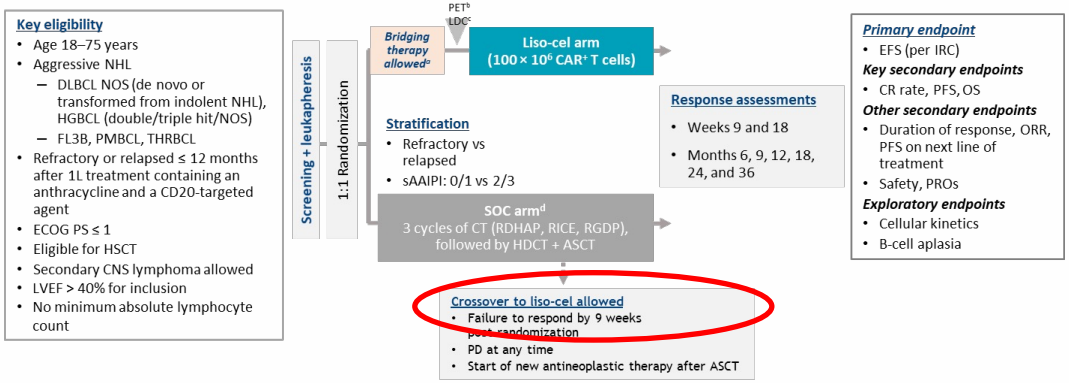
Survival Benefit Favoring Axi-Cel Was Similar Across Key Prespecified Subgroups

	Axi-Cel	SOC	Hazard Ratio	(95% CI) LCI	UCI
	No. of Patients With Events/Total No.				
Overall[a]	82/180	95/179	0.726	0.540	0.977
Age					
<65 y	56/129	64/121	0.779	0.541	1.120
≥65 y	26/51	31/58	0.691	0.401	1.190
Response to first-line therapy at randomization					
Primary refractory disease	66/133	72/131	0.773	0.553	1.080
Relapse ≤12 mo after initiation or completion of first-line therapy	16/47	23/48	0.586	0.308	1.116
Second-line age-adjusted IPI					
0 or 1	37/98	40/100	0.842	0.538	1.317
2 or 3	45/82	55/79	0.647	0.436	0.962
Prognostic marker according to central laboratory					
HGBL, double-hit	14/32	14/25	0.716	0.330	1.553
Double-expressor lymphoma	26/57	33/62	0.729	0.435	1.221

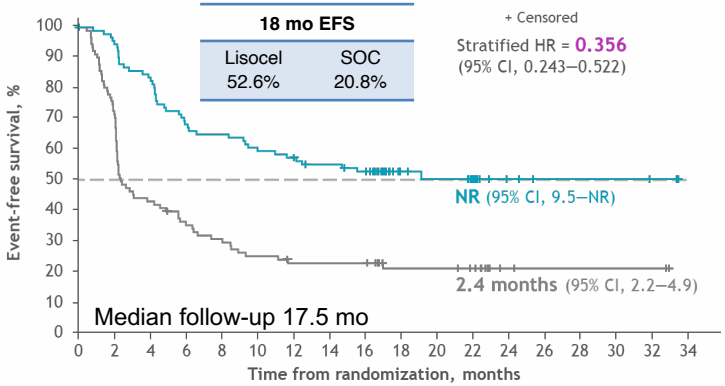


CAR T-cell as Second Line Treatment

Transform: Lisocel vs SOC



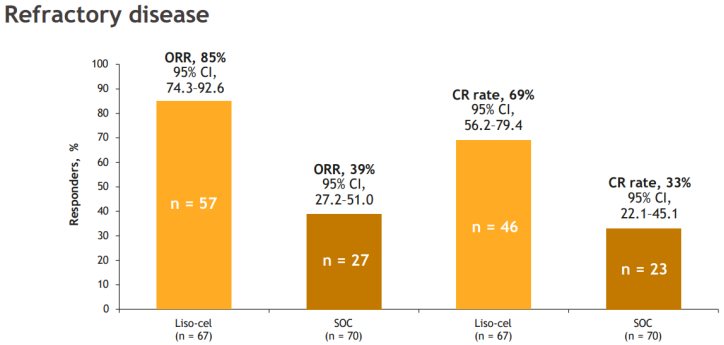
Response n (%)	Lisocel (n=92)	SoC (n=179)	p
ORR	80 (87)	45 (49)	
CR	68 (74)	40 (43)	<0.0001
Survival, mo	**Lisocel (n=92)**	**SoC (n=179)**	**HR**
Median PFS	NR	6.2	0.4
Median OS	NR	29.9	0.72

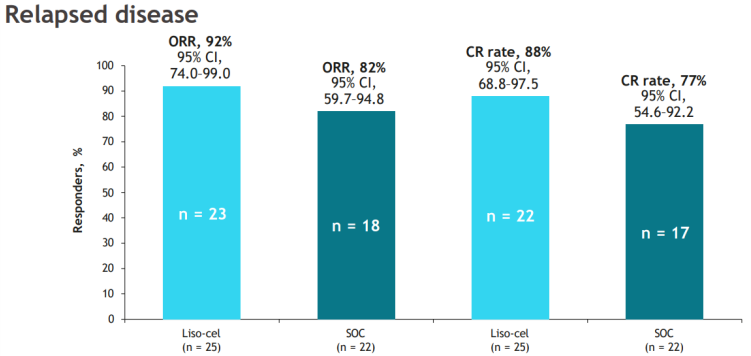


- Transform met its primary endpoint, demonstrating statistically significant improvement in efficacy with lisocel versus second-line SOC in R/R LBCL
- Liso-cel resulted in significant improvements in EFS, CR rate, and PFS. At 18 months, EFS and PFS rates with liso-cel were more than double those with SOC

Kamdar M, et al. ASH 2021 [Abstract #91]. 2022: 386-7; Abramson JS, et al. ASH 2022 [Abstract #655]

Subgroup analyses of primary refractory vs early relapsed large B-cell lymphoma from the TRANSFORM study





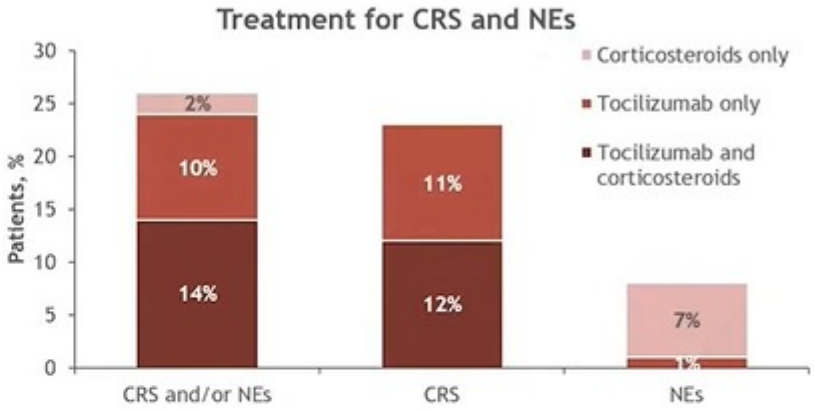
	Refractory		Relapsed	
	Liso-cel arm (n = 67)	SOC arm (n = 70)	Liso-cel arm (n = 25)	SOC arm (n = 22)
EFS per IRC				
12-month EFS rate, % (95% CI)[a]	50.0 (37.9-62.1)	18.3 (9.0-27.5)	76.0 (59.3-92.7)	36.4 (16.3-56.5)
18-month EFS rate, % (95% CI)[a]	45.4 (33.4-57.4)	16.0 (6.9-25.1)	71.8 (54.0-89.5)	36.4 (16.3-56.5)
PFS per IRC				
12-month PFS rate, % (95% CI)[a]	55.9 (43.7-68.2)	28.7 (15.7-41.7)	82.8 (67.4-98.1)	40.2 (18.7-61.7)
18-month PFS rate, % (95% CI)[a]	50.9 (38.5-63.3)	25.1 (11.9-38.2)	78.2 (61.2-95.1)	40.2 (18.7-61.7)
OS				
Median (95% CI), months[b]	29.5 (22.2-NR)	20.9 (15.1-NR)	NR (NR-NR)	NR (17.9-NR)
12-month OS rate, % (95% CI)[a]	80.4 (70.8-89.9)	67.3 (56.0-78.5)	91.7 (80.6-100.0)	86.4 (72.0-100.0)
18-month OS rate, % (95% CI)[a]	68.0 (56.7-79.3)	55.8 (43.6-67.9)	87.3 (73.9-100.0)	75.2 (56.1-94.3)

- ✓ In subgroup analyses based on prior response to 1L therapy with a median follow-up of 17.5 months, liso-cel showed benefits in EFS, PFS, and CR rate versus SOC irrespective of prior response status, consistent with primary analysis results from the overall study population

Nastoupil. ASCO 2023; Abstr 7526

TRANSFORM: TEAEs of special interest (safety set)

Patients with CRS and NEs	Liso-cel arm (n = 92)
CRS,[a] n (%)	
Any grade	45 (49)
Grade 1	34 (37)
Grade 2	10 (11)
Grade 3	**1 (1)**
Grade 4/5	**0**
Time to onset, days, median (range)	5.0 (1–63)
Time to resolution, days, median (range)	4.0 (1–16)
NE,[b] n (%)	
Any grade	10 (11)
Grade 1	4 (4)
Grade 2	2 (2)
Grade 3	**4 (4)**
Grade 4/5	**0**
Time to onset, days, median (range)	11.0 (7–17)
Time to resolution, days, median (range)	4.5 (1–30)



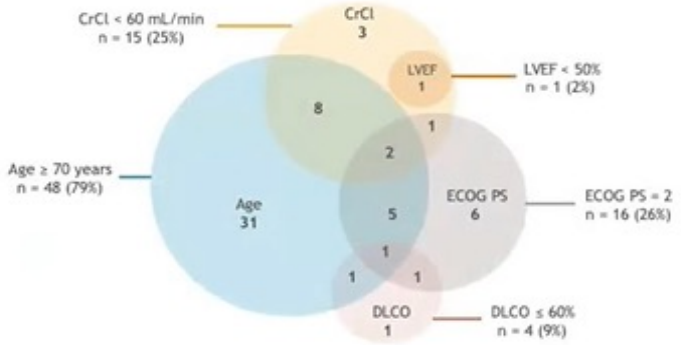
- No vasopressors or prophylactic corticosteroids were used

Other adverse events of special interest	Liso-cel arm (n = 92)	SOC arm (n = 91)
Prolonged cytopenia[c]	40 (43)	3 (3)
Grade ≥ 3 infection	14 (15)	19 (21)

Abramson et al Blood 2023

What about non-transplant eligible patients?

Pilot study: Liso-cel for 2nd line non-transplant eligible LBCL

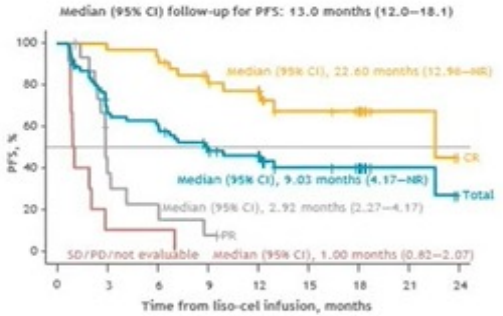


20 (33%) met ≥ 2 of the 6 protocol-specified TNI criteria

Baseline Characteristics	N=61
Median age (range)	74 (53-84)
Histology	
DLBCL NOS	54%
Transformed FL	15%
Double hit lymphoma	33%
Primary refractory disease	54%

Endpoint	
ORR	80%
CRR	54%
mDOR	12 mo (22 in CR pts)

PFS



Toxicity	%
CRS	38
Grade 1-2	36
Grade 3	2
NT	31
Grade 1-2	26
Grade 3	5

Seghal, et al. Lancet Onc 2022

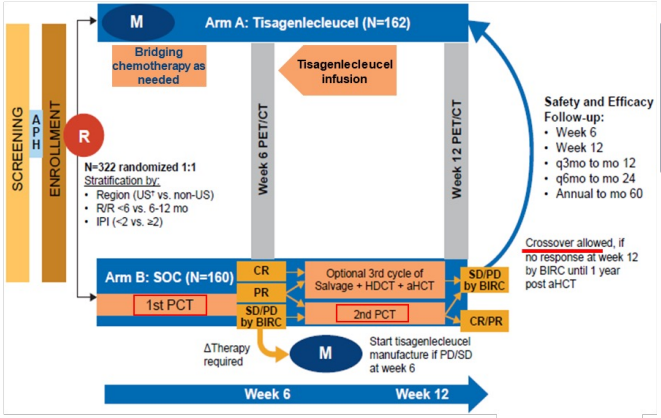
CAR T-cell as Second Line Treatment

Belinda: Tisa-cel vs SOC

Key eligibility criteria:
- Aged ≥18 y
- aNHL (DLBCL NOS,HG, 3b-FL, tFL, PMBCL)
- R/R ≤12 mo of 1L therapy[a]
- autoHCT eligible
- ECOG PS 0-1

Stratification:
- Response to 1L therapy (< 6 vs 6-12 mo)
- Region
- IPI (< 2 vs ≥ 2)

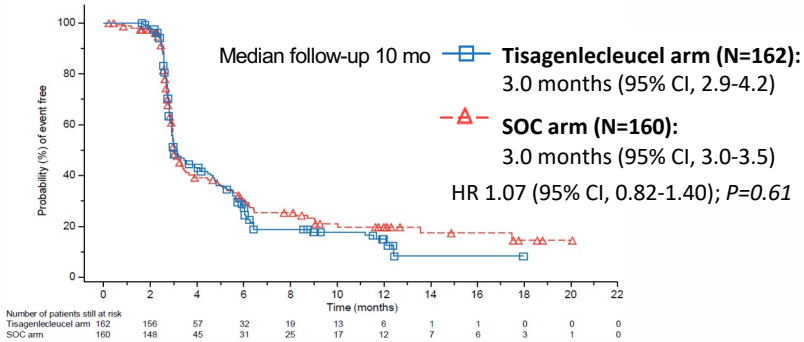
Bridging chtp allowed[b]



Primary Endpoint:
EFS defined as **time from randomization to death due to any cause, SD/PD at/after week 12 ± 1 week**

Secondary Endpoints:
- ORR at/after week 12
- Safety
- Cellular kinetics

Response n (%)	Tisacel (n=162)	SoC (n=160)	p
ORR	75 (46.3)	68 (42.5)	
CR	46 (28.4)	44 (27.5)	



- EFS was not significantly different between tisa-cel and SOC.
- Authors suggest the importance of preventing PD prior to infusion
- Effective bridging prior to CAR T-cell infusion and a shorter time to infusion for this chemotherapy-refractory patient population could be critical to improve outcomes.

Beshop M.R. et al. New Engl J Med 2022

CAR T-cell as Second Line Treatment

	ZUMA-7	Belinda	Transform
Histologies included	DLBCL NOS,* including transformed from FL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type	DLBCL NOS, including transformed from indolent NHL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type FL grade 3B, PMBCL, Intravascular LBCL, ALK + LBCL, HHV8 + LBCL	DLBCL NOS, including transformed from indolent NHL, HGBCL with MYC and BCL2/6, T/H-RLBCL, FL grade 3B, PMBCL
Product	Axi-cel, CD28/CD3zeta 2×10^6 cells/kg	Tisa-cel, 4 – 1BB/CD3zeta $0.6\text{-}6 \times 10^8$ cells	Liso-cel, 4 – 1BB/CD3zeta 1×10^8 cells
1L refractory definition	• PD as best response • SD after at least 4 cycles • PR with + biopsy or PD <12 mo from 1L start	• PD/SD as best response	• PD/SD/PR as best response • CR with progression <3 mo
1L relapsed definition	• CR followed by + biopsy <12 mo from 1L end	• Positive biopsy ≤12 mo from 1L end	• CR followed by + biopsy 3-12 mo from 1L end
Age	18+	18+	18-75
Leukapheresis time point	• At randomization • Only CAR T-cell arm	• Before randomization • All patients	• Before randomization • All patients
Stratification factors	1. Refractory vs Relapse ≤6 mo vs Relapse >6-12 mo 2. 2L AAIPI 0-1 vs 2-3	1. Refractory or relapsed ≤6 mo vs relapsed 6-12 mo 2. IPI <2 vs ≥2	1. Refractory vs relapse 2. 2L AAIPI 0-1 vs 2-3
Bridging therapy	• Dexamethasone ≤40 mg for ≤4 d	• R-ICE • R-GDP • R-DHAP • R-GemOx	• R-ICE • R-GDP • R-DHAP

	ZUMA-7	Belinda	Transform
LD chemotherapy	• Fludarabine 30 mg/m^2 × 3 d • Cyclophosphamide 500 mg/m^2 × 3 d	• Fludarabine 25 mg/m^2 × 3 d and • Cyclophosphamide 250 mg/m^2 × 3d OR • Bendamustine 90 mg/m^2 × 2 d	• Fludarabine 30 mg/m^2 × 3 d • Cyclophosphamide 300 mg/m^2 × 3 d
SOC chemotherapy	• R-ICE • R-GDP • R-DHAP • R-ESHAP	• R-ICE • R-GDP • R-DHAP • R-GemOx	• R-ICE • R-GDP • R-DHAP
Crossover to CAR T-cell therapy	No	Yes, if • <PR/CR by 12 wk (after 2 SOC regimens) • PD at any time	Yes, if • <PR/CR by 9 wk • PD at any time • Need for new therapy after 18 wk
EFS definition	Time from randomization to: • PD • Death • <PR at day 150 assessment • Start of new lymphoma therapy	Time from randomization to: • PD • Death • <PR at/after week 12	Time from randomization to: • PD • Death • ≤PR by week 9 • Start of new lymphoma therapy

- Bridging therapy: Zuma 7: 36% dex; Belinda: 83% PCT (43% > 1 cy, 12% > 1 regimen); Transform: 63% PCT (only 1 cycle allowed)
- Belinda allowed > 1 SOC regimen
- ASCT was performed in 36% of ZUMA-7 pts, 32.5% of Belinda pts and 45.6% of Transform pts.
- Median time from R to infusion was: 29 days in Zuma-7, 52 day in Belinda, UNK for Transform

The 2-year PFS was 52%

LYMPHOID NEOPLASIA

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

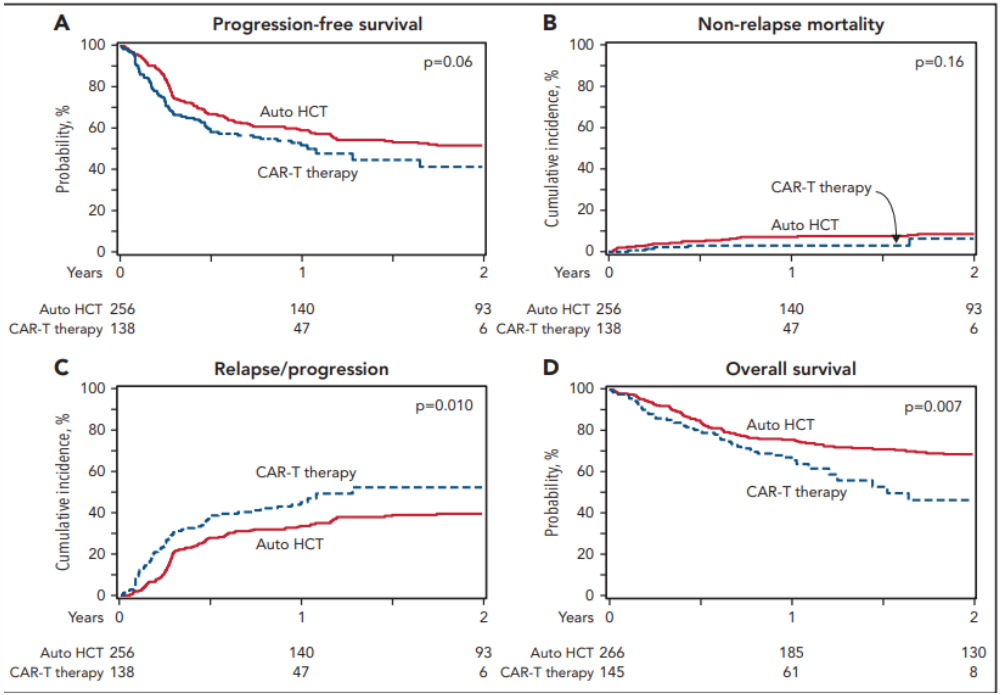
KEY POINTS

- **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.**

411 patients

61% were late relapse

The 2-year PFS was 52%



- Numbers of prior lines of therapy (median, 3 vs 2 for CAR T cells compared with ASCT)
- Burden of disease at the time of treatment.

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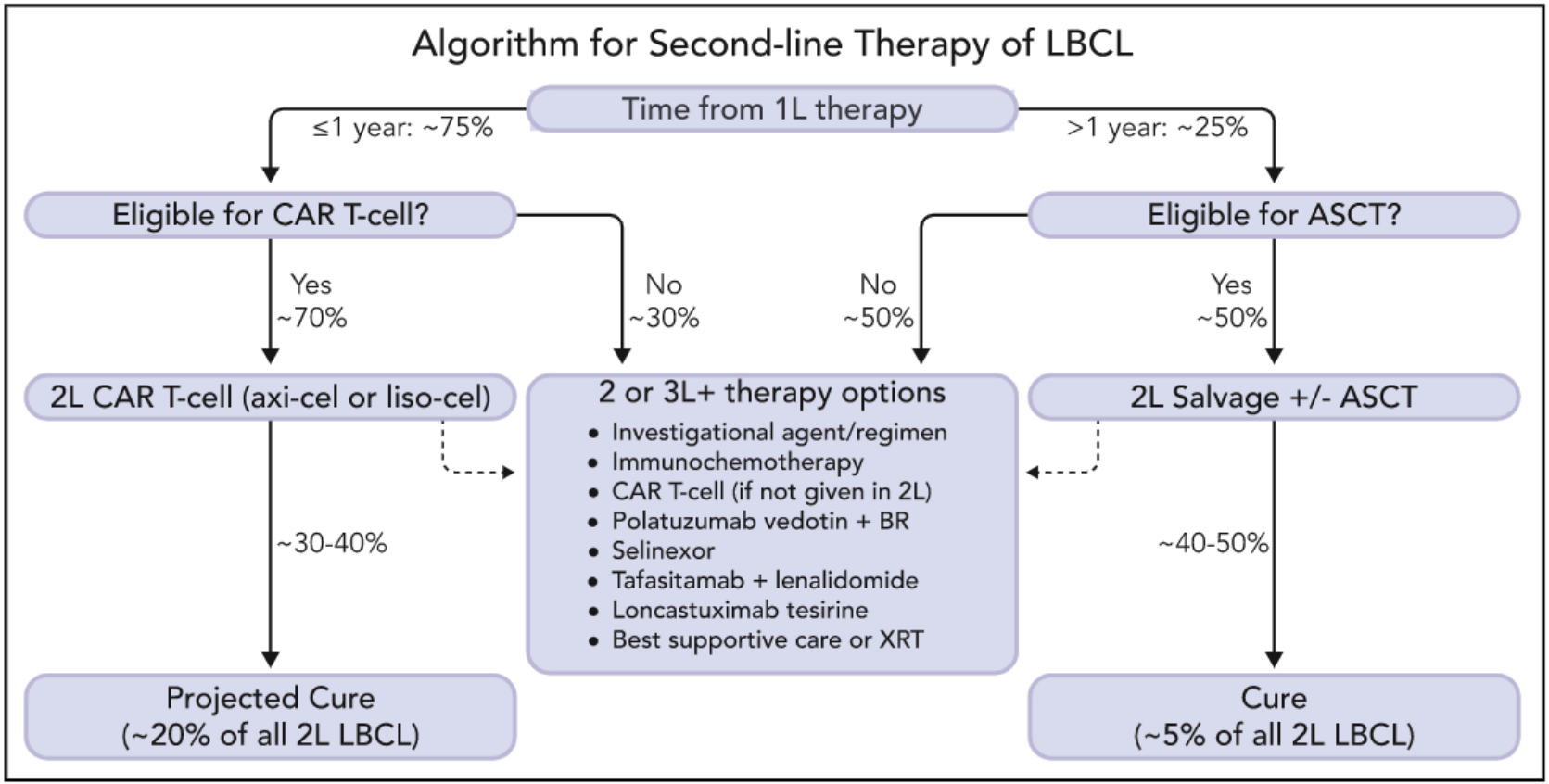
2L effective treatments in DLBCL

Chemosensivity disease

vs

Chemorefractory disease

A new treatment algorithm for patients with R/R LBCL after first-line therapy



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Grazie per l'attenzione