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1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

Avellino, Hotel de la Ville
March 30-31, 2023

CAR-T PER IL TRATTAMENTO DEI LINFOMI NON-HODGKIN

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Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Celgene						x	
Gilead Sciences						x	
Takeda						x	
Abbvie						x	
Janssen						x	
Beigene						x	
Novartis					x		
Roche					x		
Incyte							x

Agenda

- Introduction
- LBCL:

  CART as 3rd line or later therapy: phase 2 trials and Real World

  CART as 2nd line of therapy

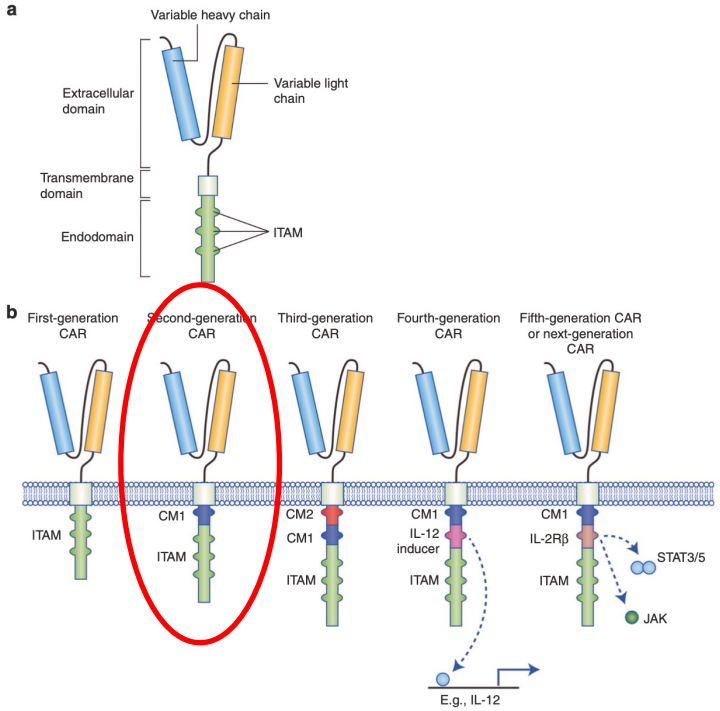
  CART as 1st line of therapy

- MCL: Results from ZUMA-2 trial

- FL: Results from ELARA and ZUMA-5

Introduction

- Patient's own T cells are engineered to express an **anti-CD19 CAR** using a viral vector (gamma retrovirus or lentivirus)
- The **target-binding domain** identifies and binds to the CD19 surface antigen of B cells
- Upon binding, the **CD3ζ activation** and **CD28 (axi-cel and brexu-cel) or 41BB (tisa-cel and liso-cel) costimulatory domains** activate the CAR T cells
- Activated CAR T cells release inflammatory cytokines and chemokines and destroy the CD19-expressing B cells



1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel	Brexucabtagene Autoleucel
Construct	Anti–CD19-**CD28**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**41BB**-CD3z	Anti–CD19-**CD28**-CD3z
FDA approval status	1. Adults patients with r/r **DLBCL**, HGBCL, tFL or **PMBCL** after **≥ 2 lines** of systemic therapy 2. Adult patients with **LBCL** that is refractory to or that relapses within 12 months of first-line chemoimmunotherapy **(II line)** 3. Adults with r/r **FL after ≥ 2** lines of systemic therapy	1. Paediatric patients with r/r B-cell ALL 2. Adults patients with r/r **DLBCL**, HGBCL or tFL after **≥2 lines** of systemic therapy 3. Adults patients with r/r **FL after ≥ 2** lines of systemic therapy	1. Adult patients with r/r **DLBCL,** HGBCL, FL grade 3B or PMBCL after **≥2 lines** of systemic therapy	1. Adult patients with **r/r MCL**
EMA approval status	1. Adults patients with r/r **DLBCL**, HGBCL, tFL or **PMBCL** after **≥ 2 lines** of systemic therapy 2. Adult patients with **r/r FL after ≥ 3** lines of systemic therapy	1. Paediatric and young patients ≤25 years of age with B-cell ALL that is refractory, relapsed post-transplant or in second or later relapse 2. Adult patients with **r/r DLBCL,** HGBCL or tFL **after ≥2 lines** of systemic therapy 3. Adult patients with **r/r FL after ≥2 lines** of systemic therapy	1. Adult patients with r/r **DLBCL, PMBCL** and FL grade 3B **(FL3B),** after ≥2 lines of systemic therapy	1. Adult patients with r/r **MCL after ≥2** lines of systemic therapy including a Bruton's tyrosine kinase inhibitor
AIFA approval status	1. Adult patients with r/r LBCL after **≥ 2 lines** of systemic therapy, including: • DLBCL NOS • HGBCL • **DLBCL arising from FL or MZL** • PMBCL	1. Paediatric and young patients ≤25 years of age with B-cell ALL that is refractory, relapsed post-transplant or in second or later relapse 2. Adult patients with r/r LBCL after ≥ 2 lines of systemic therapy, including: • DLBCL NOS • HGBCL • DLBCL arising from FL or MZL	1. Adult patients with r/r LBCL after ≥ 2 lines of systemic therapy, including: • DLBCL NOS • HGBCL • DLBCL arising from FL • PMBCL • FL3B	1. Adult patients with r/r **MCL after ≥2 lines** of systemic therapy including a Bruton's tyrosine kinase inhibitor

CART as 3rd line or later therapy: JULIET, ZUMA-1 and TRANSCEND

	Tisa-cel (Juliet) [1]	Axi-cel (Zuma-1) [2]	Liso-cel (Transcend)[3]
Source	Cryopreserved unsorted PBMCs	Fresh unsorted PBMCs	Fresh sorted PBMCs CD4:CD8 = 1:1
Pts infused, n	115 (167 enrolled)	101 (111 enrolled)	269 (344 enrolled)
BT	Allowed	Not allowed	Allowed
LD	FC (25 mg/m^2; 250 mg/m^2) or Bendamustine (90 mg/m^2)	FC (30 mg/m^2; 500 mg/m^2)	FC (30 mg/m^2; 300 mg/m^2)
CAR T-cells dose	Median: 3.0× 10^8 (range:0.1 × 10^8 to 6.0 × 10^8 ; target: 5 × 10^8)	2x10^6 cells/Kg or fixed 2x10^8 cells for pts weighed ≥100 kg	DL1 50x10^6 ; DL2: 100x10^6, DL3: 150x10^6 CAR T-cells
CRS grading	UPenn scale	Lee 2014	Lee 2014
NE grading	CTCAE vers 4.03	CTCAE vers 4.03	CTCAE vers 4.03
1st endpoint[3]	ORR by IRC	ORR by IRC	ORR by IRC, AEs, DLT
2nd endpoints	DOR; time to response; OS; PFS; EFS, cell kinetics, safety	DOR; OS; PFS; EFS, time to progression, TTNT, disease specific survival, cell kinetics, safety	CRR, DOR, PFS, OS, cellular kinetics
Response evaluation	CT at 1 mo and PET at 3 mo from infusion	PET at 1 mo from infusion	PET at 1 mo from infusion

1.Schuster SJ, et al. *Lancet Oncol* 2021:22(10):1403–15; 2. Neelapu SS, et al. *Blood* 2022; 3. Abramson JS, et al. Lancet. 2020;396(10254):839-852

CART as 3rd line or later therapy: JULIET, ZUMA-1 and TRANSCEND

Pts characteristics	Tisa-cel (Juliet) [1]	Axi-cel (Zuma-1) [2]	Liso-cel (Transcend)[3]
Median age, y	56 (46-64)	58 (23-76)	63 (54-70)
Stage III-IV, n (%)	88 (77%)	86 (85%)	NA
IPI ≥ 2, n (%)	84 (73%)	48 (48%)^	NA
LDH > UNL, n (%)	NA	85 (84%)	58 (22%) > 500 U/L
CNS involvement	**Not allowed**	**Not allowed**	**7 (5%)**
DLBCL ABC, n (%)	41 (36%)	NA	NA
DH or TH, n (%)	**20 (17%)**	**4 (4%)**	**36 (13%)**
tFL, n (%)	21 (18%)	16 (16%)	78 (29%)
PMBCL, n (%)	Not allowed	8 (8%)	15 (6%)
FL grade 3B, n(%)	**Not allowed**	**Not allowed**	**3 (1%)**
N of prev lines of therapy, median	3 (2-3)	3 (2-4)	3 (2-4)
Refractory to last therapy, n	63 (55%)	80 (79%)	181 (67%)
BT, n (%)	**104 (90%)**	**Not allowed**	**159 (59%)**
LD, n (%)	107 (93%)	101 (100%)	269 (100%)
Time from apheresis to delivery, median	NA (54 days from enrollment)	17 days	24 days (17-51)

1.Schuster SJ, et al. *Lancet Oncol* 2021:22(10):1403–15; 2. Neelapu SS, et al. *Blood* 2022; 3. Abramson et al. Lancet. 2020;396(10254):839-852 ^IPI 3-4

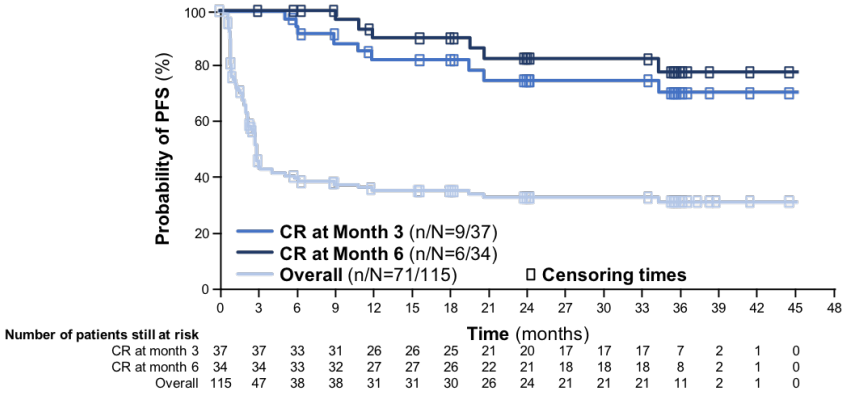
CART as 3rd line or later therapy: JULIET trial

Efficacy (median fup: 40.3 mo)	N=115
ORR, % (n)	53 (61)
CR, % (n)	39 (45)
Median DoR, mo	NR
Median PFS, mo	2.9 (2.3-5.2)
Median OS, mo*	11.1 (6.6-23-9)
Median EFS, mo*	2.8 (2.1-3.06)

Safety	N=115
CRS, %	
Any-grade	57
Grade ≥3	**23**
Neurological events, %	
Any-grade	20
Grade ≥3	**11**
Grade ≥3 prolonged cytopenias, %	34

No treatment related death

PFS



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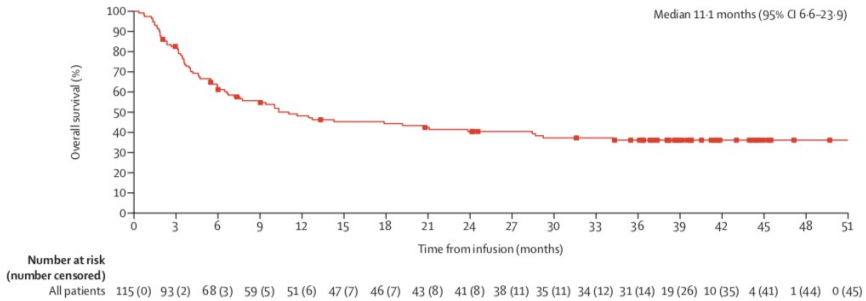


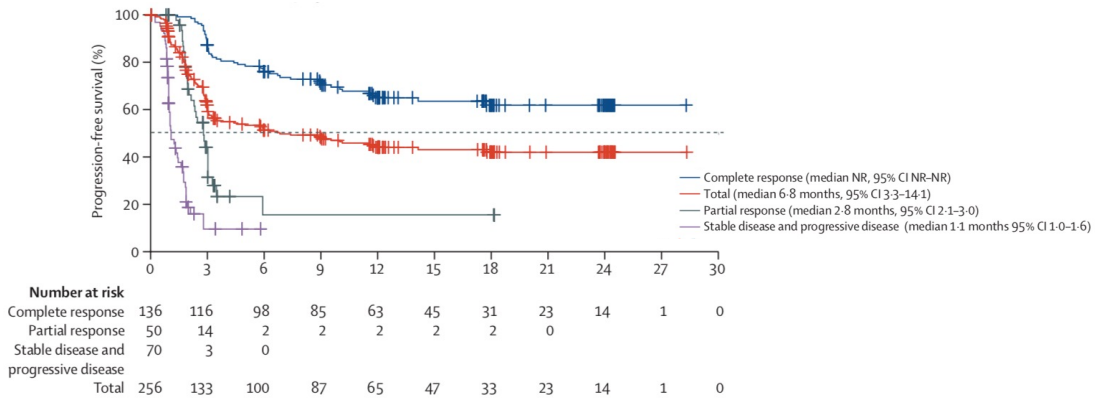
CART as 3rd line or later therapy: TRANSCEND trial

Efficacy (median fup: 18.8 mo)	N=256
ORR, % (n)	73 (186)
CR, %	53 (136)
Median DoR, mo	NR (8.6-NR)
Median PFS, mo	6.8 (3.3-14.1)
Median OS, mo	21.1 (13.3-NE)

Safety	N=269
CRS, %	
Any-grade	42
Grade ≥3	**2**
Neurological events, %	
Any-grade	30
Grade ≥3	**10**
Grade ≥3 prolonged cytopenias	37

7 (3%) pts died due to AEs related to Liso-cel

PFS



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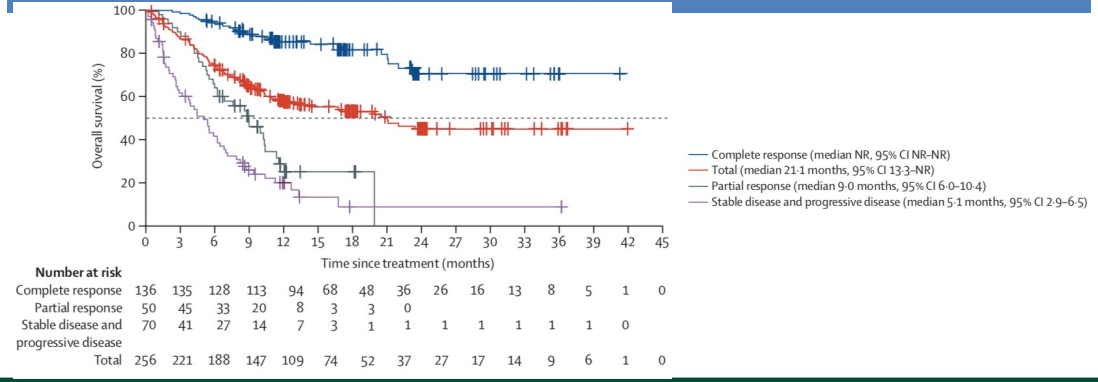


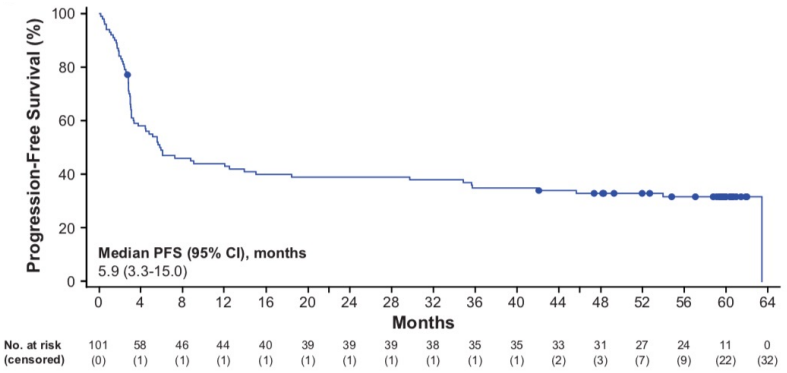
CART as 3rd line or later therapy: ZUMA-1 trial

Efficacy (median fup: 63.1 mo)	N=101
ORR, % (n)	83 (84)
CR, %	58 (59)
Median DoR*, mo	11.1 (4.2-51.3)
Median PFS, mo	5.9 (3.3-15)
Median OS, mo	25.8 (12.8-NE)
Median EFS, mo	5.7 (3.1-13.9)
Median disease specific survival	NR

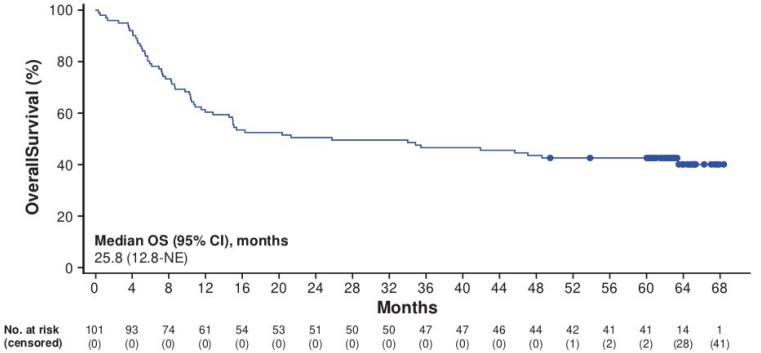
Safety	N=101
CRS, %	
Any-grade	93
Grade ≥3	**11**
Neurological events, %	
Any-grade	64
Grade ≥3	**30**
Grade ≥3 prolonged cytopenias	38

2 pts died due to AEs related to Axi-cel

PFS

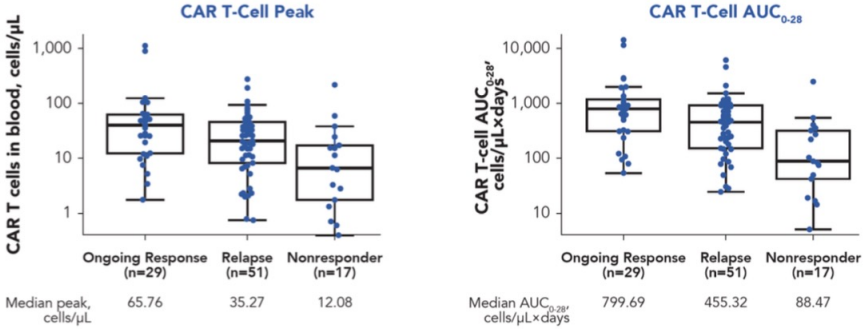


OS

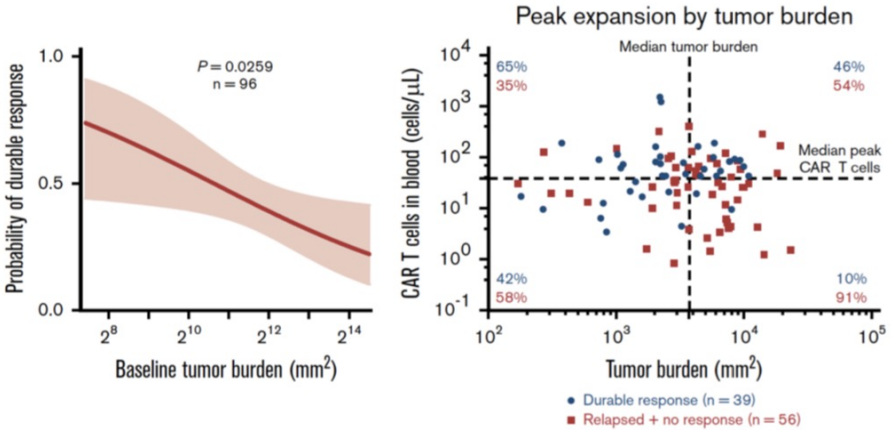


1. Neelapu SS, et al. *Blood* 2022. *median DOR NR for those pts who obtained a CR after week 4

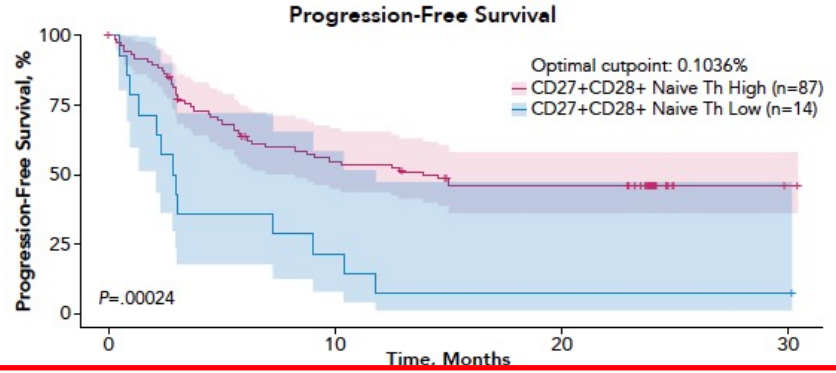
Early CART cell expansion associated with ongoing response at 5 years[1]



Patients with high tumor burden have lower CART cell expansion[3]



CD27+CD28+ naïve T cells in apheresis associated with CART cell product fitness and better efficacy[2]



CART cell fitness is inversely proportional to the number of previous line of therapy → Early referral!

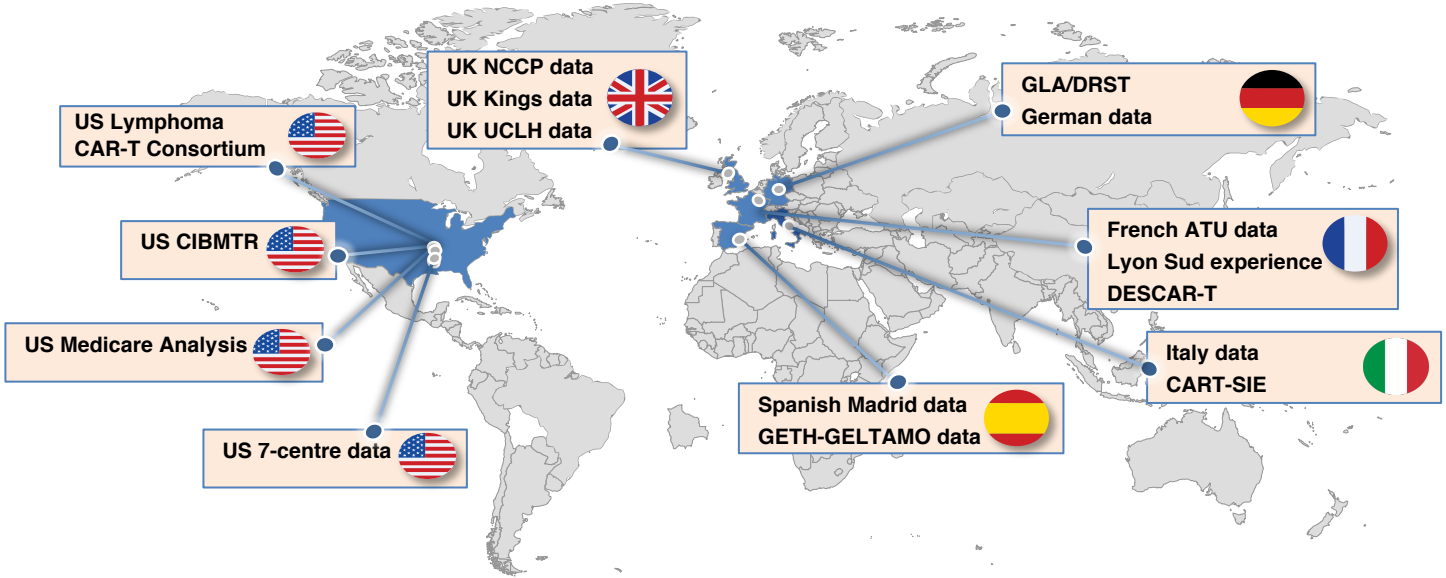
# Prior Lines	Quartile (# Subjects)	Doubling Time	Median CAR AUC_{Dy0-28}	%ORR (n, %)	%Ongoing @12Mth (n, %)
Healthy Donor	n=152	1.34	-	-	
≤2 Lines	Q1 (n=31)	1.42	469.3	28 (90%)	12 (39%)
3 Lines	Q2 (n=29)	1.51	476.6	28 (97%)	10 (34%)
4 Lines	Q3(n=28)	1.7	491.4	23 (82%)	13 (46%)
≥5 Lines	Q4 (n=12)	1.68	211.0	5 (42%)	3 (25%)

1. Jacobson et al, ASH 2021. 2. Budka et al, *AACR* 2021, Abstract #CT166, 3. Locke et al. Blood 2020

CAR-T as 3rd or later line: THE REAL WORLD SETTING

Results between pivotal trials and real-world settings may differ due to

- Patients selection
- Trial design (e.g., bridging therapy, outcome assessment)
- Evolution of toxicities management guidelines



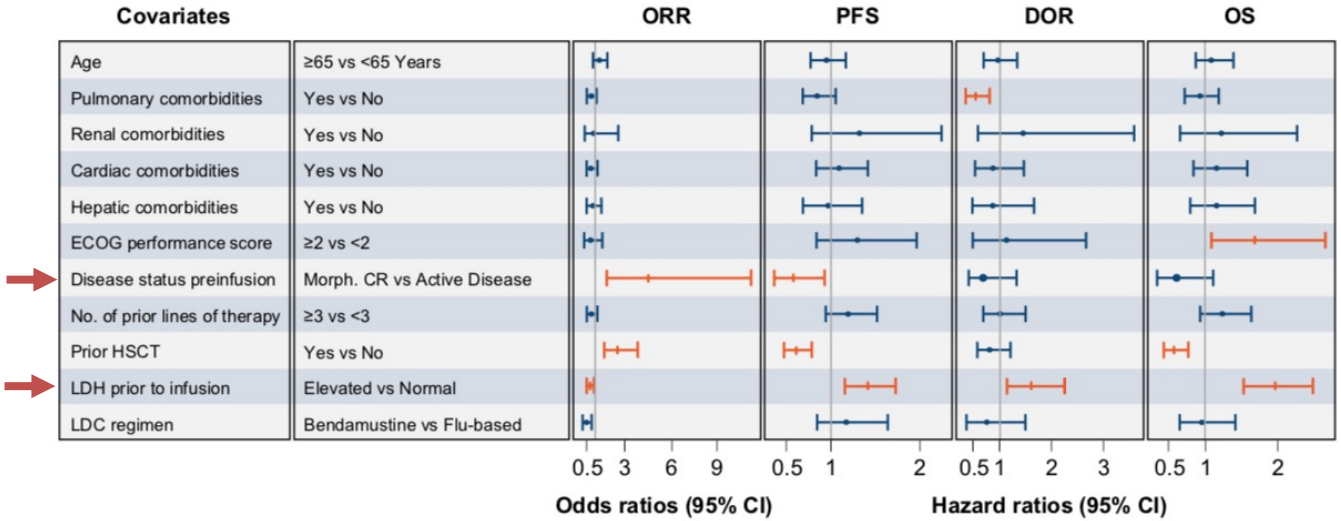
REAL WORLD EXPERIENCE

	JULIET (115)[1,]		CIBMTR (1159)[2]		GELTAMO (75)[3]		ZUMA-1 (101)[4]		US lymphoma CART cell consortium (275)[5]		CIBMTR (122)[6]	
Median follow-up	40.3 mo		24 mo		14.1 mo		63.1 mo		13.8		10.4 mo	
PTs ineligible to ZUMA1	NA		NA		NA		NA		43%		62%	
Bridging therapy	90%		unk		87%		Not allowed		53%		55%	
Best objective response	ORR	CR	ORR	CR	ORR	CR	ORR	CR	ORR	CR	ORR	CR
	53%	39%	59.5%	44.5%	60%	32%	83%	58%	82%	64%	70%	50%
Median DoR	NR		52.6% at 24 mo		8.9 mo		11.1 mo		NR		11 mo	
Median PFS	2.9 mo		28.4% at 24 mo		3 mo		5.9 mo		8.3 mo		4.5 mo	
Median OS	11.1 mo		43.6% at 24 mo		10.7 mo		25.8 mo		NR		NR	
Any grade CRS	66 (57%)*		58.2%§		53 (71%)§		94 (93%)^		251 (91%) ^		114 (93%) ^	
Grade ≥ 3 CRS	26 (23%)		6%		4 (5%)		12 (11%)		19 (7%)		19 (16%)	
Any grade NE	23 (20%) **		22.5%§		11 (15%) §		65 (64%) **		189 (69%) **		85 (70%) **	
Grade ≥ 3 NEs	13 (11%)		7.4%		1 (1%)		35 (30%)		85 (31%)		43 (35%)	

* grading by Upenn; ** grading by CTCAE vers 4.3; § grading by Lee 2019; ^grading by Lee 2014.

1.Schuster SJ, et al. Lancet Oncol 2021; 22:1403-15. 2. Landsburg DJ. et al, ASH 2022; 3. Iacoboni G et al, Cancer Medicine 2021; 4. Neelapu SS, et al. *Blood* 2022.; 5.Nastoupil L.J. et al, J Clin Oncol 2020; 6 Jacobson C et al, J Clin Oncol 2020;

TISA-CEL: CIBMTR REAL WORLD EXPERIENCE

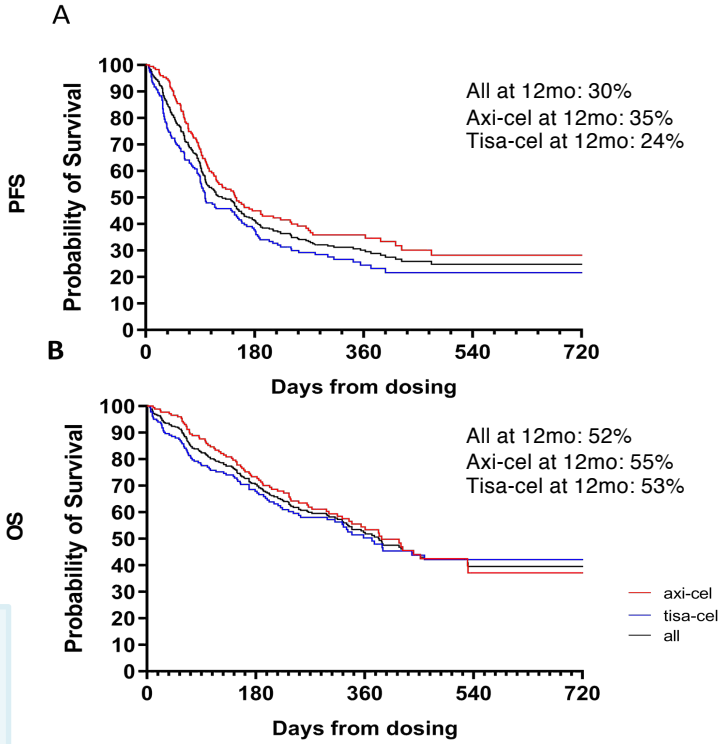


- Data from the largest real-world cohort of patients treated with tisacel, with a median of 2 years' follow-up, reveal durable efficacy and a favorable long-term safety profile.
- **Morphologic CR** and **normal LDH** prior to infusion are associated with **improved efficacy and/or safety outcomes**, which may support the use of debulking and/or bridging therapy to lower disease burden prior to infusion

Landsburg DJ. et al, ASH 2022.

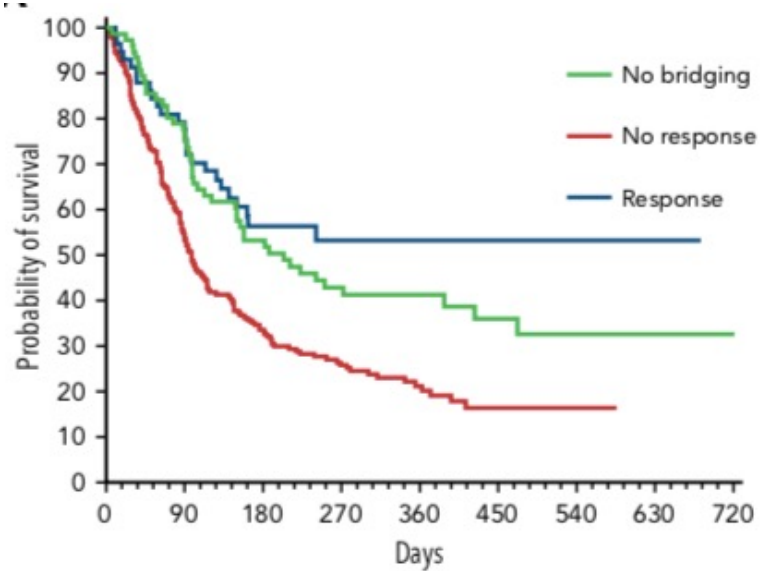
GERMAN LYMPHOMA ALLIANCE REAL LIFE EXPERIENCE

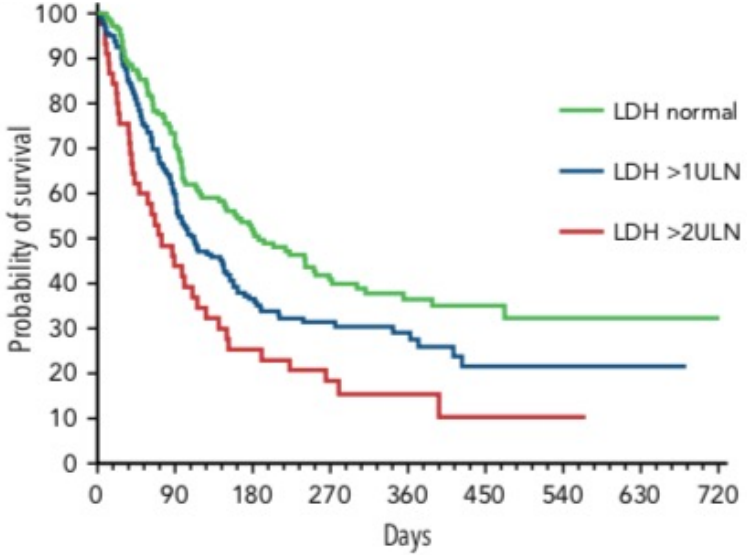
	All, n (%)	Axi-cel (173), n (%)	Tisa,cel (183) n (%)	P
CRS, all grade	259 (73)	141 (81)	118 (65)	.003
CRS, grade ≥ 3	42 (12)	18 (10)	24 (13)	n.s.
ICANS, all grade	116 (33)	76 (44)	40 (22)	<.0001
ICANS, grade ≥ 3	40 (11)	28 (16)	12 (7)	.004
Neutropenia, grade 4	261 (81)	133 (84)	109 (75)	.062
Thrombocytopenia, grade 4	115 (37)	NA	NA	NA



Compared with tisa-cel, axi-cel was associated with better disease control (ORR and PFS at 12 mo) but had a less favorable safety profile (CRS, ICANS and NRM) and comparable survival.

GERMAN LYMPHOMA ALLIANCE REAL LIFE EXPERIENCE



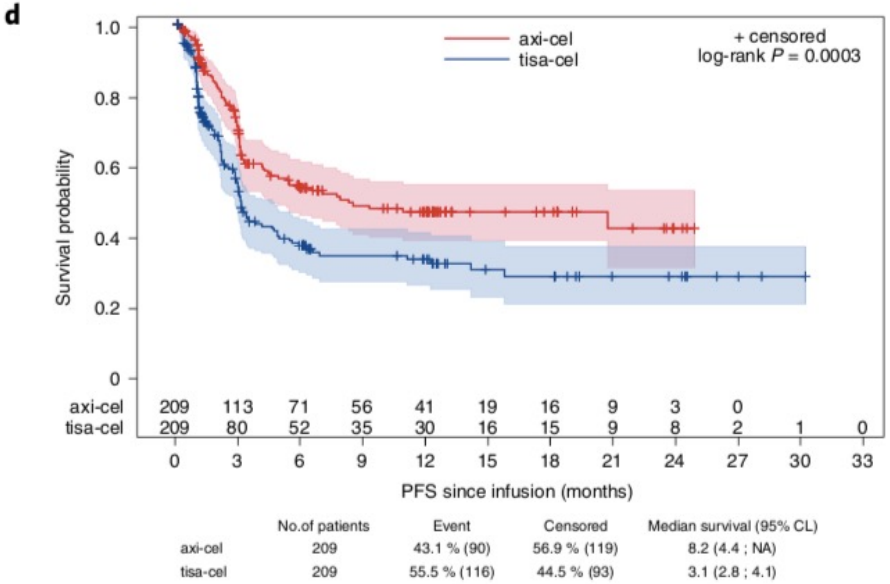


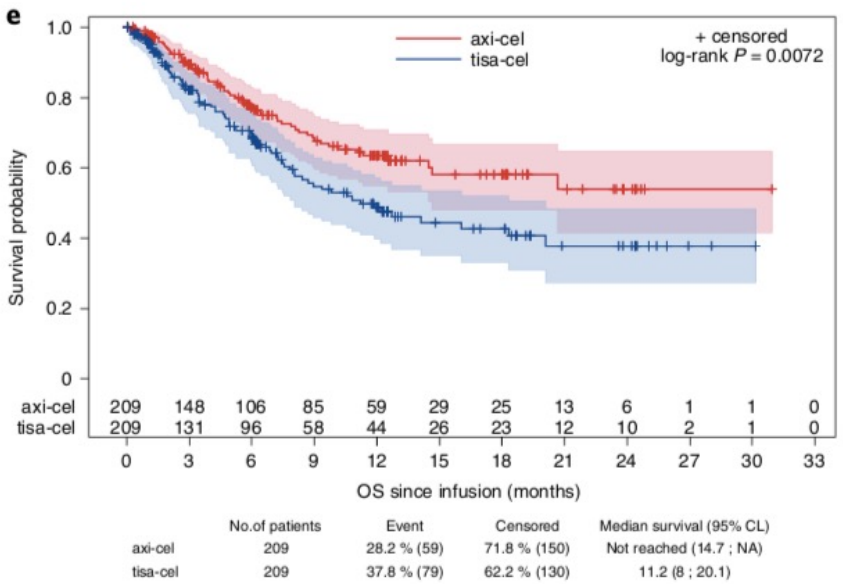
Predictors of PFS and OS are: response to BT, ECOG ($\leq$1 vs >1), LDH at LD.

DESCAR-T REGISTRY: THE PROPENSITY SCORE ANALYSIS

- Propensity score reflects the probability of receiving tisa-cel or axi-cel conditional on an exhaustive list of 14 pre-infusion covariates.
- A propensity score matching (PSM) is based on matching patients with similar propensity score with the aim to create a balanced covariate distribution between r/r DLBCL patients treated with axi-cel or tisa-cel between July 2018 and October 2021 across 25 centers in France (DESCART registry).

DESCAR-T REGISTRY: THE PROPENSITY SCORE ANALYSIS





Axi-cel had significantly higher response rates and prolonged survival compared with tisa-cel, regardless tumor bulk (≤ 5 cm vs > 5 cm) and patient age (≤70 vs > 70 y)

Bachy E. et al. Nat Med Oct 2022

DESCAR-T REGISTRY: THE PROPENSITY SCORE ANALYSIS

Table 3 | Toxicity after CAR T infusion according to CAR T product in the PSM cohorts

	axi-cel		tisa-cel		P
	n = 209		n = 209		
CRS of any grade	180	(86.1%)	158	(75.6%)	0.006
Grade 1–2	169	(80.9%)	139	(66.5%)	<0.001
Grade ≥3	11	(5.3%)	19	(9.1%)	0.130
ICANS of any grade	102	(48.8%)	46	(22.0%)	<0.001
Grade 1–2	73	(34.9%)	40	(19.1%)	<0.001
Grade ≥3	29	(13.9%)	6	(2.9%)	<0.001

Table 3 | Toxicity after CAR T infusion according to CAR T product in the PSM cohorts

	axi-cel		tisa-cel		P
	n = 209		n = 209		
Cytopenia of any grade at M1	135	(64.6%)	82	(39.2%)	<0.001
Grade 1–2	64	(30.6%)	56	(26.8%)	0.387
Grade ≥3	71	(34.0%)	26	(12.4%)	<0.001
Cytopenia of any grade at M3	75	(35.9%)	29	(13.9%)	<0.001
Grade 1–2	51	(24.4%)	21	(10.0%)	<0.001
Grade ≥3	24	(11.5%)	8	(3.8%)	0.003

Axi-cel had significantly higher toxicity profile compared with tisa-cel, but no difference was seen regarding grade 5 AE

Bachy E. et al. Nat Med Oct 2022

SOC second-line treatment for R/R LBCL: HDCT and ASCT

- 10-15% of pts are primary refractory (incomplete response/relapse within 6 mo)[1];
- 20-25% relapse within 2 years after 1st line[1];
- Outcome correlates with timing of progression or relapse: pts with refractory disease have the worst outcome, with a median OS of 6 mo[2];
- PARMA trial established ASCT as SOC (5y EFS 46% vs 12%)[3];
- In the rituximab era, early relapse (< 1 year) and primary refractory pts have a failure rate > 80% with salvage cht and ASCT[4,5];
- Patients who obtain CR2 after salvage cht are better after ASCT, than those with < CR[4,5].

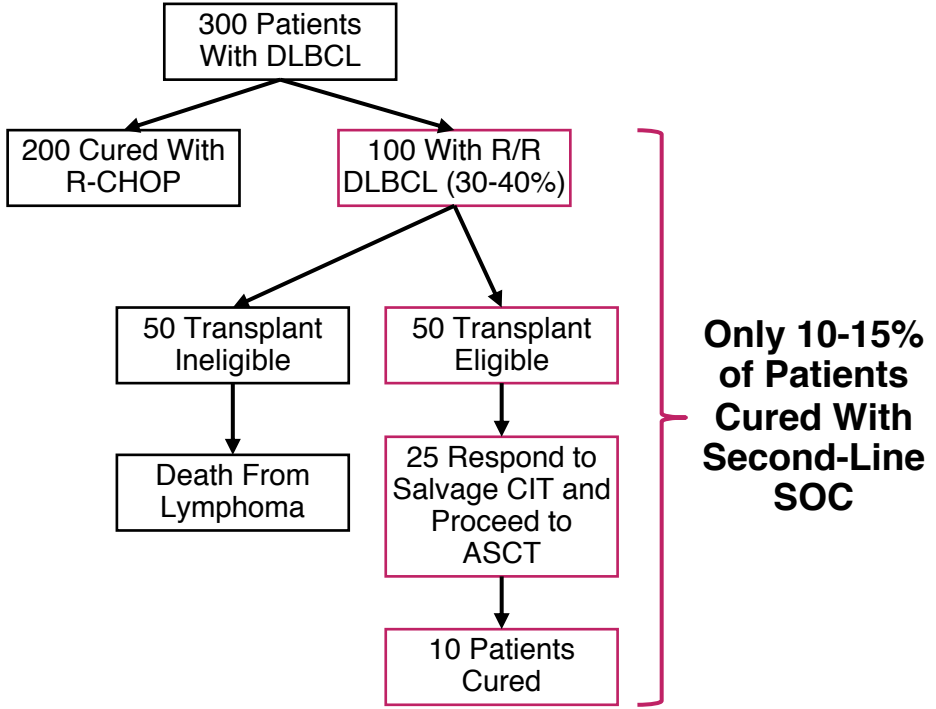
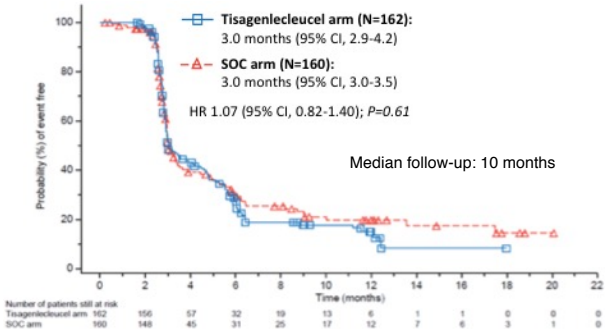


Figure adapted from Friedberg. *Hematology Am Soc Hematol Educ Program.* 2011;2011:498-505. 1. Sehn LH et al. *N Engl J Med.* 2021;384(9):842-85; 2. Crump M, et al. *Blood.* 2017;130:1800-8. 3. Philip T, et al. *N Engl J Med.* 1995;333(23):1540-1545; 4.Crump M, et al. *J Clin Oncol;* 2014;32:3490-6; 5. Gisselbrecht C, et al. *J Clin Oncol.* 2010;28:4184-90

CART as 2nd line of therapy

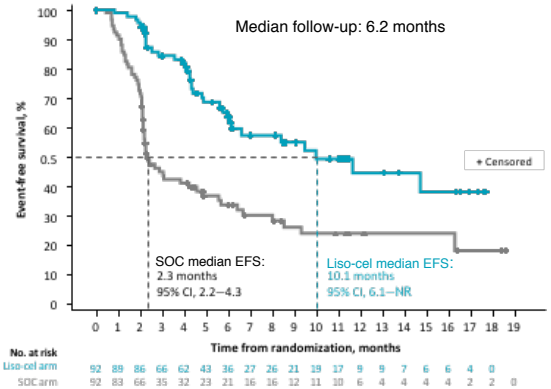
Belinda: Tisa-cel in 2nd line[1]



EFS events defined as PD/SD after day 71 (12 weeks) or death at any time.

ORR: 46.3% Tisacel vs 42.5% SoC
CR: 46% Tisacel vs 44% SoC

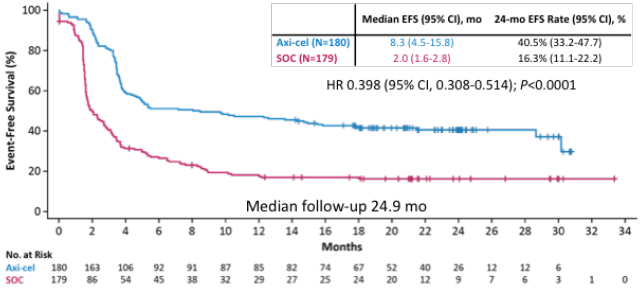
Transform: Liso-cel in 2nd line[2]



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

ORR: 86% Lisocel vs 48% SoC
CR: 66% Lisocel vs 39% SoC
Median PFS: 14.8 mo Lisocel vs 5.7 mo SOC

ZUMA-7: Axi-cel in 2nd line[3]



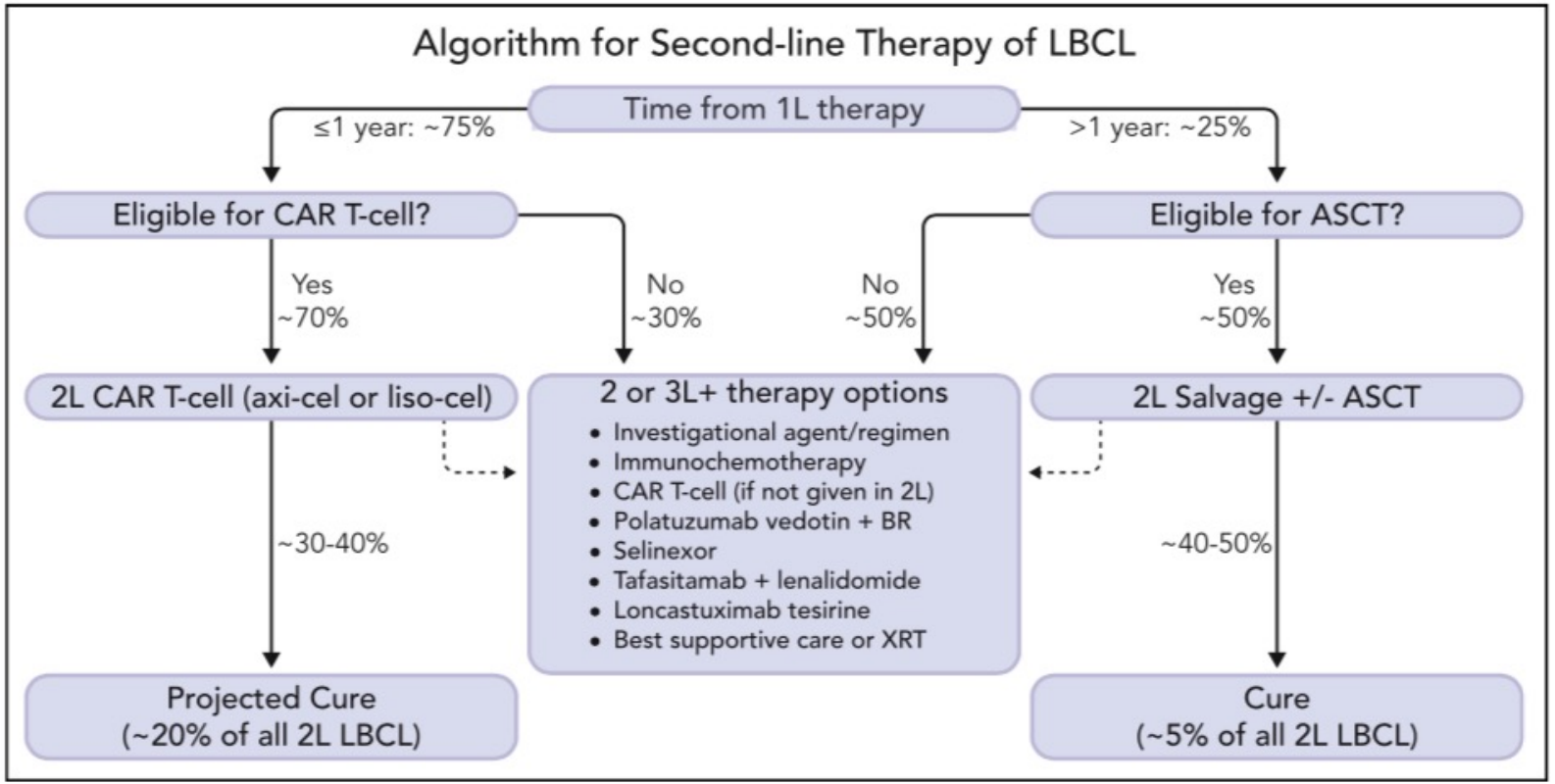
ORR: 83% Axicel vs 50% SoC
CR: 65% Axicel vs 32% SoC
Median PFS: 14.7 mo Axicel vs 3.7 mo SOC

1.Beshop M.R. et al. New Engl J Med. 2022: 386-7; 2. Kamdar M, et al. ASH 2021 [Abstract #91] 3. Locke F.L. et al, New Engl J Med; 2022: 386;7

	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


Algorithm for Second-line Therapy of LBCL
Time from 1L therapy
≤1 year: ~75%
>1 year: ~25%
Eligible for CAR T-cell?
Eligible for ASCT?
Yes
~70%
No
~30%
No
~50%
Yes
~50%
2L CAR T-cell (axi-cel or liso-cel)
2 or 3L+ therapy options
Investigational agent/regimen
Immunochemotherapy
CAR T-cell (if not given in 2L)
Polatuzumab vedotin + BR
Selinexor
Tafasitamab + lenalidomide
Loncastuximab tesirine
Best supportive care or XRT
2L Salvage +/- ASCT
~30-40%
~40-50%
Projected Cure
(~20% of all 2L LBCL)
Cure
(~5% of all 2L LBCL)

CART as 1st line of therapy: ZUMA-12 trial

ZUMA-12: Multicenter phase 2 study of axi-cel as part of first-line therapy in patients with high-risk LBCL

High-Risk LBCL
- High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations, or
- LBCL with IPI score ≥ 3 any time before enrollment

Systemic Therapy
- 2 Cycles of an anti-CD20 mAb + anthracycline-containing regimen

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5)

Additional Key Inclusion Criteria
- Age ≥ 18 years
- ECOG 0 – 1

→ **Enrollment / Leukapheresis** → **Optional Nonchemotherapy Bridging Therapy[a]** →

Conditioning Chemotherapy + Axi-Cel Infusion
- Conditioning: Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, and −3
- Axi-Cel: Single IV infusion of 2 × 10^6 CAR T cells/kg on Day 0

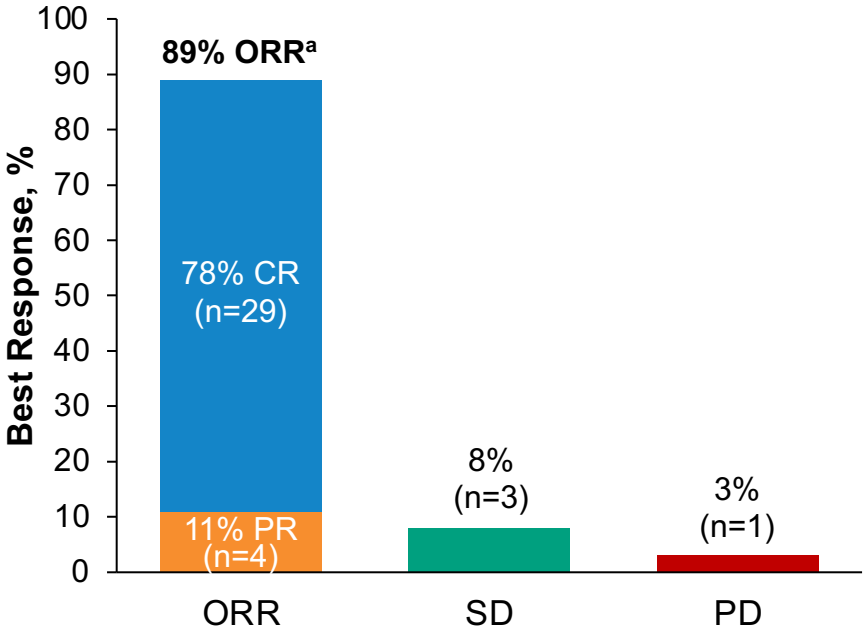
→

Primary Endpoint
- CR (investigator-assessed per Lugano classification)[1]

Key Secondary Endpoints
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739. Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

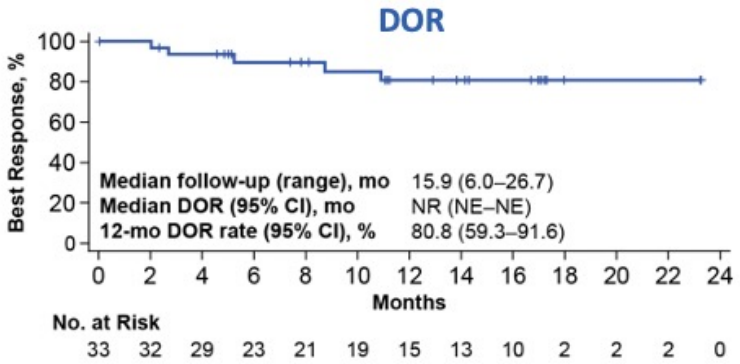
CART as 1st line of therapy: ZUMA-12 trial

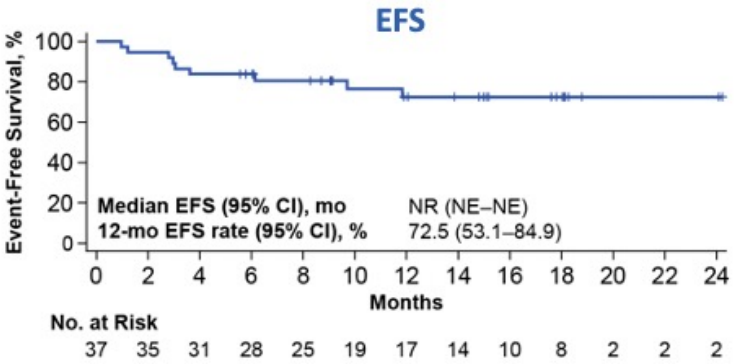


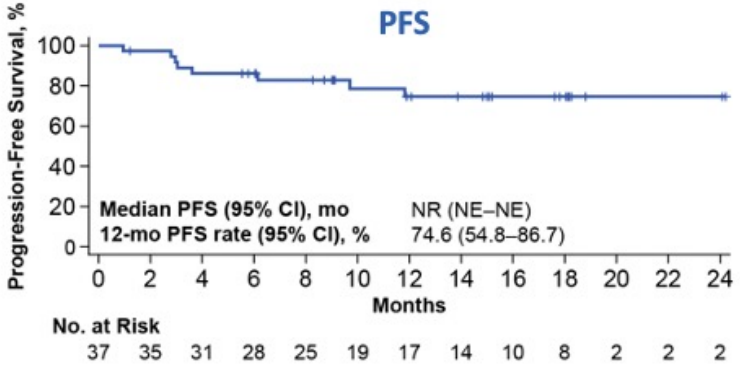
	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients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

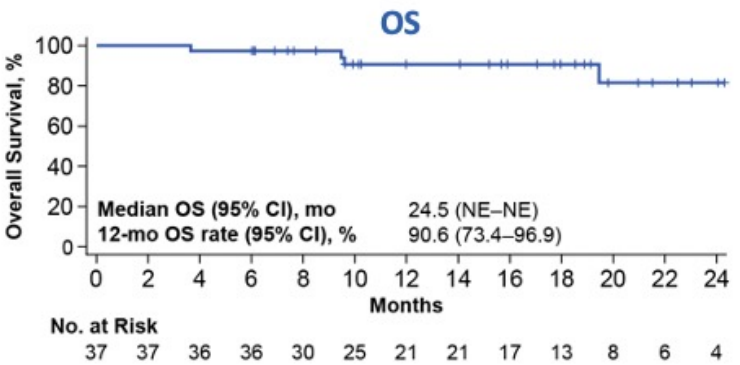
Neelapu SS et al. 2021 ASH Annual Meeting. Abstract 739. Neelapu SS et al. *Nat Med.* 2022;28(4):735-742.

ZUMA-12 primary analysis: Efficacy









Neelapu et al, ASH 2021, Abstract 739

CART for the treatment of LBCL patients: Conclusions

In 3rd or later line of therapy:

- Real world experiences confirm the phase 2 trial results in term of safety and efficacy.
- Axicel seems to induce higher response rates and prolonged survival compared with tisa-cel, despite is higher toxicity.
- Grade ≥ 3 ICANS and long term hematological toxicity are still difficult AEs to manage.
- Durable responses at 5 years were strongly associated with peak CAR T-cell expansion, which is associated with tumor burden and T-cell fitness in apheresis material.

In 2nd line of therapy:

- Axicel and lisocel are becoming the new SoC for pts with refractory or relapsed (< 12 mo from 1st line) DLBCL
- More data are necessary to define the long term toxicity

MCL: Results from ZUMA-2 trial

Phase 2

Enrollment/ Leukapheresis	Optional Bridging Therapy[a]	Conditioning Chemotherapy	CAR T Cell Dose	Follow-up Period
R/R MCL (1 – 5 prior lines of therapy)	Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily	Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3	2×10^6 KTE-X19 cells/kg single IV infusion on Day 0	First tumor assessment on Day 28[b]

Primary Endpoint

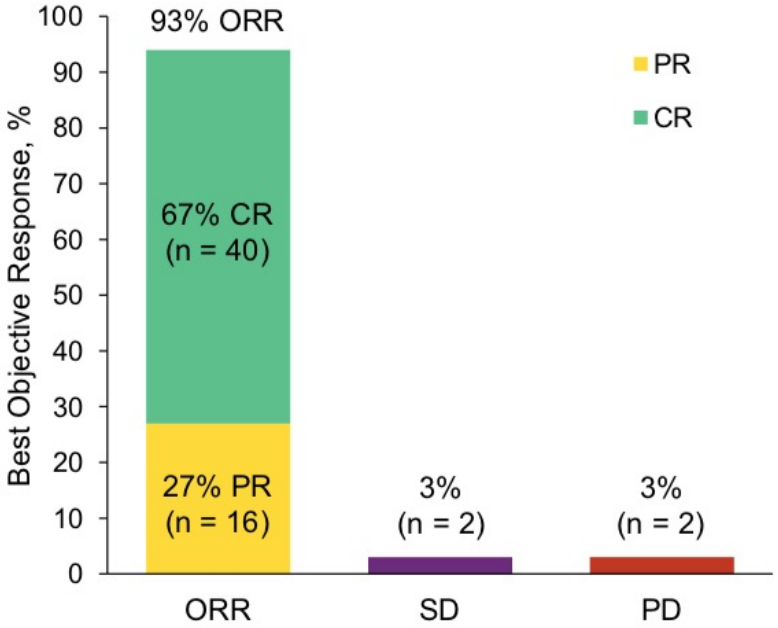
- ORR (IRRC-assessed per the Lugano classification[2])

Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- Levels of CAR T cells in blood and cytokines in serum

1. Wang M et al, N. Engl. J. Med 2020

MCL: Results from ZUMA-2 trial

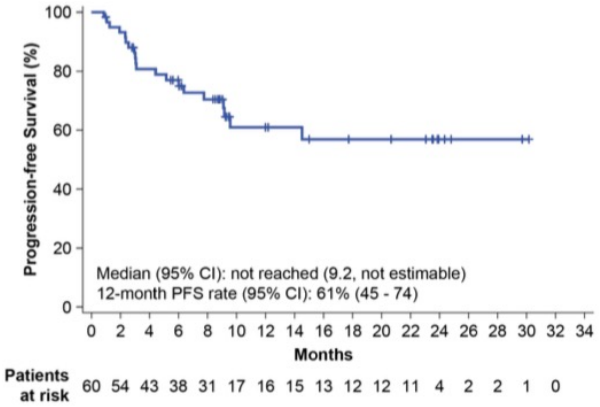


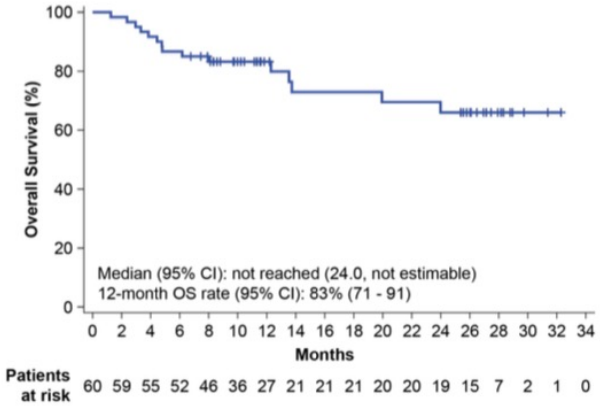
- 74 pts enrolled, 68 pts (92%) were infused
- Median follow-up: 12.3 months
- The median time from KTE-X19 infusion to initial response was 1 month (range o.8-3.1)
- The median time from KTE-X19 infusion to CR was 3 month (range 0.9 – 9.3)
- Among the 42 pts who initially had a PR or SD, 24 (57%) achieved a CR after a median of 2.2. months (1.8 – 8.3)
- Median DOR was not reached

1. Wang M et al, N. Engl. J. Med 2020

MCL: Results from ZUMA-2 trial

- Median PFS and median OS were not reached after a median follow-up of 12.3 months

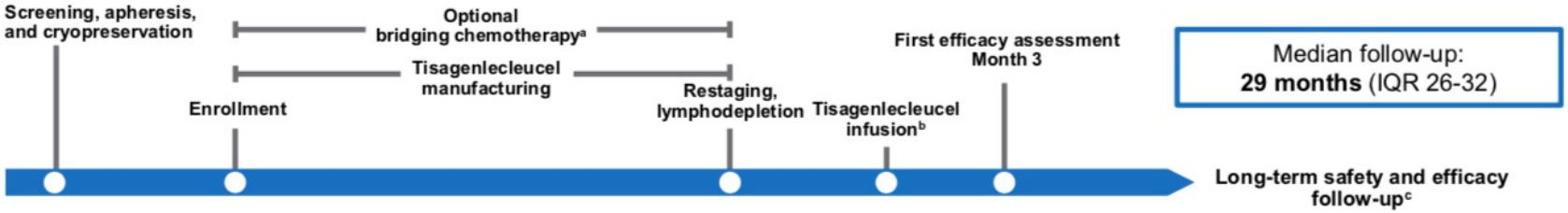




KTE-X19[1] AE, n (%)	Treated patients (N: 68)
Any grade CRS	62 (91%)
Grade ≥ 3 CRS*	10 (15%)
Any grade NE	43 (63%)
Grade ≥ 3 NEs**	21 (31%)
Non relapse mortality	0

1. Wang M et al, N. Engl. J. Med 2020

FL: Results from ELARA phase 2 trial



Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • Relapsed/refractory disease[d] • No evidence of histological transformation/FL3B • No prior anti-CD19 therapy or allogeneic HSCT	Tisagenlecleucel dose range (single IV infusion) was $0.6\text{-}6\times10^8$ CAR-positive viable T cells	**Primary:** CRR by IRC **Secondary:** ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- 18% (17/97) of patients received tisagenlecleucel in the outpatient setting

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; FL3B, FL grade 3B; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Every 3 months until Month 12, and every 6 months until end of study. [d]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT.

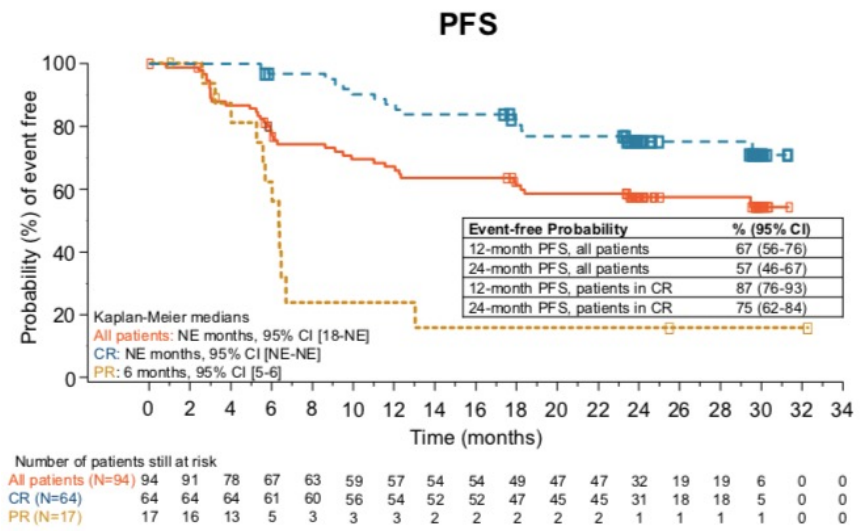
FL: Results from ELARA phase 2 trial (median fup 29 mo)

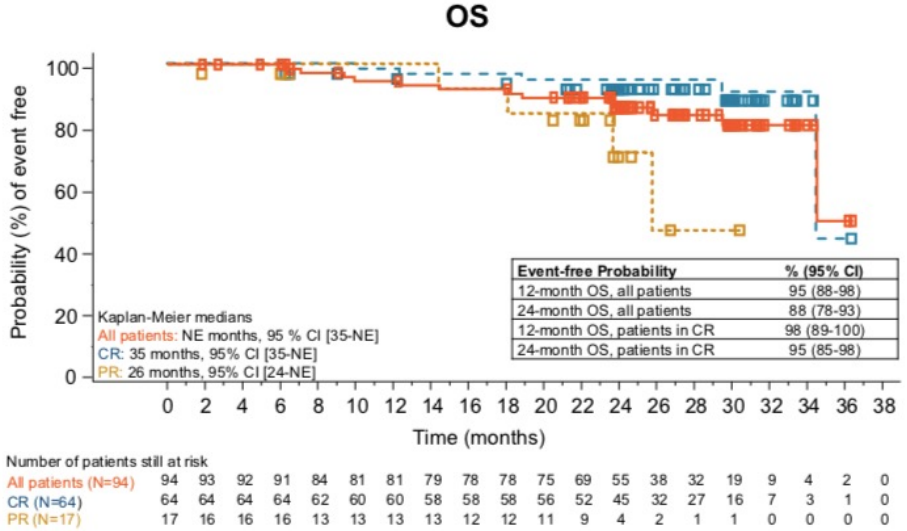
Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR[a]	68 (58-77)[b]
ORR[c]	86 (78-92)[b]

Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky disease[e]	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

Higher rates of durable responses were observed in most patients in high risk disease subgroups who have poor prognosis with current non CAR T-cell therapy

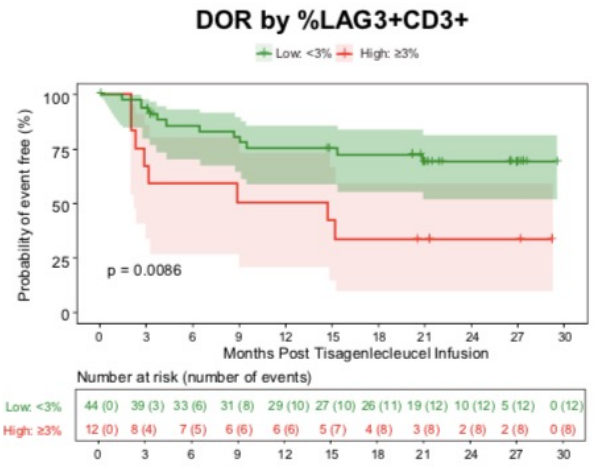
FL: Results from ELARA phase 2 trial (median fup 29 mo)

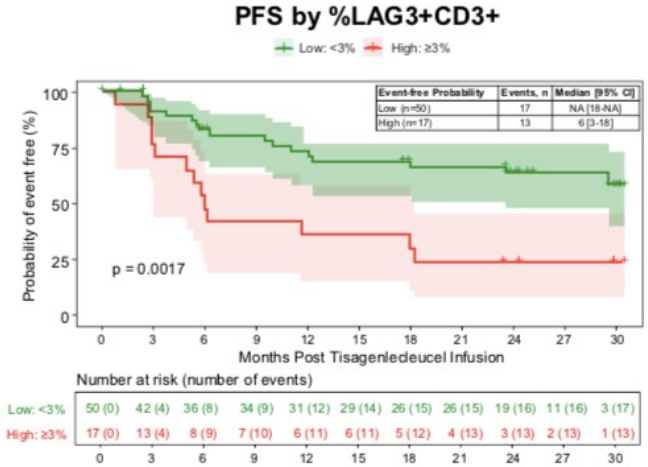




Median DoR and TTNT: NR

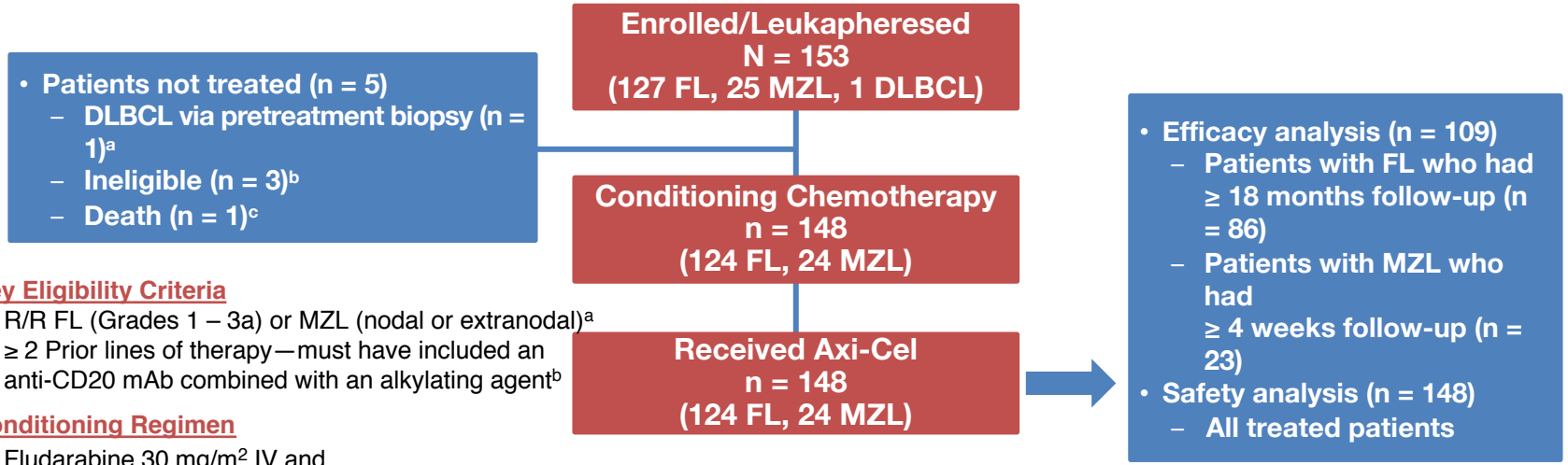
ELARA: Exploratory Correlative Biomarker Analyses





- Higher baseline metabolic tumor volume is associated with shorter PFS and DoR
- Lower pre-LD serum TNF-a and IL-10 levels correlated with tumor volume and prolonged PFS
- Lower tumor-infiltrated LAG3+ exhausted T-cell (< 3% of total T-cells), representing a favorable TME, is associated with longer DOR and PFS

FL: Results from ZUMA-5 phase 2 trial



Key Eligibility Criteria

- R/R FL (Grades 1 – 3a) or MZL (nodal or extranodal)[a]
- ≥ 2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent[b]

Conditioning Regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days –5, –4, –3

Axi-Cel: 2 × 10^6 CAR+ cells/kg

Primary Endpoint

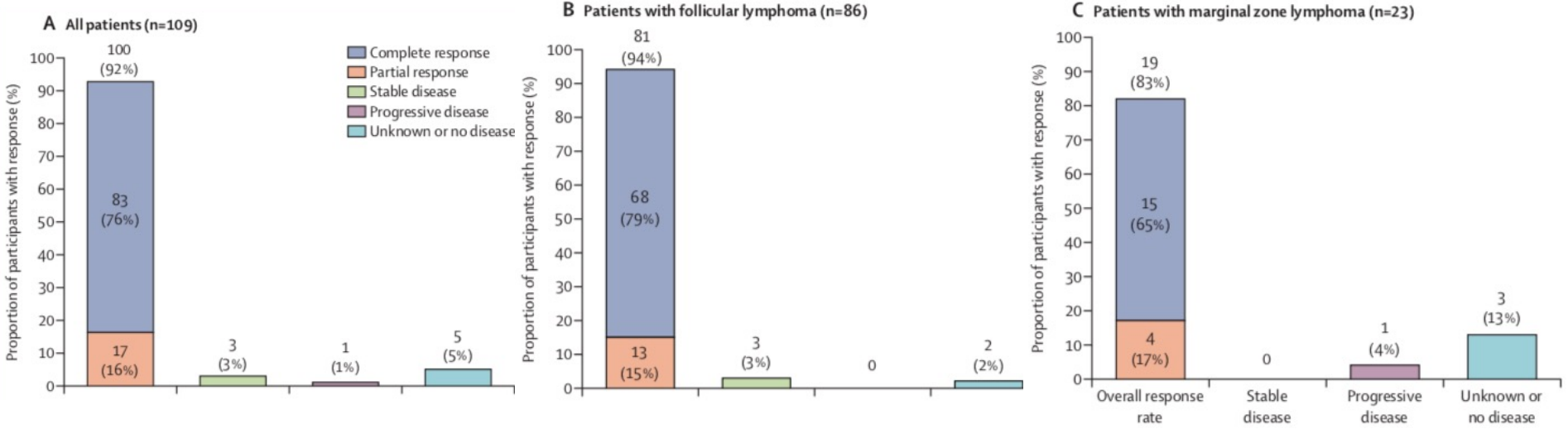
- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC-assessed)
- Investigator-assessed ORR[1]
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

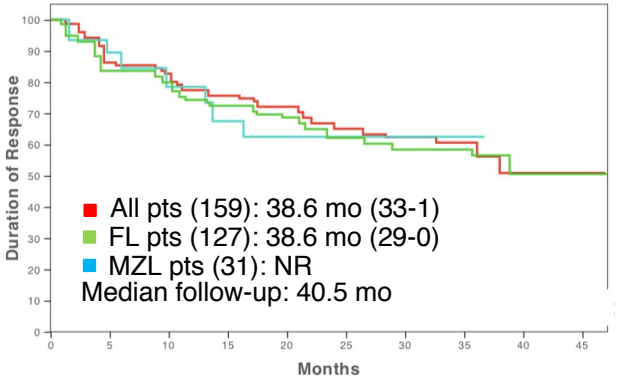
FL: Results from ZUMA-5 phase 2 trial (3y fup)

ORR and CRR were similar to the 2-year analysis[1]

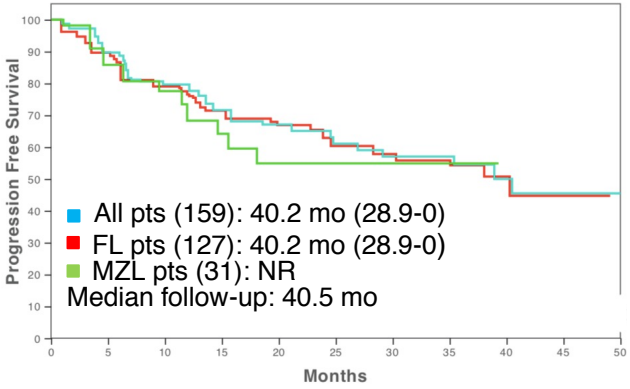


FL: Results from ZUMA-5 phase 2 trial (3y fup)

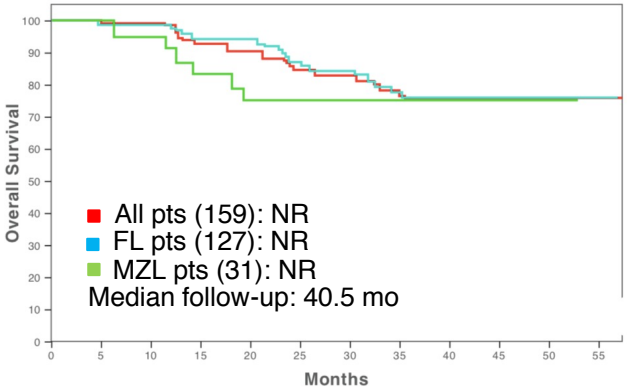
median DoR



median PFS



median OS



- Late progression or death due to lymphoma or study treatment were uncommon and no new safety signals arose since the 2-year analysis.
- At data cut-off, 15 deaths were lymphoma specific: 11 due to complications of underlying lymphoma and 3 due to AEs related to study treatment (1 covid-19 pneumonia, 1 multi organ failure in the context of CRS, and 1 PML)

CART for the treatment of FL patients: Conclusions

- Tisagenlecleucel and Axicel induce **high rates of durable responses** in all patients including those with **high-risk disease characteristics** such as POD24 and high baseline tumor burden;
- Median DOR, PFS, and OS were not reached in the ELARA trial after >2 years of follow-up;
- Median DoR, PFS and OS were 38.6 mo, 40.2 mo and NR respectively in the ZUMA-5 after > 3 years of follow-up
- **Tisagenlecleucel** was found to be **well-tolerated** and feasible for **out-patient administration**;
- In both trial, exploratory biomarker analyses suggest that a favorable TME and decreased inflammatory status were associated with improved clinical outcomes;

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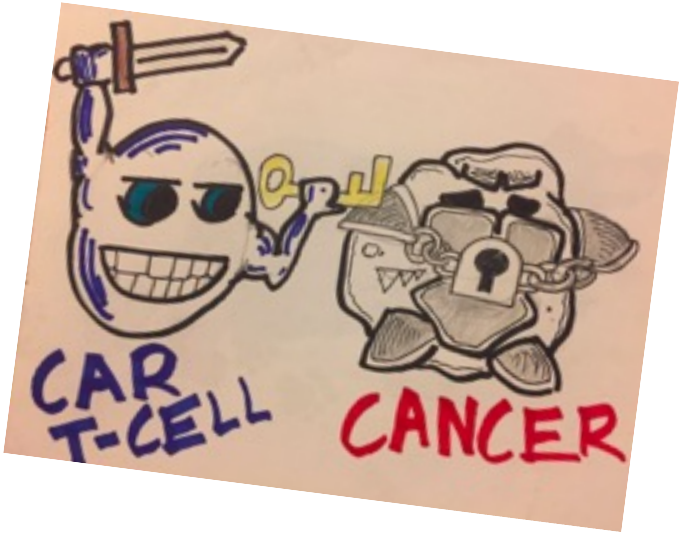
UO Medicina Nucleare
UO Neurologia
UO Neuroradiologia
UO Terapia Intensiva
UO Radioterapia
Tutto il personale infermieristico dei reparti
DSV, BCM, II e I Sezione



GRAZIE PER L'ATTENZIONE