con il patrocinio di

AIL Caserta Valentina Picazio
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE - LINFOMI E MIELOMA

SIE
Società Italiana
di Ematologia

2024:

È già ora di abbandonare la chemioterapia nella malattia recidivata/refrattaria?

Napoli, Hotel Paradiso • 29–30 aprile 2024

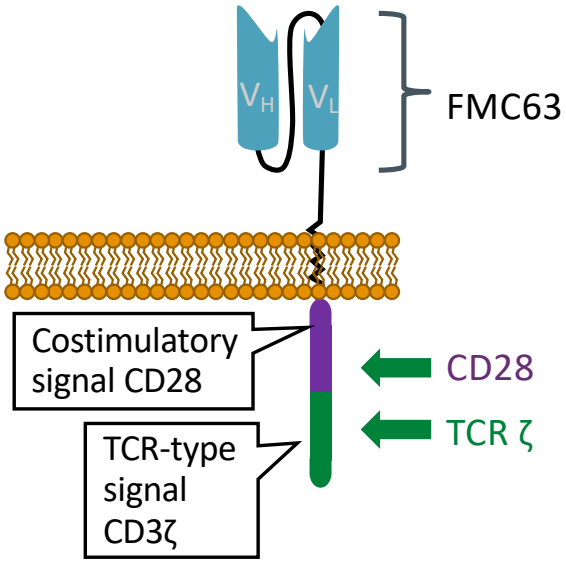
DLBCL – Indicazioni alla terapia con CAR-T: quale e quando utilizzarla

Massimo MARTINO

CD19-Targeted CAR T-Cell Products in DLBCL

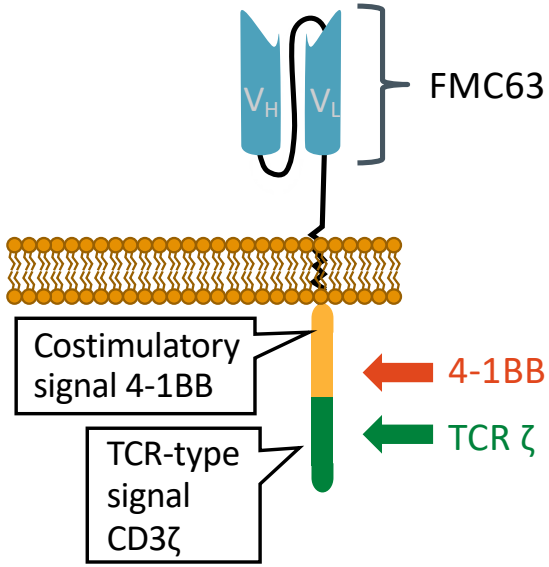
Axicabtagene ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



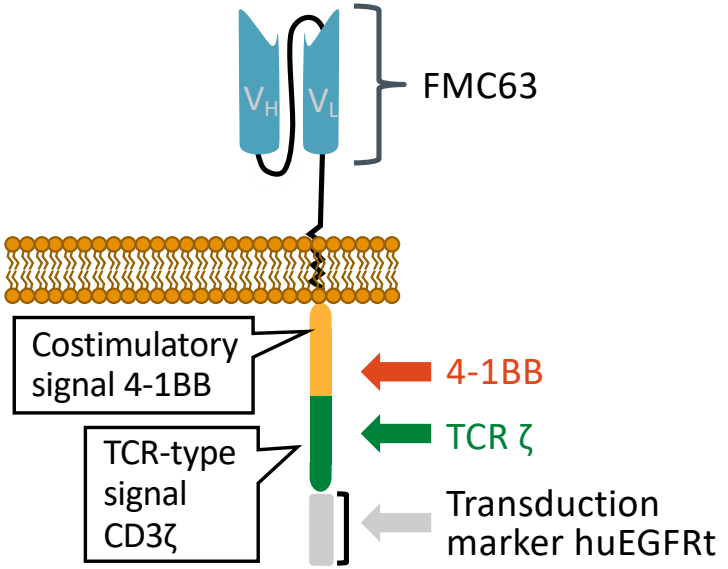
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



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

Management of Relapsed DLBCL:

Focus on Refractory/Early Relapsed Disease

CAR T-Cells vs SoC in High-Risk DLBCL

- High-risk DLBCL refractory to first-line treatment or relapsed with in 12 mo of first-line chemoimmunotherapy (anthracycline + CD20 mAb)

ZUMA-7[1]

Axi-cel
(± bridging steroids)

- Flu/Cy + axi-cel 2 x 10^6/kg
- ***Optional bridging therapy; only steroids permitted***
- ***Crossover not planned***
- Primary endpoint: EFS
- N = 359

Salvage chemotherapy ± auto-transplant

TRANSFORM[3]

(Lisocabtagene maraleucel in R/R LBCL)

- Cy/Flu + liso-cel 1.0 x 10^8 cells
- ***Bridging therapy allowed***
- ***Crossover to liso-cel allowed if no response by 9 wk,***
- Primary endpoint: EFS
- N = 184

BELINDA[2]

Tisa-cel
(± bridging therapy)

- Flu/Cy or bendamustine + tisa-cel 0.6-6.0 x 10^8 cells
- ***Platinum-based bridging permitted***
- ***Crossover if SD or progression ≥12 wk***
- Primary endpoint: EFS
- N = 322

1. Locke. NEJM. 2021;386:640. 2. Bishop. NEJM. 2021;386:629. 3. Kamdar. Lancet. 2022;399:2294.

ZUMA-7: Axicabtagene Ciloleucel vs SoC in R/R Large B-Cell Lymphoma

- Global, multicenter, randomized phase III trial

Stratified by 1L treatment response, 2L age-adjusted IPI

Patients ≥18 yr of age with LBCL; ECOG PS 0-1; R/R disease with ≤12 mo of adequate 1L CIT (including anti-CD20 mAb and an anthracycline); intent to proceed to HDT-ASCT (N = 359)

Axi-cel 2 x 10^6 CAR T-cells/kg after conditioning chemotherapy (n = 180)

Conditioning regimen: cyclophosphamide 500 mg/m^2/day + fludarabine 30 mg/m^2/day on Days 5, 4, and 3 prior to CAR T-cell infusion. Optional bridging therapy limited to corticosteroids (no CIT).

SoC*
(2-3 cycles of investigator-selected, protocol-defined, platinum-based CIT)
(n = 179)

CR/PR → **HDT-ASCT** (n = 64)

No CR/PR → **Off-Protocol Tx**†

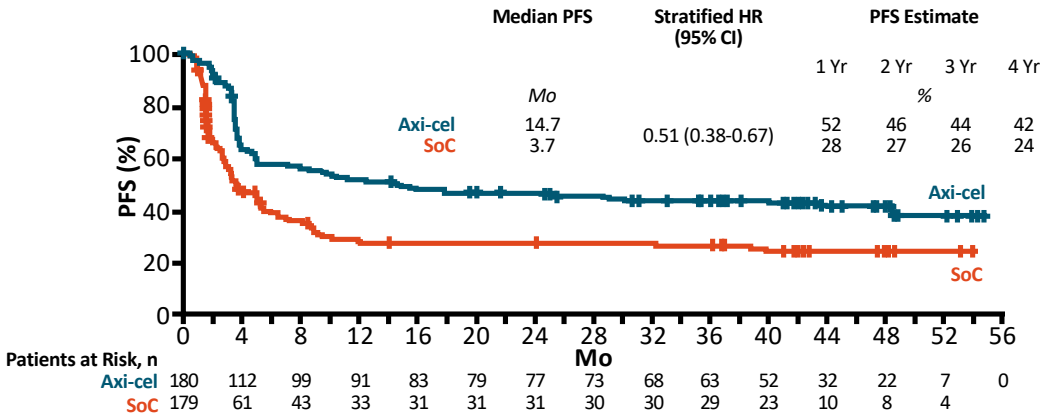
*SoC included R-GDP, R-DHAP, R-ICE, or R-ESHAP. †56% received subsequent cellular immunotherapy.

- **Primary endpoints:** EFS (BICR)
- **Key secondary endpoints:** ORR and OS (tested hierarchically)
- **Other secondary endpoints:** PFS, safety, PROs
- **Median follow-up:** 24.9 mo

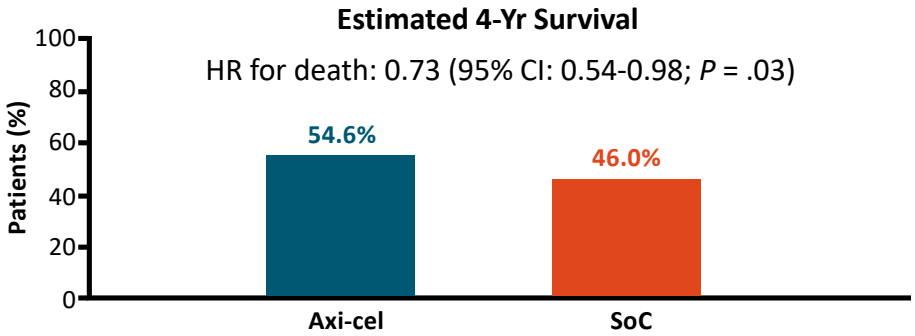
Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2.

ZUMA-7: Survival and ORR With Second-line Axi-cel vs SoC in Primary Refractory or Early Relapsed B-Cell Lymphomas

Event, n/N (%)	Axi-cel (N = 170) Grade ≥3	SoC (N = 168) Grade ≥3
Febrile neutropenia	6/170 (4)	46/168 (27)
CRS	11/170 (6)	—
▪ Pyrexia	14/157 (9)	—
▪ Hypotension	18/157 (11)	—
▪ Sinus tachycardia	3/157 (2)	—
▪ Chills	0/157	—
▪ Headache	2/157 (1)	—
▪ Hypoxia	13/157 (8)	—
Neurologic events	36/170 (21)	1/168 (1)
▪ Tremor	2/170 (1)	0
▪ Confusional state	9/170 (5)	0
▪ Aphasia	12/170 (7)	0
▪ Encephalopathy	20/170 (12)	0
▪ Paresthesia	1/170 (1)	0
▪ Delirium	3/170 (2)	1/168 (1)



Median follow-up: 47.2 mo

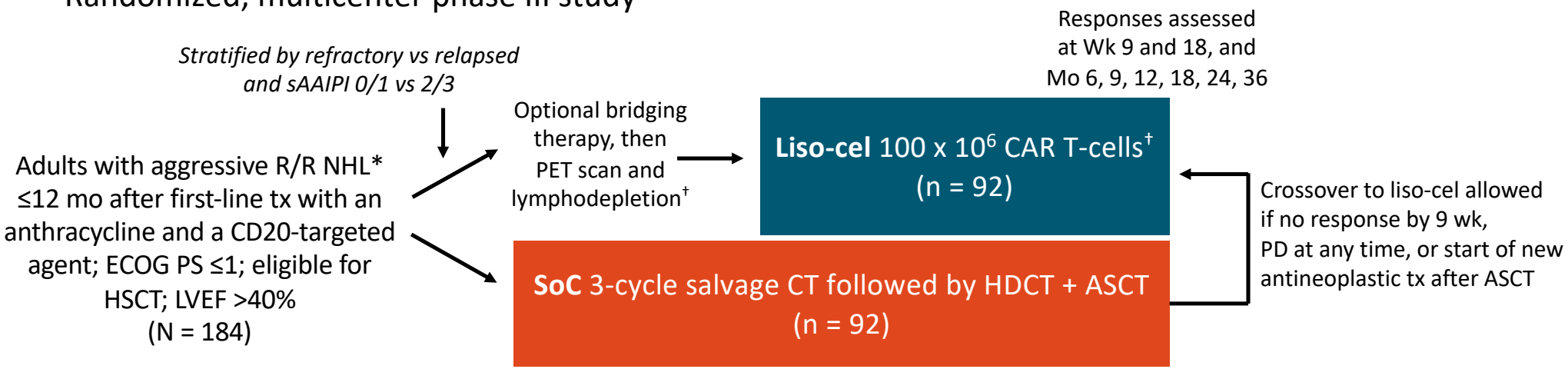


- ORR: 83% (axi-cel) vs 50% (SoC); p.001
  - **CR: 65% (axi-cell) vs 32% (SoC)**

Westin. NEJM. 2023;389:148. Locke. NEJM. 2022;386:640.

TRANSFORM: Lisocabtagene Maraleucel vs Salvage Chemo + ASCT in Relapsed/Refractory Aggressive NHL

- Randomized, multicenter phase III study



*DLBCL NOS, HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL.
†Fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2 x 3 days.

- Primary endpoint: EFS per IRC
- Key secondary endpoints: CR, PFS, OS
- Exploratory endpoints: cellular kinetics, B-cell aplasia
- Primary refractory: 75% in both arms
- Double- or triple-hit lymphoma: 24%

Kamdar.. Lancet. 2022;399:10343.

TRANSFORM: Primary Analysis of Response, Survival, and Safety With Liso-cel vs SoC in Early Relapsed LBCL

Adults with aggressive R/R NHL ≤12 mo after first-line tx with an anthracycline and a CD20-targeted agent; ECOG PS ≤1; eligible for HSCT; LVEF >40% (N = 184)

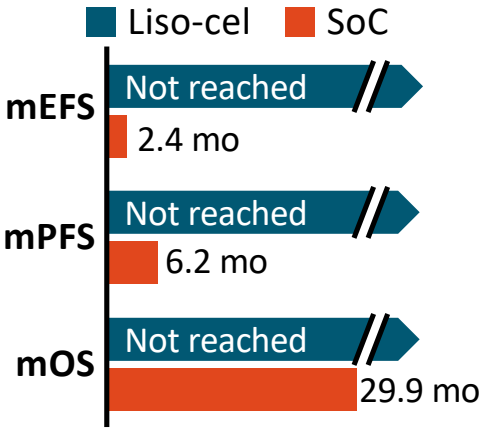
Optional bridging therapy*, then PET scan and lymphodepletion → **Liso-cel** 100 x 10^6 CAR T-cells (n = 92)

SoC 3-cycle salvage CT followed by HDCT + ASCT (n = 92)

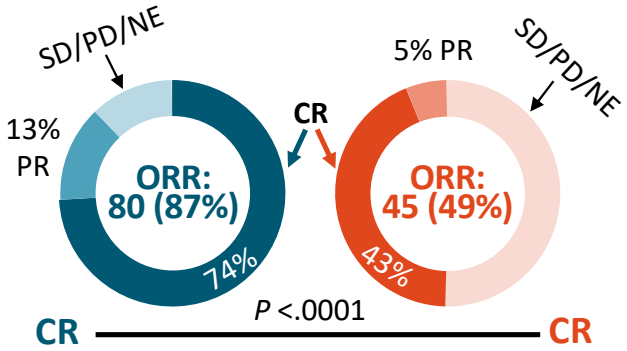
Crossover to liso-cel allowed if no response by 9 wk, PD at any time, or start of new antineoplastic tx after ASCT

*33% received bridging tx; 97% received liso-cel

Efficacy (Median f/u: 17.5 Mo)



Stratified HR	18 Mo Rate Diff
EFS: HR: 0.356; not retested	+31.8%
PFS: HR: 0.400; *P* <.0001	+29.4%
OS: HR: 0.724; *P* = .0987	+12.5%



TEAE, %	Liso-cel (n = 92)		SoC (n = 91)	
	Any	Gr ≥3	Any	Gr ≥3
Any	100	92	99	89
Serious	48	--	49	--
Leading to death	2		2	
CRS†	49	1	0	0
NE†	11	4	0	0

†No grade 4/5 event.

Abramson. Blood. 2023;141:1675.

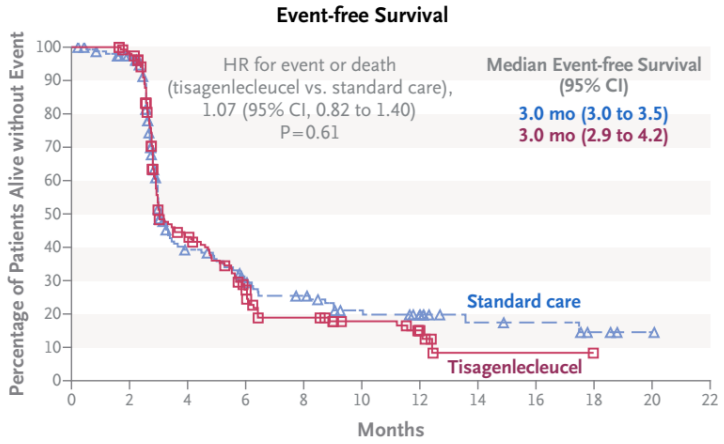
Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

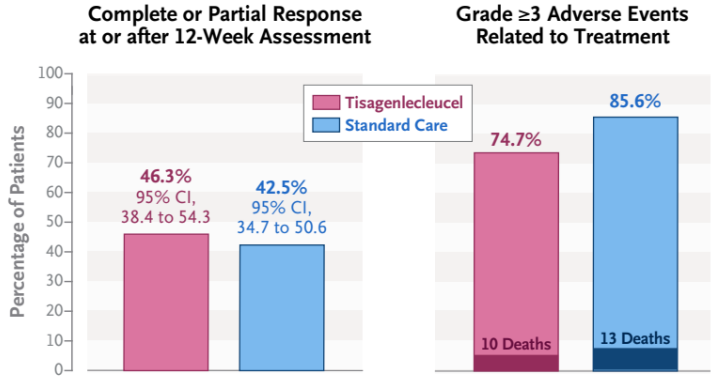
Bishop MR et al. DOI: 10.1056/NEJMoa2116596

CLINICAL TRIAL

Design: An international, randomized, phase 3 trial compared the efficacy and safety of tisagenlecleucel with those of standard-care second-line therapies in patients with refractory or early relapsed aggressive B-cell lymphoma.

Intervention: 322 patients 18 years of age or older with confirmed aggressive B-cell lymphoma that was refractory to or relapsed within 12 months after first-line therapy were randomly assigned to receive tisagenlecleucel with optional bridging therapy or standard care comprising combination chemotherapy and autologous hematopoietic stem-cell transplantation in patients having a response. The primary end point was event-free survival — the time from randomization to stable or progressive disease at or after week 12 or death at any time.





CONCLUSIONS

Second-line tisagenlecleucel did not result in longer event-free survival than standard-care second-line therapy in patients with refractory or early relapsed aggressive B-cell lymphoma.

	ZUMA-7 AXI-CEL	TRANSFORM LISO-CEL	BELINDA TISA-CEL
Median time to infusion	13 days	NK	52 days
Received ASCT	36%	47%	33%
Received CAR-T	94%	97%	96%
HGBCL with gene rearrangements in *MYC* and *BCL2*, *BCL6*, or both	17% CAR-T 14% SOC	24% CAR-T 23% SOC	20% CAR-T 12% SOC
Cross-over	Not permitted	66%	50.6%
Bridging therapy	36% only glucocorticoids	63%	83.3%

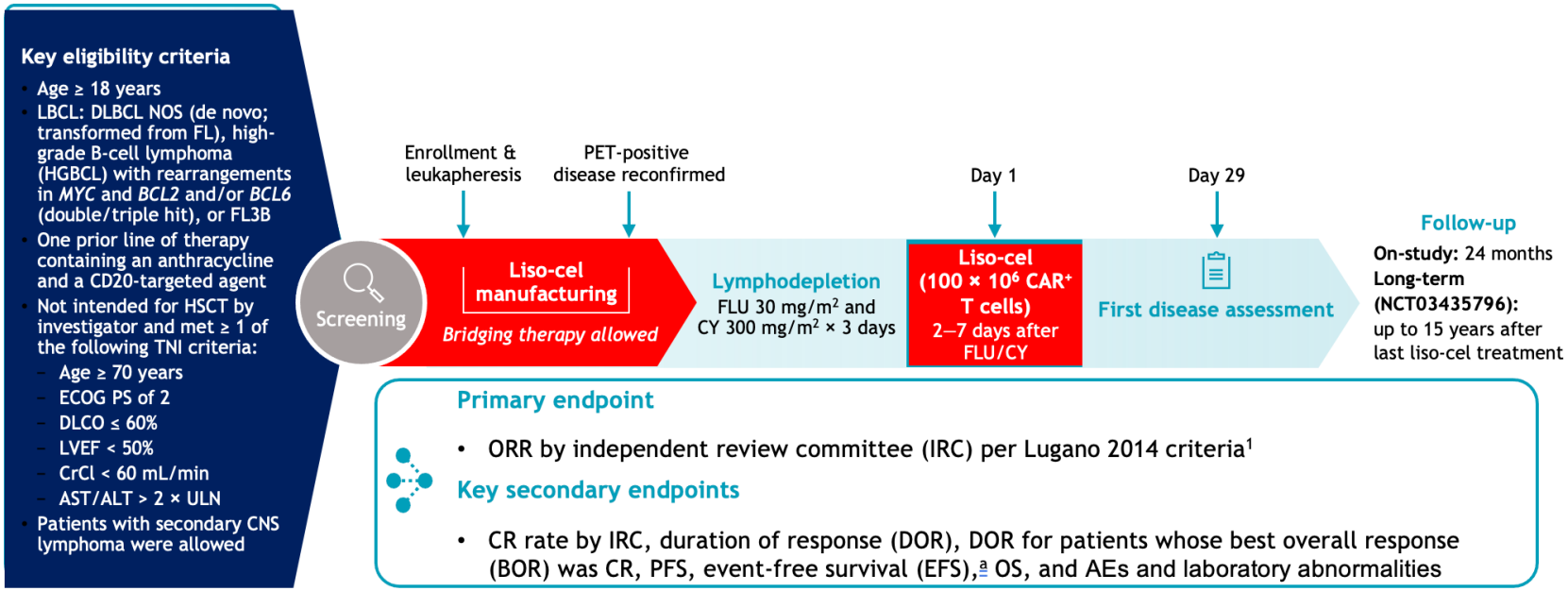
When to Use CAR T-Cell Therapy in Second-line Setting

- Primary refractory disease or remission lasting ≤12 mo after first-line therapy
- *Or* second line in patients ineligible for ASCT but eligible for liso-cel
- Choice of product depends on pheresis slot availability
- Median follow-up (ZUMA-7 and TRANSFORM)
  - Axi-cel: 47.9 mo[1]
  - Liso-cel: 17.9 mo[2]

1. Locke. NEJM. 2022;386:640. 2. Kamdar. Lancet. 2022;399:2294.

Lisocabtagene maraleucel as second-line therapy for relapsed or refractory large B-cell lymphoma in patients not intended for hematopoietic stem cell transplant: final analysis of the phase 2 PILOT study

PILOT study design



Sehgal et al. *Abstract number 105*

Baseline demographics and disease characteristics

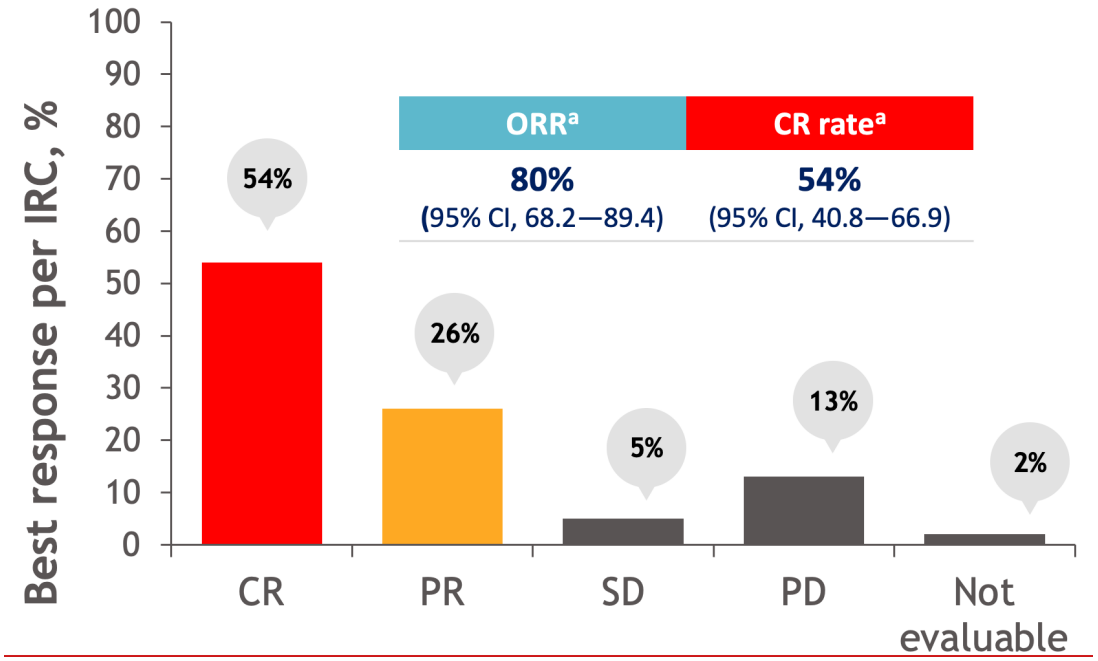
	Liso-cel—treated analysis set (n = 61)
Age, y	
Median (range)	74 (53—84)
≥ 65 to < 75, n (%)	27 (44)
≥ 75, n (%)	28 (46)
Histology, n (%)	
DLBCL NOS	33 (54)
Transformed FL	9 (15)
HGBCL	18 (30)
FL3B	1 (2)
Relapsed or refractory, n (%)	
Relapsed total / ≤ 12 mo / > 12 mo	28 (46) / 13 (21) / 15 (25)
Refractory[a]	33 (54)
Received bridging therapy,[b] n (%)	32 (52)

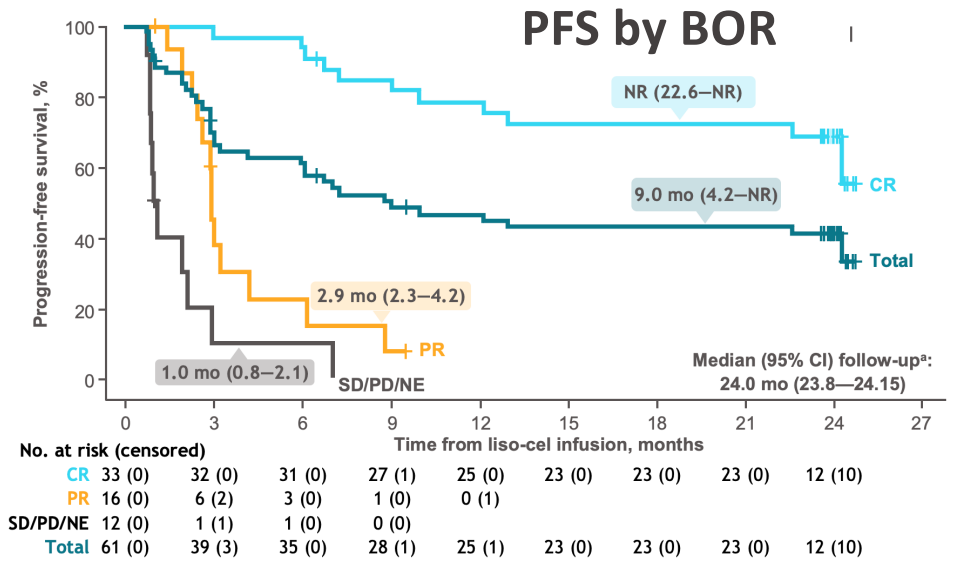
Transplant not intended characteristics

	Liso-cel—treated analysis set (n = 61)
Age, y ≥ 70, n (%)	48 (79)
Screening ECOG PS of 2, n (%)	16 (26)
CrCl < 60 mL/min, n (%)	15 (25)
DLCO ≤ 60%,[a] n (%)	4 (7)
LVEF < 50%, n (%)	1 (2)
AST/ALT > 2 × ULN, n (%)	0

Sehgal et al. *Abstract number 105*

Liso-cel—treated efficacy analysis set (n = 61)





	Total (n = 61)	CR (n = 33)
12-mo rate (95% CI)[b]	46.6% (33.4—58.8)	78.4% (59.9—89.1)
18-mo rate (95% CI)[b]	42.9% (29.9—55.2)	72.1% (53.2—84.4)

Abstract number 105

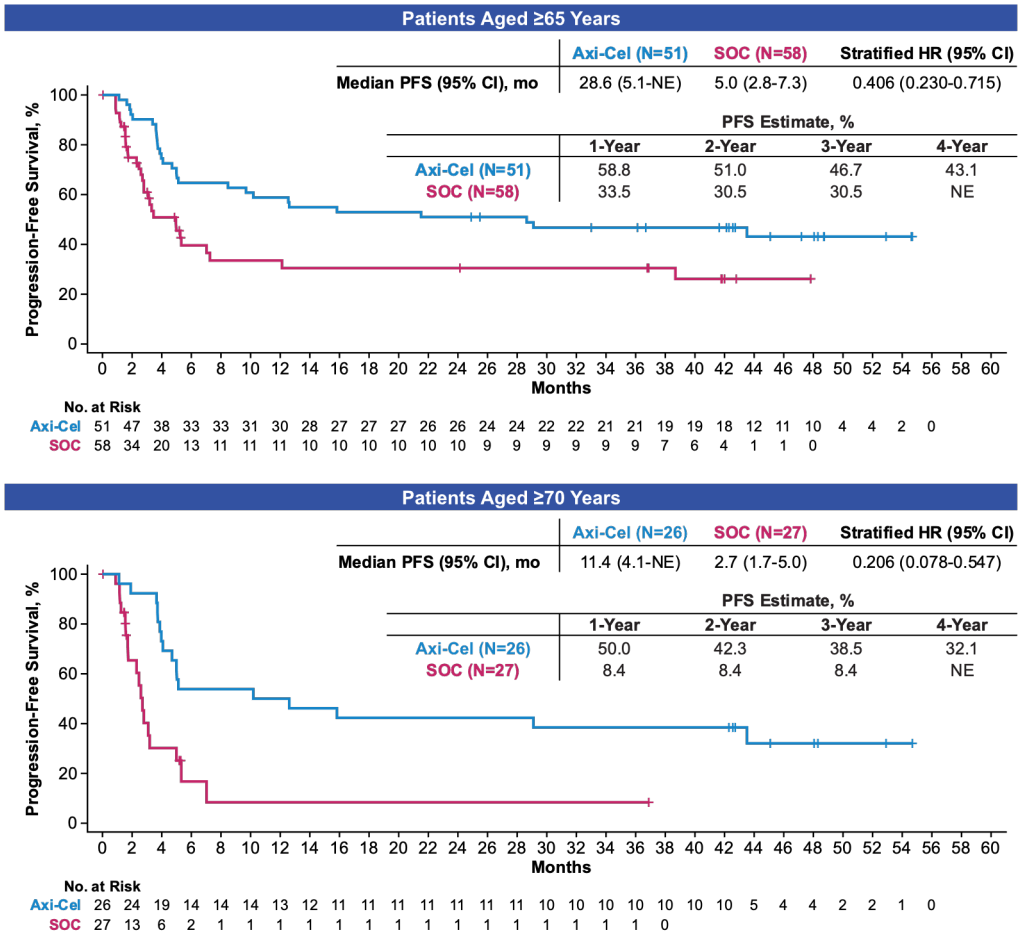
Improved Overall Survival With Axicabtagene Ciloleucel vs Standard of Care in Second-Line Large B-Cell Lymphoma Among the Elderly: A Subgroup Analysis of ZUMA-7

Kersten et al. ASH 2023, Abstract 1761

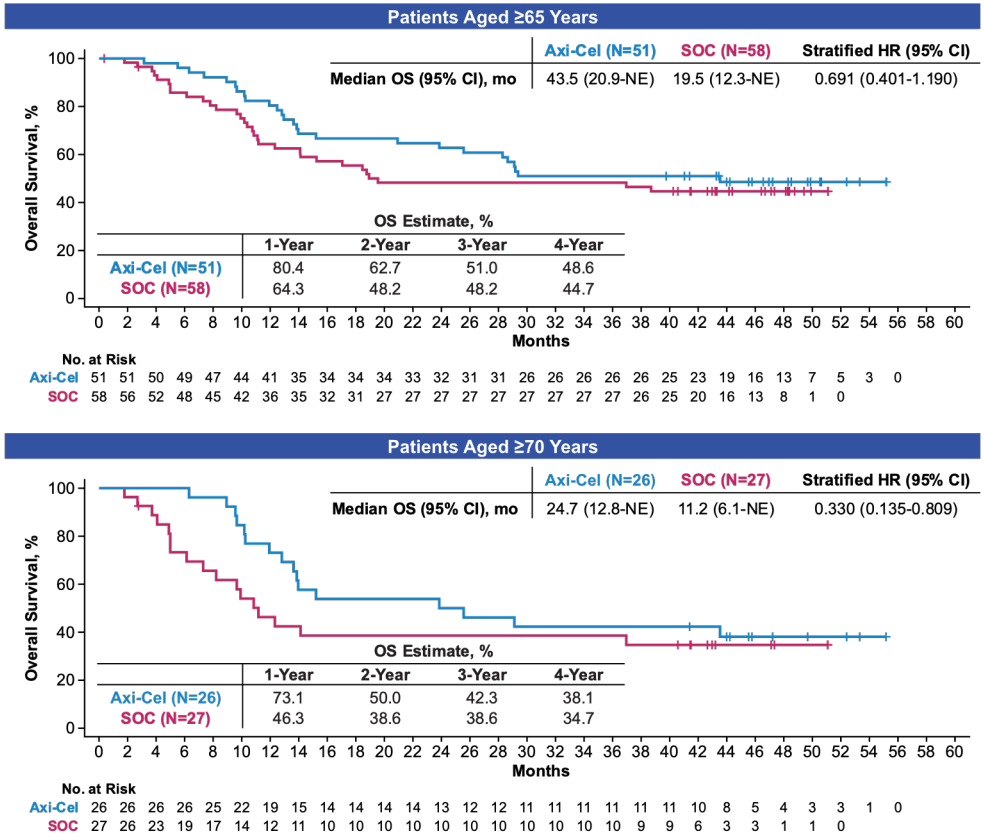
- In ZUMA-7 (NCT03391466), the first randomized, global, multicenter, Phase 3 study of axi-cel versus standard of care (SOC) as second-line treatment in patients with early R/R LBCL, axi-cel showed significantly improved event-free survival (EFS) compared with second-line SOC (hazard ratio [HR], 0.398, *P*<.0001; median 8.3 versus 2.0 months, respectively; 24-month EFS rate: 41% versus 16%, respectively; 24.9-month median follow-up)[1]
  - Similar findings were observed among patients aged ≥65 years, whereby axi-cel was safely administered and resulted in improved EFS, response rates, and quality of life compared with SOC[2]
- At a median follow-up of 47.2 months, results from the ZUMA-7 primary overall survival (OS) analysis demonstrated superior OS in the intention-to-treat (ITT) population (HR, 0.726; 95% CI, 0.540-0.977; one-sided *P*=.0168)[3]

1. Locke FL, et al. *N Engl J Med.* 2022;386:640-654. 2. Westin JR, et al. *Clin Cancer Res.* 2023;29:1894-1905. 3. Westin JR, et al. *N Engl J Med.* 2023;389:148-157.

PFS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years



OS of Axi-Cel Versus SOC in Patients Aged ≥65 Years and ≥70 Years



Kersten et al. ASH 2023, Abstract 1761

781 Autologous Transplant (auto-HCT) Is Associated with Improved Clinical Outcomes Compared to CAR-T Therapy in Patients (pts) with Large B-Cell Lymphoma (LBCL) Achieving a Complete Remission

Program: Oral and Poster Abstracts
Type: Oral
Session: 731. Autologous Transplantation: Clinical and Epidemiological: Role of Autologous Stem Cell Transplantation in Multiple Myeloma and Lymphomas: A Therapeutic Approach

Monday, December 11, 2023: 10:30 AM

Mazyar Shadman, MD, MPH[1,2], *Kwang Wooahn, PhD*[3*], *Manmeet Kaur*[4*], *Mohamed A. Kharfan-Dabaja, MD, MBA*[5], *Alex F. Herrera, MD*[6], *Craig S Sauter, MD*[7] *and Mehdi Hamadani, MD*[8]

Pts who are intended to receive CAR-T, commonly require interim therapy before leukapheresis, where in a small fraction may achieve a complete remission (CR). Having chemosensitive disease, these pts can be considered for auto-HCT. Also, there are reports indicating the efficacy of CAR-T therapy in CR pts (Strati et al., Haematologica, 2023; Wudhikarn et al., Blood Adv, 2022)

Shadman S, et al. Abstract #781. Presented at the 65th ASH

LBCL who were in a CR

Pts aged 18-75 years with DLBCL or primary mediastinal lymphoma who received CAR-T (between 2018-2021) or auto-HCT (between 2015-2021) while in a CR by PET or CT endpoints.

No. Patients in CR	**360**
CAR-T	79
Tisa-Cel	53%
Axi-Cel	46%
Liso-Cell	1%
Auto-HCT	**281**

Table-1: Selected baseline characteristics

	CAR-T	auto-HCT	P-value
Age, years	64	59	0.14
Extra-nodal disease	58%	63%	0.37
Refractory disease to first-line	29%	20%	0.22
Prior lines of therapy, n	3	2	**<0.01**
Early treatment failure (within 12 months)	72%	58%	**0.02**
Elevated LDH before treatment	37%	31%	**0.04**
high-grade B-cell lymphoma with MYC and BCL2 or BCL6 rearrangement	14%	27%	**0.03**

Shadman S, et al. Abstract #781. Presented at the 65th ASH

Univariate analysis

	CAR-T	Auto-HCT	
2-years RR	48%	27.8%	p < 0.001
2-year PFS	47.8%	66.2%	p < 0.001
2-year OS	65.6%	78.9%	P=0.037
2-year TRM	4.1%	5.9%	P=0.673
Patients with early (12 months) treatment failure			
No. Patients	57	163	
2-years RR	45.9%	22.8%	P<0.001
2-year PFS	48.3%	70.9%	P<0.001
No differences in 2 year OS or TRM			

Multivariate analysis

CAR-T was associated with higher risk of relapse (HR 2.18; p < 0.0001) and an inferior PFS (HR 1.83; p=0.0011) compared to auto-HCT. There was no difference in the risk of TRM (HR 0.59; p=0.36) or OS (HR 1.44; p=0.12).

Progression-Free Survival

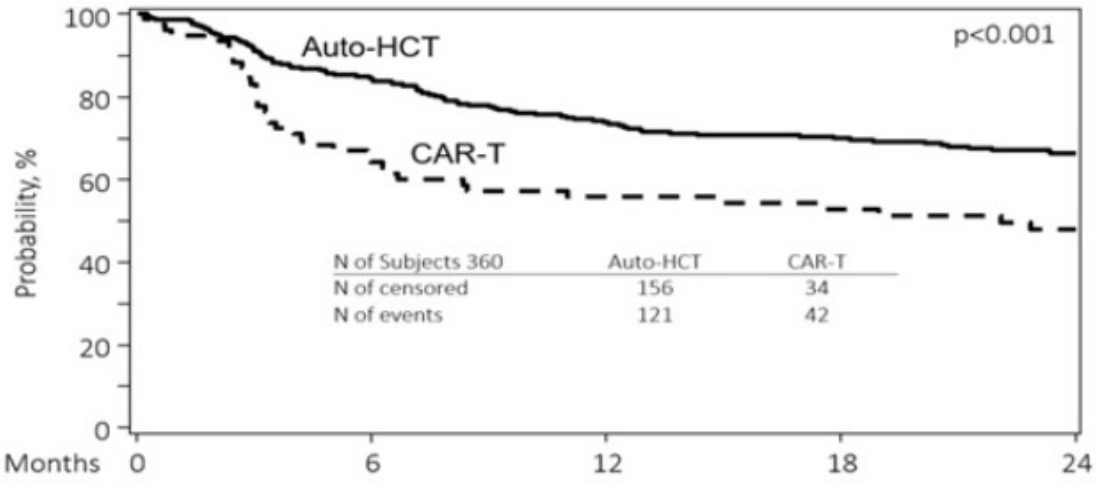


Figure-1: PFS in pts with LBCL who received auto-HCT vs. CAR-T while in CR

Median follow-up:
CAR-T - 24.7 months (range 3.3-49.4)
Auto-HCT - 49.7 months (range 3.0-95.4)

Shadman S, et al. Abstract #781. Presented at the 65th ASH

Treatment of DLBCL in the Third-line Setting:

Focus on CAR T-Cell Therapy

Summary of Baseline Characteristics of CAR T-Cell Studies After ≥1 Prior Lines of Therapy

Characteristic	ZUMA-1[1-3] Axi-cel (n = 101)	JULIET[3,4] Tisa-cel (n = 111)	TRANSCEND NHL 001[3,5] Liso-cel (n = 269)
Median age, yr (range)	58 (23-76)	58 (22-76)	63 (18-86)
▪ ≥65 yr, %	24	23	42
HGBCL/DHL/THL, %	6	17	13
Previous ASCT, %	21	49	33
No. of prior lines of tx, median (range)	3 (2-4)	3 (1-6)	3 (1-8)
▪ 1 line, %	3	5	3
▪ 2 lines, %	28	44	45
▪ ≥3 lines, %	69	51	25
▪ ≥4 lines, %	--	21	26
Refractory to last tx, %	98	45	67
Received bridging tx, %	0	92	59

1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Westin. Am J Hematol. 2021;96:1295. 4. Schuster. NEJM. 2019;380:45. 5. Abramson. Lancet. 2020;396:839.

Summary of Efficacy of CAR T-Cell Studies After ≥1 Prior Line of Therapy

Characteristic	ZUMA-1[1] Axi-cel (n = 101)	JULIET[2] Tisa-cel (n = 115)	TRANSCEND NHL 001[3] Liso-cel (n = 257)
Median DoR, mo (95% CI)	11.0 (4.2-51.3)	NR (10.0-NE)	23.1 (8.6-NR)
Median OS, mo (95% CI)	25.8 (12.8-NE)	11.1 (6.6-23.9)	27.3 (16.2-45.6)
Median PFS, mo (95% CI)	5.9 (3.3-15.0)	2.9 (2.3-5.2)	6.8 (3.3-12.7)
Median follow-up, mo	63.1	40.3	19.9

1. Neelapu. Blood. 2023;141:2307. 2. Schuster. Lancet Oncol. 2021;22:1403. 3. Abramson. Blood. 2024;143:404.

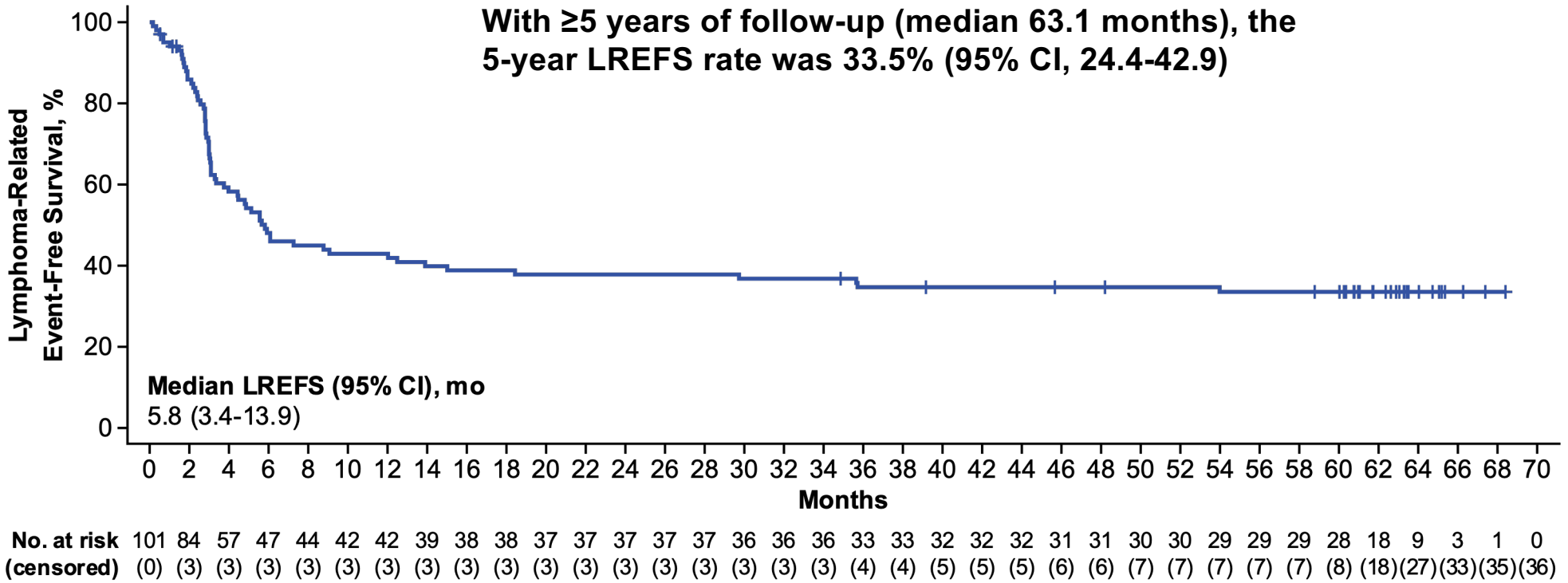
Curative Potential of Axicabtagene Ciloleucel (Axi-Cel): an Exploratory Long-Term Survival Assessment in Patients with Refractory Large B-Cell Lymphoma from ZUMA-1

Sattva S. Neelapu, MD[1]; Caron A. Jacobson, MD, MMSc[2]; Armin Ghobadi, MD[3]; David B. Miklos, MD, PhD[4]; Lazaros J. Lekakis, MD[5]; Clare Spooner, MBBS[6]; Jenny J. Kim, MD, MS[6]; Harry Miao, MD, PhD[6]; Allen Xue, PhD[6]; Yan Zheng, MS[6]; and Frederick L. Locke, MD[7]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Washington University School of Medicine, St Louis, MO, USA; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA; [6]Kite, a Gilead Company, Santa Monica, CA, USA; and [7]Moffitt Cancer Center, Tampa, FL, USA

Neelapu et al. ASH 2003 Abstract 4864)

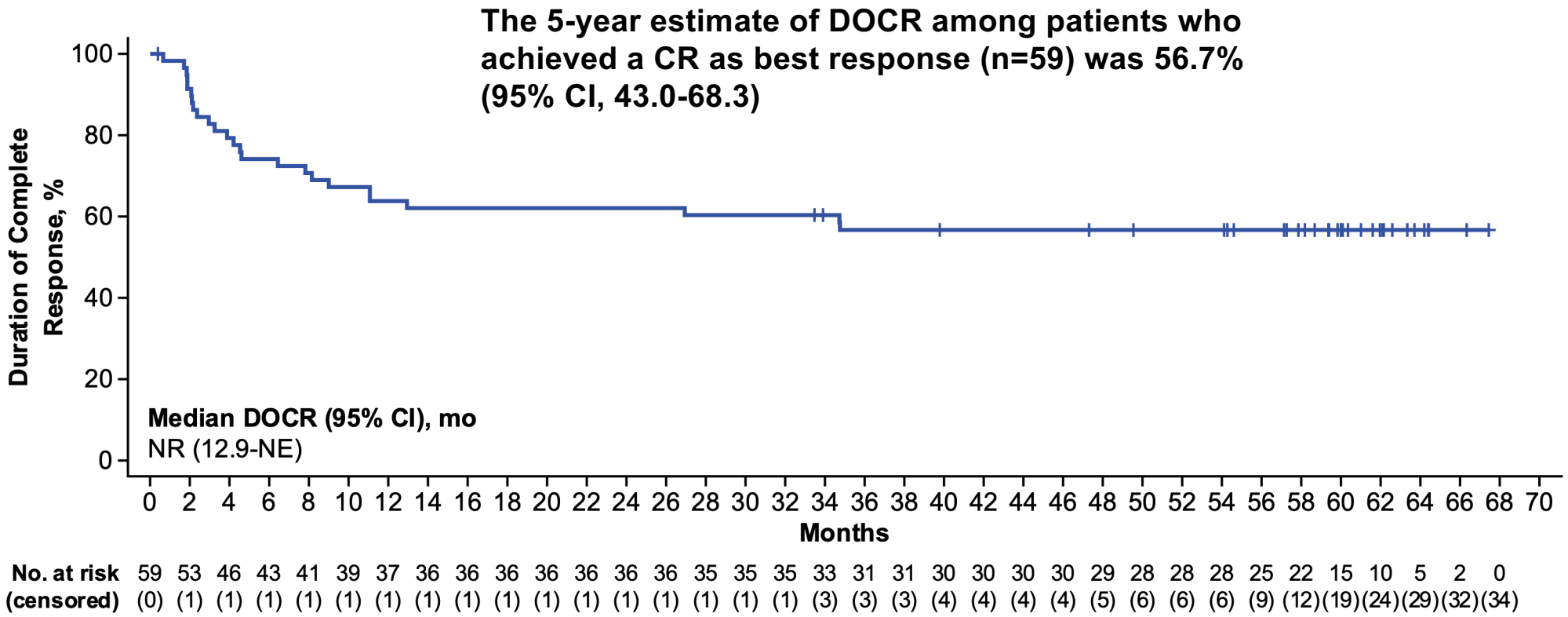
Lymphoma-Related Event-Free Survival



Neelapu et al. ASH 2003 Abstract 4864)

LREFS, lymphoma-related event-free survival, mo, month.

Duration of Complete Response



Neelapu et al. ASH 2003 Abstract 4864

DOCR, duration of complete response; mo, month; NE, not estimable; NR, not reached.

228 Efficacy of Chimeric Antigen Receptor T-Cell Therapy Is Not Impaired By Previous Bispecific Antibody Treatment in Patients with Large B-Cell Lymphoma

Program: Oral and Poster Abstracts
Type: Oral
Session: 705. Cellular Immunotherapies: Late Phase and Commercially Available Therapies: Translational Data and Prognostic Factors
Hematology Disease Topics & Pathways:
Research, Biological therapies, Lymphomas, Bispecific Antibody Therapy, Clinical Research, B Cell lymphoma, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, real-world evidence, aggressive lymphoma, Therapies, therapy sequence, Lymphoid Malignancies

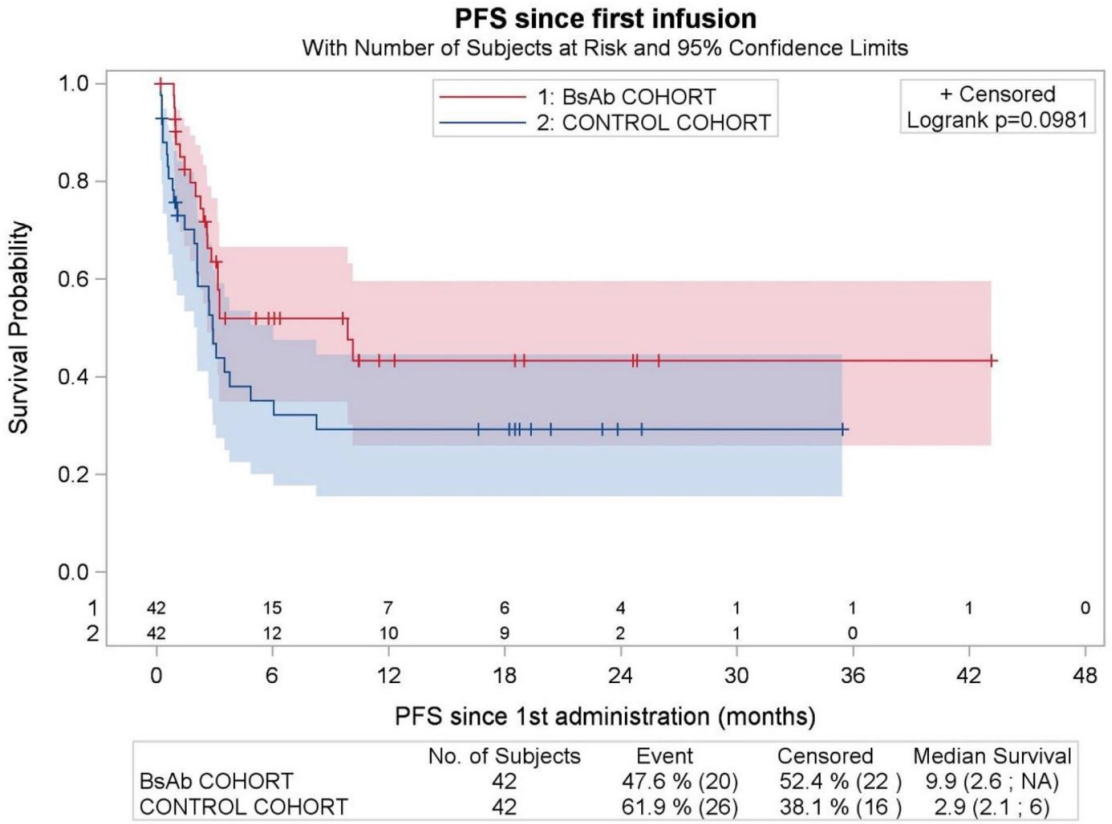
Saturday, December 9, 2023: 3:15 PM

Gloria Iacoboni, MD[1*], *Gilles Crochet, MD*[2*], *Audrey Couturier, MD*[3*], *Emmanuel Bachy, MD, PhD*[4*], *Josu Iraola*[1*], *Thomas Gastinne, MD*[5*], *Charles Herbaux, MD, PhD*[6*], *Tom Fradon*[7*], *Mi Kwon*[8], *Romain Gounot*[9*], *Nuria Martinez-Cibrian, MD*[10*], *Cristina Castilla-Llorente, MD*[11*], *Manuel Guerreiro, MD*[12*], *Clementine Sarkozy*[13*], *Jose Aspa-Cilleruelo*[1*], *Vincent Camus, MD*[14*], *Stephanie Guidez*[15*], *Adrien Chauchet*[16*], *Eric Deconinck*[16], *Krimo Bouabdallah, MD*[17*], *Pere Barba, MD*[1], *Roch Houot, MD, PhD*[3*] *and Franck Morschhauser*[18]

Introduction: Potential T-cell exhaustion after bispecific antibody (BsAb) treatment remains an open question, raising the theoretical concern that prior BsAb exposure could affect subsequent chimeric antigen receptor (CAR) T-cell efficacy. Clinical data on CAR T-cell outcomes after prior BsAb treatment in the setting of large B-cell lymphoma (LBCL) are scarce and highly awaited to better define treatment sequencing in relapsed/refractory (R/R) patients.

Methods: We conducted a retrospective, international study including R/R LBCL patients treated with CD19-targeted CAR T-cells at 15 centers between July 2018 and January 2023 who had been exposed to BsAbs prior to apheresis. Then, we identified a control cohort from patients included in the DESCAR-T Registry (n=764). We carried out a 1:1 propensity score matching (PSM) to achieve balance between cohorts; 13 baseline covariates were included in the PSM. We compared response rates, survival outcomes and toxicity after CAR T-cell therapy, according to previous BsAb exposure.

Variables	BsAb cohort n=42	Control cohort n=42	SMD
Patient and lymphoma characteristics			
Male gender, n (%)	29 (69)	31 (74)	-0.085
Age, median years (range)	63 (31-82)	67 (21-78)	0.061
Histology, n (%)			
- DLBCL/HGBL	35 (83)	31 (74)	0.196
- PMBL/Transformed	7 (17)	11 (26)	
> 2 prior lines, n (%)	36 (86)	36 (86)	0
Previous SCT, n (%)	8 (19)	7 (17)	-0.05
Bulky disease, n (%)	15 (36)	19 (45)	0.16
CRP > 3mg/dL, n (%)	16 (38)	12 (29)	-0.164
LDH > 2xULN, n (%)***	12 (29)	16 (38)	0.168
ECOG >1, n (%)***	4 (10)	3 (7)	-0.069
CAR-T related characteristics			
Axi-cel, n (%)	22 (52)	20 (48)	-0.078
Months between last prior treatment and CAR-T infusion, median (IQR)	2.7 (2.3-3.8)	2.5 (2.0-3.5)	0.201
Response to bridging, n (%)			
- Responder	8 (19)	5 (12)	-0.159
- Non responder	26 (62)	22 (52)	
- No bridge	5 (12)	11 (26)	
- Not evaluated	3 (7)	4 (10)	
Year of CAR-T infusion ≥2020, n (%)	29 (69)	29 (69)	0



Iacoboni G ASH 2023, Abstract 228

Table 1. Clinical characteristics.

	PMBCL (*N* = 70)	Other LBCL (*N* = 190)	*p* value
Sex			0.0312
Female	34 (49%)	64 (34%)	
Male	36 (51%)	126 (66%)	
Age			0.0001
Mean (SD)	35.0 (11.4)	55.9 (12.3)	
Median [Q1, Q3]	33.0 [27.0, 41.8]	57.5 [50.0, 65.0]	
Disease status			0.0048
Refractory	63 (90.0%)	141 (74%)	
Relapse	6 (9%)	46 (22%)	
Missing	1 (1%)	3 (2%)	
Ann Arbor			0.0001
I–II	43 (61%)	64 (34%)	
III–IV	27 (39%)	126 (66%)	
LDH			0.0958
Mean (SD)	255 (243)	344 (574)	
Median [Q1, Q3]	190 [154, 264]	203 [167, 314]	
Missing	4 (6%)	8 (4%)	
IPI			0.0078
<3	55 (79%)	113 (59%)	
≥3	15 (21%)	74 (39%)	
Missing	0	3 (2%)	
Bulky disease			0.0015
No	29 (42%)	122 (64%)	
Yes	40 (57%)	66 (35%)	
Missing	1 (1%)	2 (1%)	
Number of previous treatments			0.3055
Mean (SD)	2.60 (0.858)	2.49 (0.832)	
Median [Q1, Q3]	2 [2, 3]	2 [2, 3]	
Missing	0	3 (2%)	
Previous ASCT			0.0778
No	58 (83%)	136 (72%)	
Yes	12 (17%)	54 (28%)	

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LYMPHOMA

Axicabtagene ciloleucel treatment is more effective in primary mediastinal large B-cell lymphomas than in diffuse large B-cell lymphomas: the Italian CART-SIE study

Annalisa Chiappella[1✉], Beatrice Casadei[2], Patrizia Chiusolo[3], Alice Di Rocco[4], Silva Ljevar[5], Martina Magni[1], Piera Angelillo[6], Anna Maria Barbui[7], Ilaria Cutini[8], Anna Dodero[1], Francesca Bonifazi[2], Maria Chiara Tisi[9], Stefania Bramanti[10], Maurizio Musso[11], Mirko Farina[12], Massimo Martino[13], Mattia Novo[14], Giovanni Grillo[15], Francesca Patriarca[16], Giulia Zacchi[17], Mauro Krampera[18], Martina Pennisi[1], Eugenio Galli[3], Maurizio Martelli[4], Andrés J. M. Ferreri[6], Silvia Ferrari[7], Riccardo Saccardi[8,21], Anisa Bermema[1], Anna Guidetti[1,19], Rosalba Miceli[5], Pier Luigi Zinzani[2,20] and Paolo Corradini[1,19]

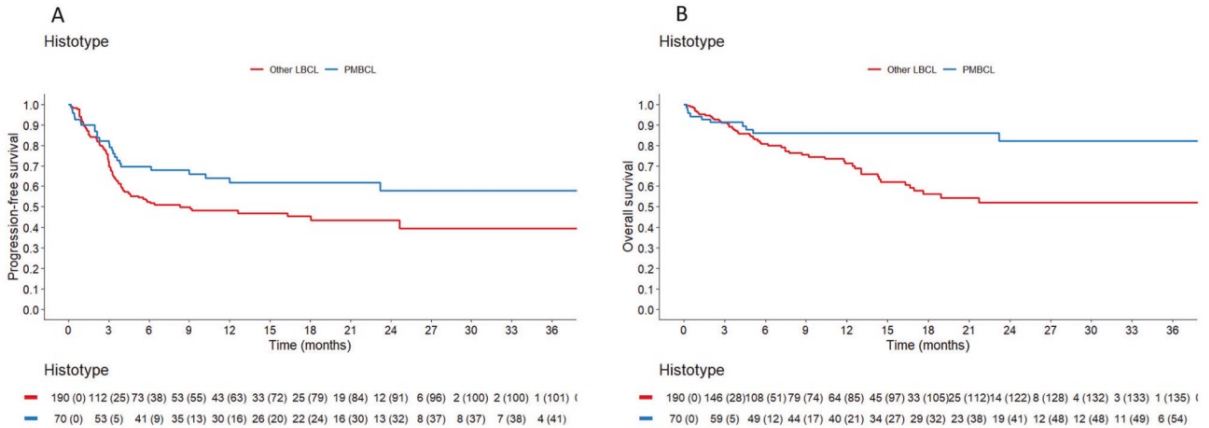


Fig. 2 Progression-free survival and Overall survival. A Progression-free survival. PMBCL primary mediastinal B-cell lymphoma, other LBCL large B-cell lymphoma other than primary mediastinal B-cell lymphoma. Log-rank test *p* value 0.0386. **B** Overall survival. PMBCL primary mediastinal B-cell lymphoma, other LBCL large B-cell lymphoma other than primary mediastinal B-cell lymphoma. Log-rank test *p* value 0.0034.

Chiappella et al. Leukemia 2024

Axicabtagene ciloleucel demonstrates superior progression-free survival compared to Tisagenlecleucel in Large B-Cell Lymphomas: results of the Italian CART-SIE study

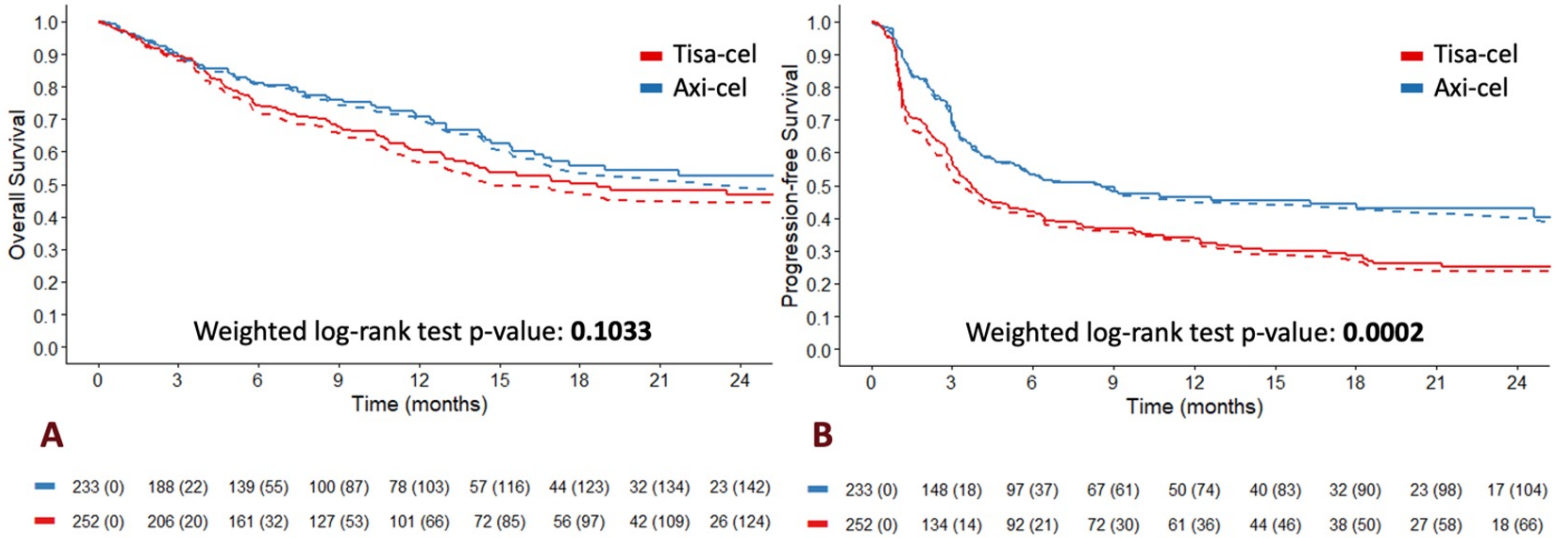


Figure 2 – Survival of Tisa-cel versus Axi-cel before and after Propensity Score Weighting – **Panel A**: Overall Survival, **Panel B**: Progression Free Survival

Unpublished data - NO PHOTO

First line

POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting
della Società Americana
di Ematologia

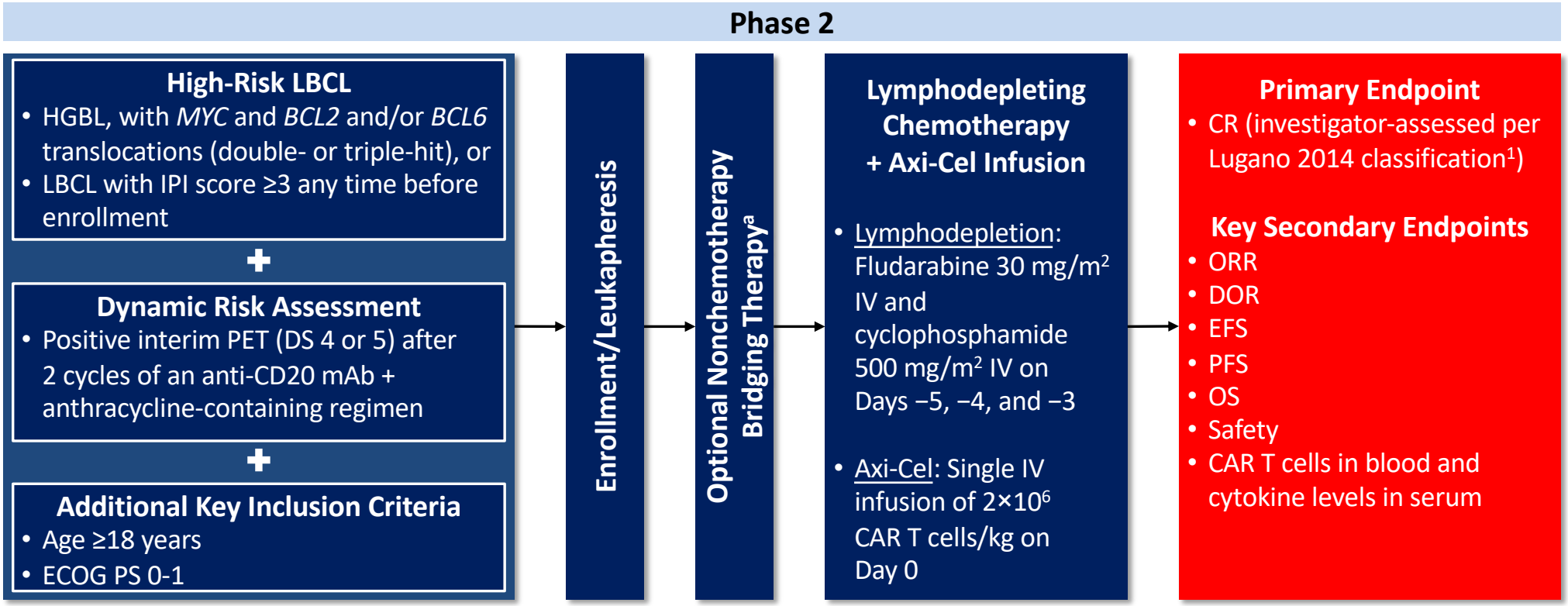
Verona, 15-16-17 Febbraio 2024

3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma

Julio C. Chavez, MD[1]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[2]; Javier Munoz, MD, MS, MBA, FACP[3]; Matthew L. Ulrickson, MD[3]; Catherine Thieblemont, MD, PhD[4]; Olalekan O. Oluwole, MD, MPH, MBBS[5]; Alex F. Herrera, MD[6]; Chaitra S. Ujjani, MD[7]; Yi Lin, MD, PhD[8]; Peter A. Riedell, MD[9]; Natasha Kekre, MD, MPH, FRCPC[10]; Sven de Vos, MD, PhD[11]; Christine Lui, MS[12]; Jacob Wulff, DrPH[12]; Chad M. Williams, PhD[12]; Weixin Peng, MS[12]; Ioana Kloos[12]; Hairong Xu, MD, PhD[12]; and Sattva S. Neelapu, MD[13]

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Victoria, Australia; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Hôpital Saint Louis, Paris, France; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]City of Hope National Medical Center, Duarte, CA, USA; [7]Seattle Cancer Care Alliance, Fred Hutchinson Cancer Center, Seattle, WA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL, USA; [10]The Ottawa Hospital, Ottawa, ON, Canada; [11]David Geffen School of Medicine at UCLA, Santa Monica, CA, USA; [12]Kite, a Gilead Company, Santa Monica, CA, USA; and [13]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ZUMA-12 Study Design



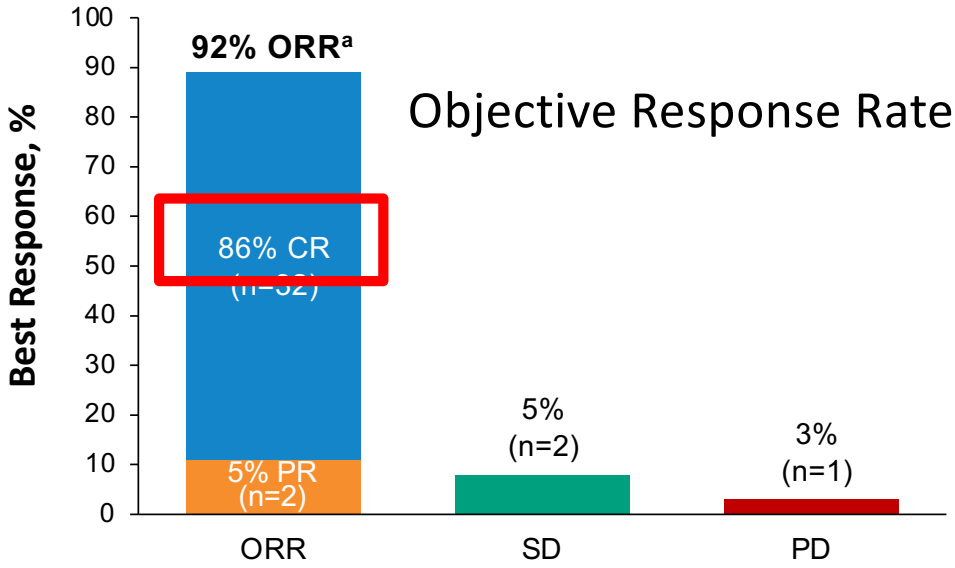
[a] Administered after leukapheresis and completed prior to initiating lymphodepleting chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

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 PS, 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.

Chavez et al. ASH 2023, Abstract 894

At data cutoff, median follow-up for all patients treated with axi-cel was 40.9 months (range, 29.5-50.2)

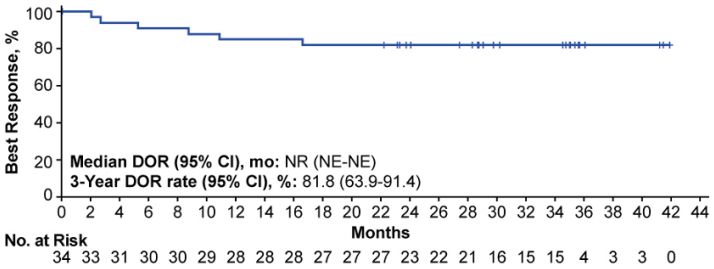


	Efficacy Evaluable n=37
Overall CR rate, % (95% CI)	86 (71-95)
DHL/THL and IPI score ≥3 (n/N)	4/4 100 (40-100)
DHL/THL only (n/N)	5/6 83 (36-100)
IPI score ≥3 only (n/N)	23/27 85 (66-96)
Patients converted from PR/SD to CR, n (%)	9 (24)
PR to CR	8 (22)
SD to CR	1 (3)

- In the efficacy-evaluable population, the CR rate was slightly higher than in the primary analysis[1] due to an additional number of patients converting from PR to CR
- Responses were ongoing in 73% of response-evaluable patients at data cutoff

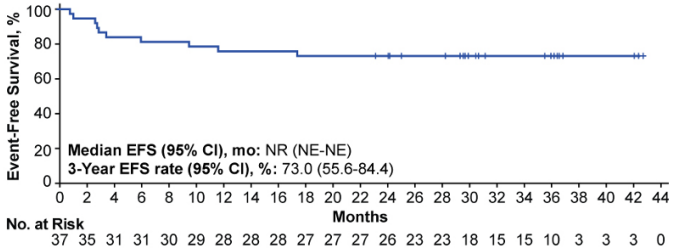
Chavez et al. ASH 2023, Abstract 894

Duration of Response



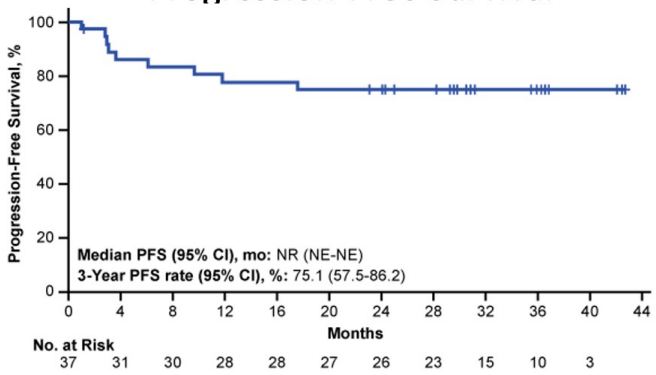
- With extended follow-up since the primary analysis, median DOR was not reached in efficacy-evaluable patients
- Among patients who achieved a CR as best response, the 3-year DOR rate was 84.4% (95% CI, 66.5-93.2)

Event-Free Survival

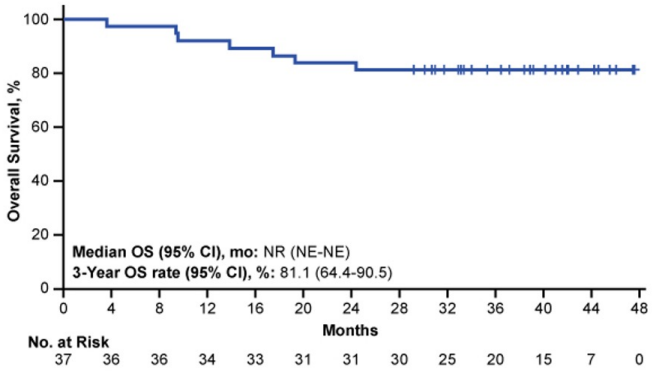


- Median EFS was not reached in efficacy-evaluable patients; the 3-year EFS rate was 73% (95% CI, 55.6-84.4) and a plateau in the curve emerged by Month 18
- Among patients who achieved a CR as best response, the 3-year EFS rate was 84.4% (95% CI, 66.5-93.2)

Progression-Free Survival



Overall Survival



- Medians for PFS and OS were not reached in efficacy-evaluable patients
- Among patients who achieved a CR as best response, the 3-year PFS and OS rates were 84.4% (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

Chavez et al. ASH 2023, Abstract 894

Effectiveness of CAR-T treatment toward the potential risk of second malignancies

Study	Characteristics	Disease	No. Patients	Secondary malignancy	Median Follow-Up
ZUMA-7 Ref. 27	First randomized, global, multicenter, Phase 3 study of axi–cel versus standard of care as second–line treatment in patients with, axi–cel showed significantly improved event–free survival (EFS) compared with second–line SOC (hazard ratio [HR], 0.398, P<.0001; median 8.3 versus 2.0 months; 24–month EFS rate: 41% versus 16%	Early R/R LBCL	Axi–Cel, ≥65 Years N=51 SOC, ≥65 Years N=58	Axi–Cel, ≥65 Years 1 (2%) Acute myeloid leukemia SOC, ≥65 Years 0 (0%)	46.6 months
ZUMA-12 Ref. 29	Phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment. In the primary efficacy analysis (n=37; median follow-up of 15.9 months), axi-cel demonstrated a high rate of durable responses with an investigator-assessed CR rate of 78% (and an ORR of 89%	high-risk LBCL	37	1 esophageal adenocarcinoma,	40.9 months
Real-world Ref- 31	Commercial use of liso-cel based on a postmarketing study using data collected at the Center for International Blood and Marrow Transplant Research (CIBMTR)	R/R LBCL	396	Squamous cell skin malignancy 5 (1%) Myelodysplasia 3 (1%) Basal cell skin malignancy 2 (< 1%) Gastrointestinal malignancy 2 (< 1%) Melanoma 1 (< 1%) Myeloproliferative neoplasm 1 (< 1%)	
PILOT Ref. 35	Open-label phase 2 study evaluated the efficacy and safety of liso-cel in patients not intended for HSCT after 1 prior line of therapy. In the primary analysis, the primary endpoint was met with an ORR of 80%	R/R LBCL	61	2 (4%) Squamous cell carcinoma of skin and malignant external ear neoplasm (n = 1) Myelodysplastic syndrome (n = 1)	18.2 months
Elara Ref. 38	Phase II, single-arm, global, multicenter, open-label trial investigating the efficacy and safety outcomes of tisagenlecleucel in adults after ≥2 treatment lines or who relapsed after autologous stem cell transplant (autoSCT)	r/r FL	97	2 (squamous cell carcinoma and bladder transitional	29.0 months
ZUMA-5 Ref. 40	Axi-Cel; Single-arm, registrational, phase 2 trial ≥18 years; ≥2 prior systemic therapies that must have included an anti-CD20 monoclonal antibody combined with an alkylating agent.	R/R iNHL, including FL (grade 1-3a) and MZL (nodal or extranodal;	159 (127 FL, 31 MZL, 1DLBCL)	5 (unknown origin, unrelated to axi-cel)	36 months
CARTITUDE-1 Ref. 50	Single-arm, open-label, multicenter, phase Ib/II study conducted in patients to characterize the safety of cilta-cel and confirm the recommended phase II dose (phase Ib) and evaluate clinical efficacy	RRMM	97	20 secondary primary malignancies were reported in 16 patients; all were unrelated to cilta-cel. 9 hematologic SPM, including 1 low-grade B-cell lymphoma, 6 myelodysplastic syndrome, and 3 cases of fatal acute myeloid leukemia (AML; 1 patient had both myelodysplastic syndrome and fatal AML) 4 patients had squamous cell carcinoma; 1 of these also had basal cell carcinoma. 1 patient had basal cell carcinoma that was present before cilta-cel infusion. 1 patient each had malignant melanoma, adenocarcinoma, or myxofibrosarcoma, and 1 patient had prostate cancer in addition to his squamous cell carcinoma and AML reported above.	27.7 months
LEGEND-2 Ref. 51	phase 1, single-arm, open-label study	RRMM	74	2 lung cancers at 8 and 32 months 1 esophageal cancer at 15 months 1 Cervical cancer at 8 months, after the CAR-T cell infusion	47.8 months

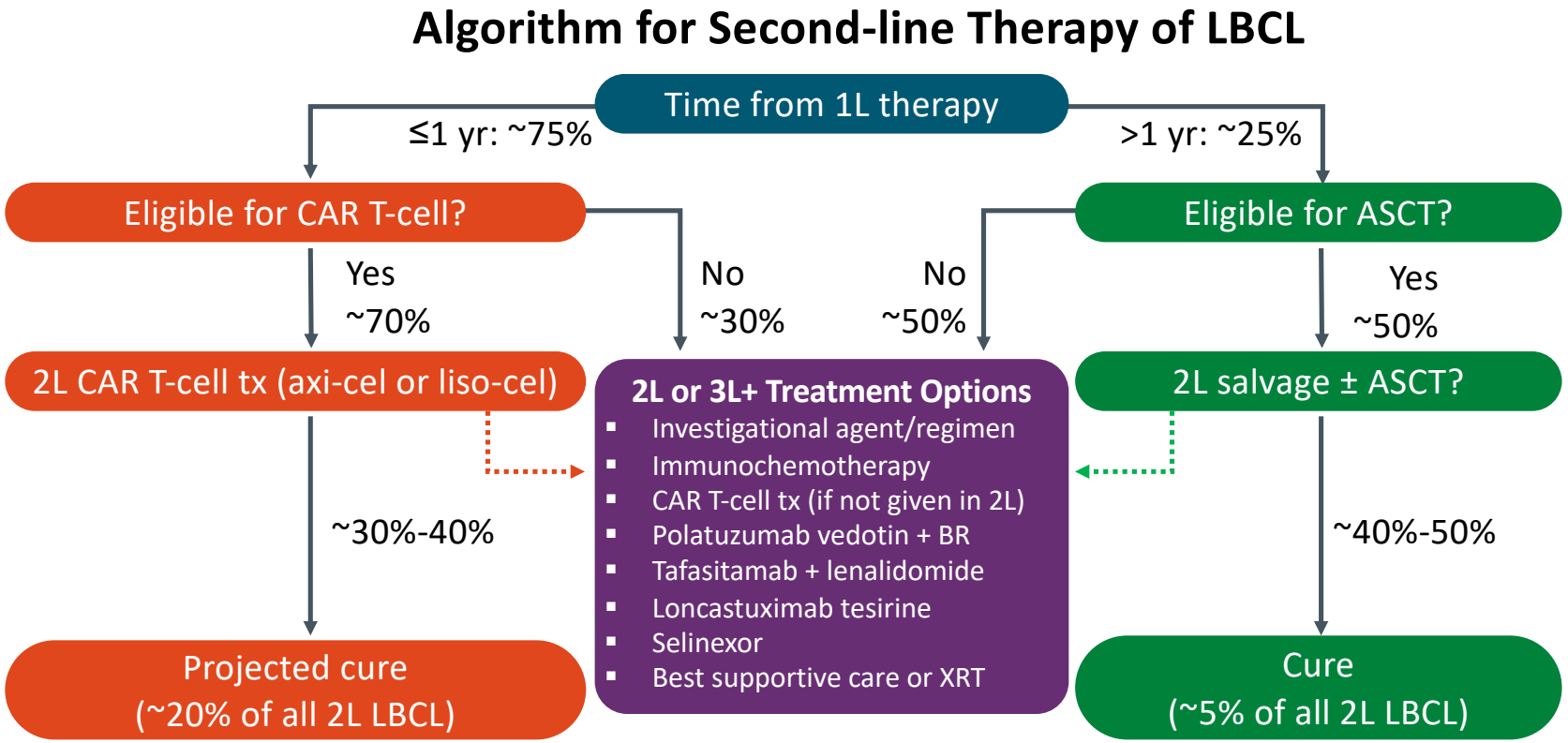
Martino et al. Front. Immunol. Volume 15 - 2024 | doi: 10.3389/fimmu.2024.1384002

Proposed classification of transplant indications for adults—2022

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
LBCL	CR1 (intermediate/high IPI at diagnosis)	GNR/III	GNR/III	GNR/III	CO/I	GNR/III
	Untested relapse	GNR	GNR	GNR	GNR	S/I
	Chemosensitive early relapse, ≥CR2	CO/II	CO/II	D/III	CO/I	S/II
	Chemosensitive late relapse, ≥CR2	CO/II	CO/II	D/III	S/II	CO/II
	Chemosensitive relapse after auto-HSCT failure	CO/II	CO/II	CO/III	GNR/III	S/II
	Refractory disease	CO/II	CO/II	CO/III	GNR/I	S/I
	Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/II	D/III

Bone Marrow Transplantation (2022) 57:1217 – 1239

CD19-Targeted CAR T-Cell Therapy Has Dichotomized Management of R/R DLBCL



Westin. Blood. 2022;139:2737.