Il ruolo dei CAR-T nel trattamento del LBCL

Giorgia Battipaglia

Professore Associato – Università degli studi di Napoli Federico II

Responsabile Unità clinica e CAR-T coordinator – AOU Federico II di Napoli

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Azienda Ospedaliera Universitaria Federico II
Integrata con il Servizio Sanitario Regionale

Disclosures of Giorgia Battipaglia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead					x	x	
BMS						x	
Novartis					x		

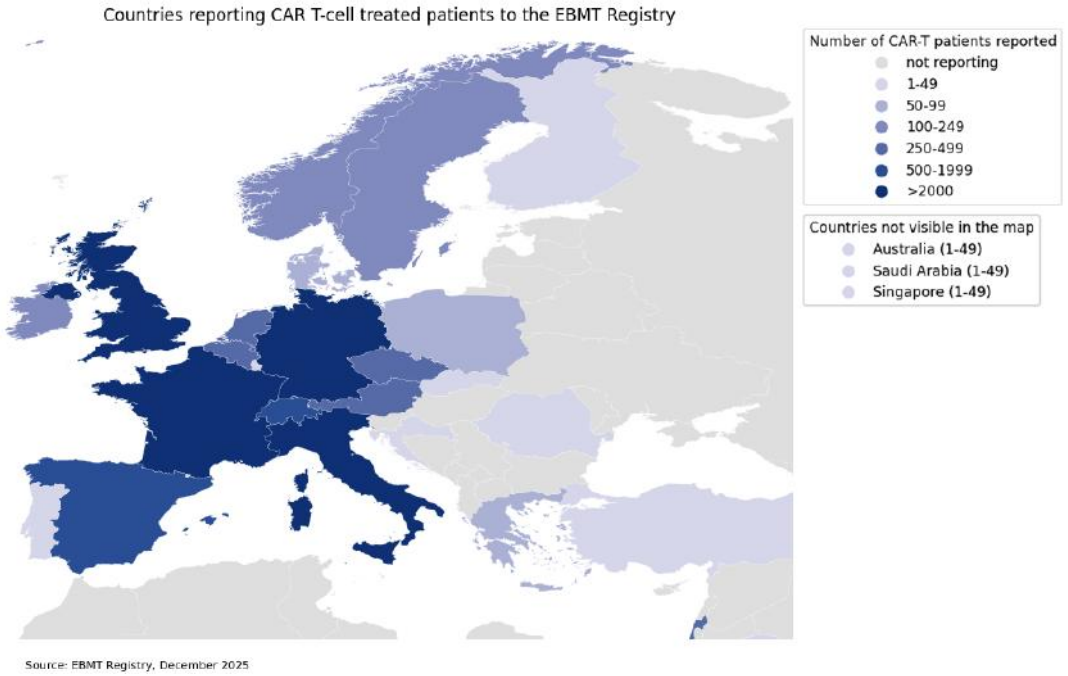
Redefining treatment algorithm of LBCL

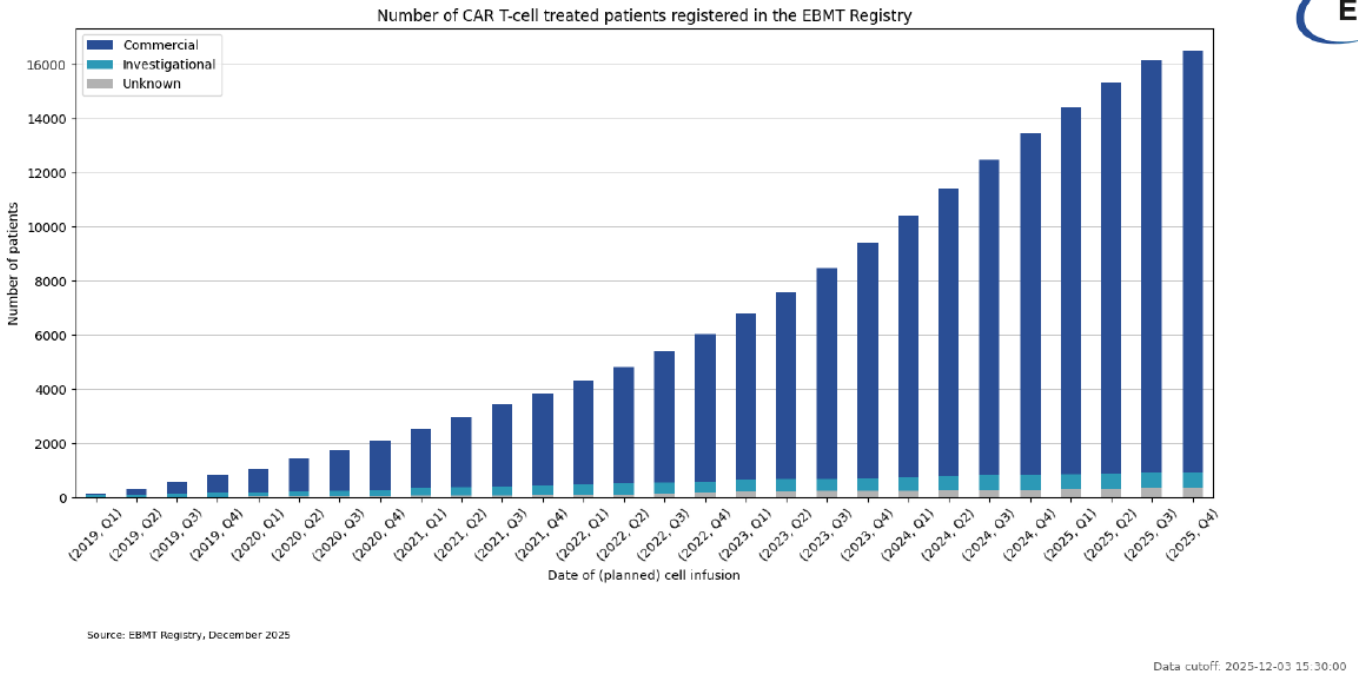
- CAR-T therapy has significantly improved outcomes in R/R LBCL showing high response rates and durable remissions across clinical trials and real-world settings

- Initially positioned in later lines, providing a curative option for heavily pretreated patients

- Now established as a standard of care in second line for early R/R

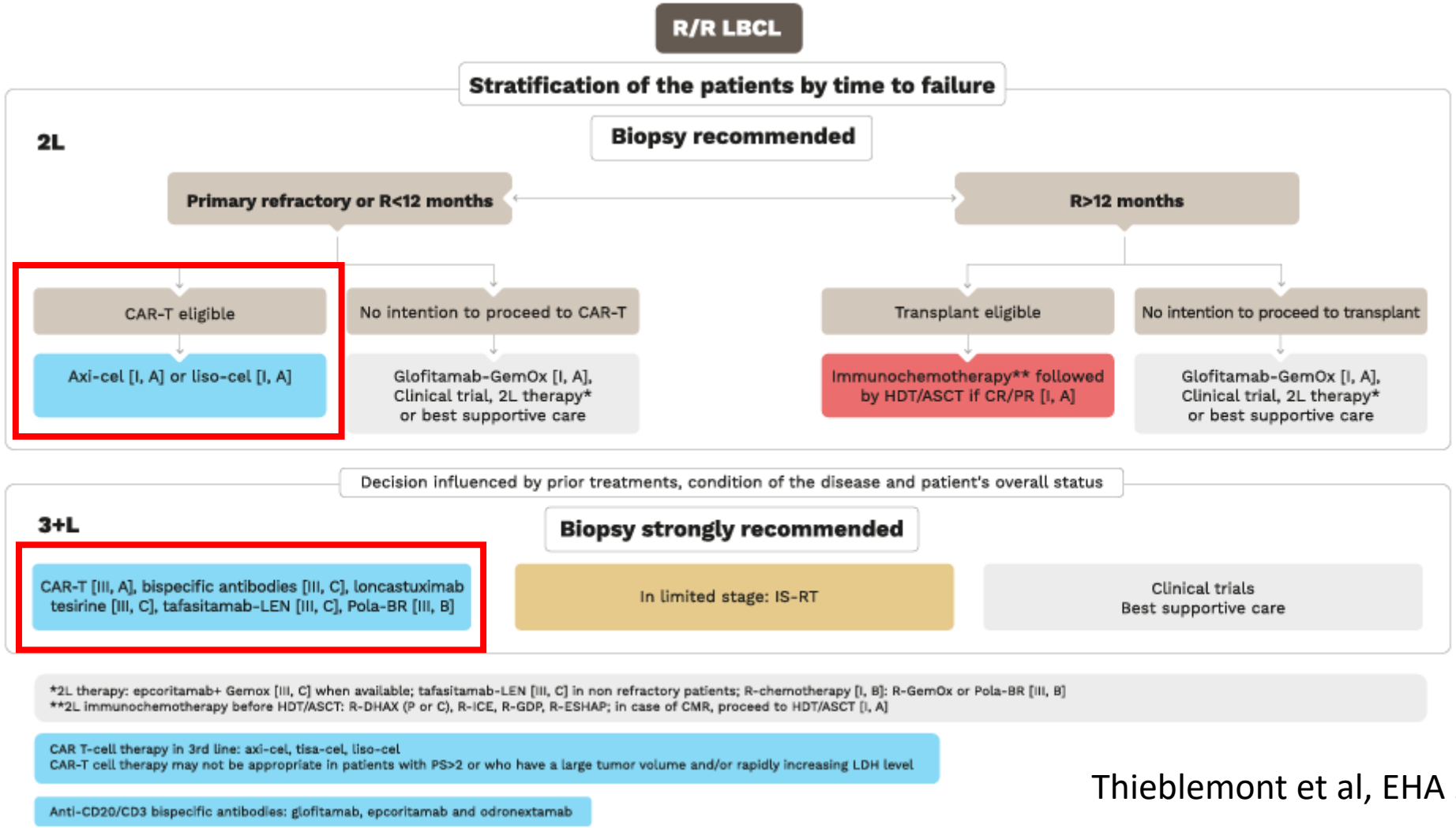
Increasing CAR-T use over years





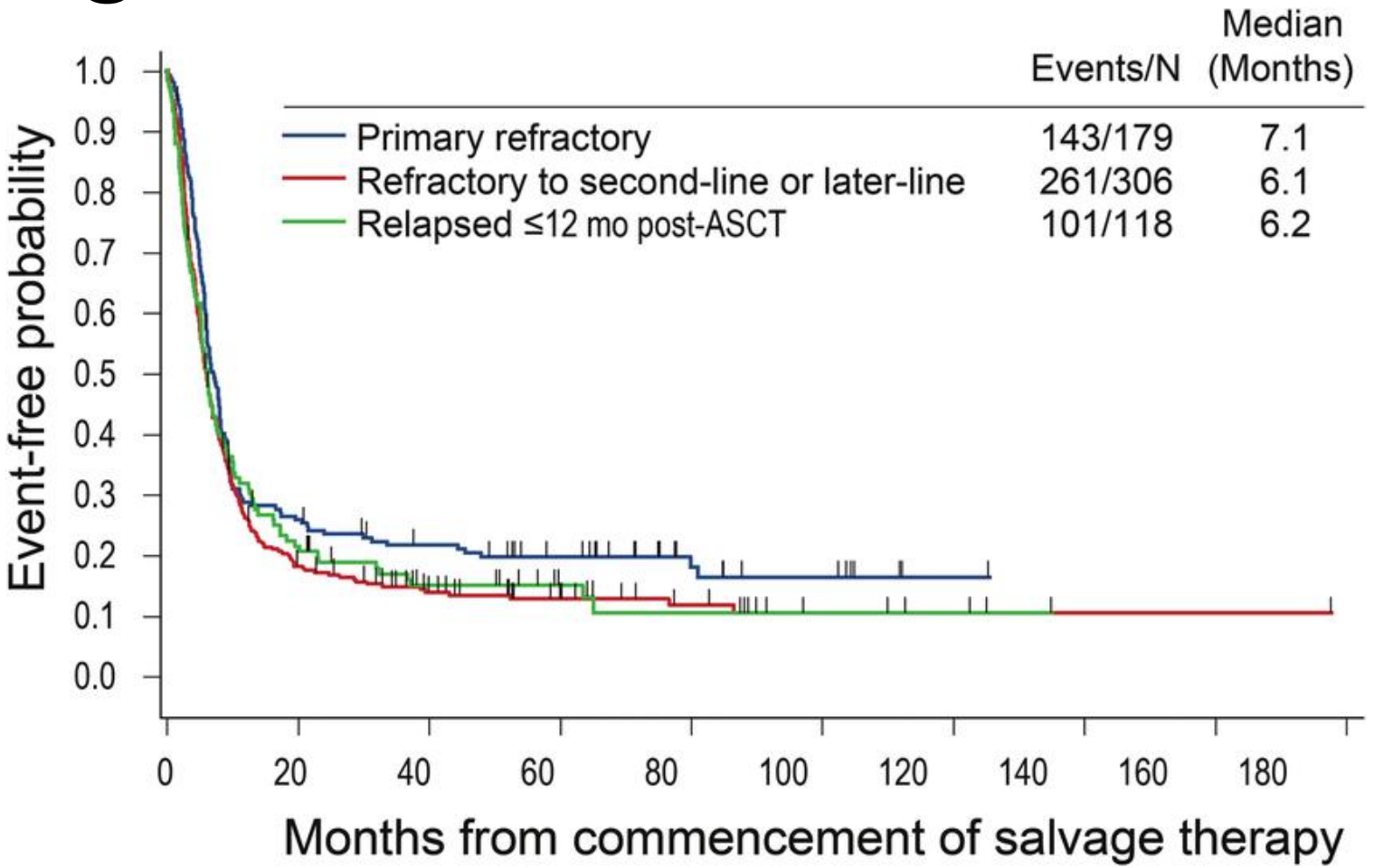
Courtesy of Annalisa Ruggeri

CAR-T in the treatment of R/R LBCL



Thieblemont et al, EHA 2025 guidelines

Poor prognosis of R/R LBCL



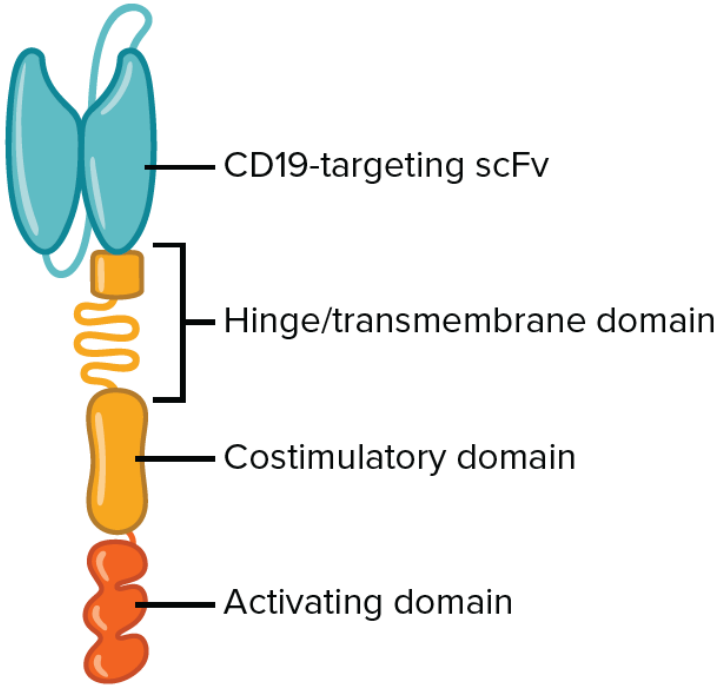
Crump et al, Blood 2017

Pivotal CAR-T trials in LBCL>2L

ZUMA-1 (axi-cel) ✓

JULIET(tisa-cel) ✓

TRANSCEND NHL 001 (liso-cel) ✓



ZUMA-1: axicel in LBCL>2L

Key Eligibility Criteria for ZUMA-1

- Refractory LBCL (DLBCL, PMBCL, TFL)
- No response to last chemotherapy or relapse ≤12 months post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Lymphodepleting Regimen

- Cyclophosphamide 500 mg/m^{2}and fludarabine 30 mg/m^{2}for 3 days

Axi-Cel

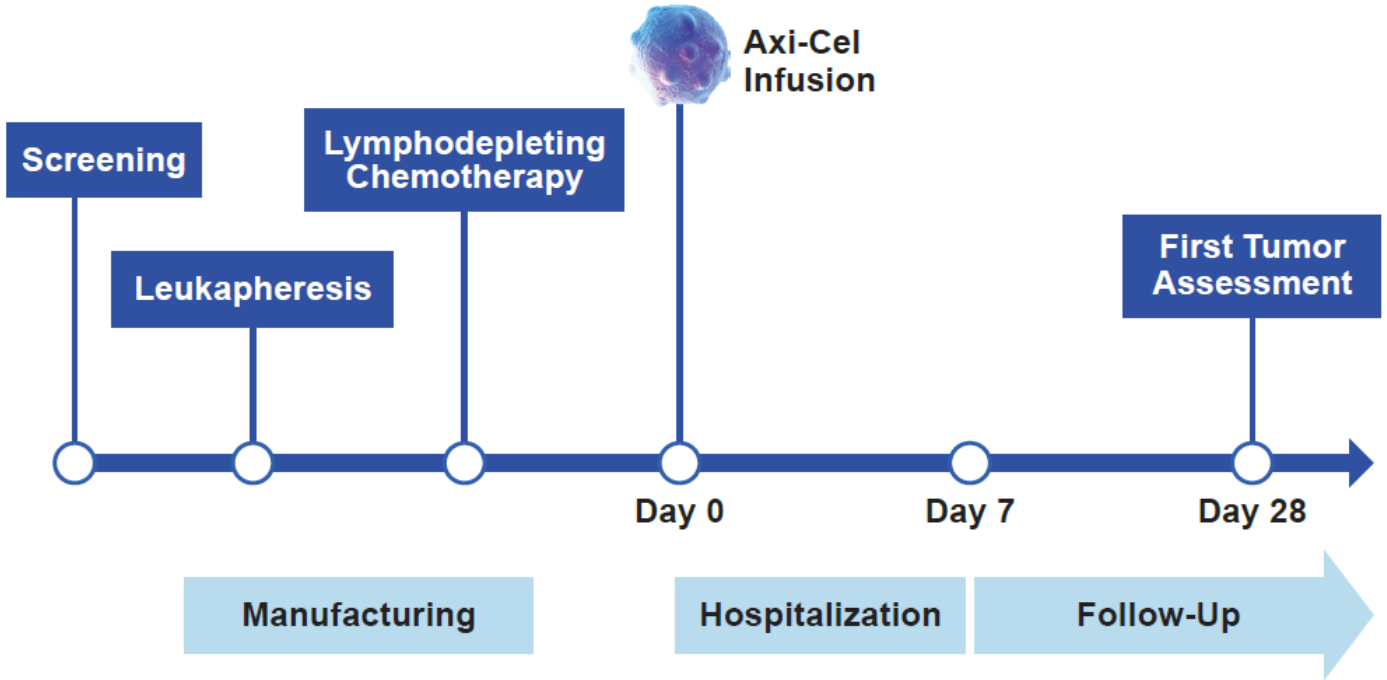
- 2×10^{6}CAR+ cells/kg

Primary Endpoint

- ORR, with first response assessment 4 weeks post-infusion

Key Additional Endpoints

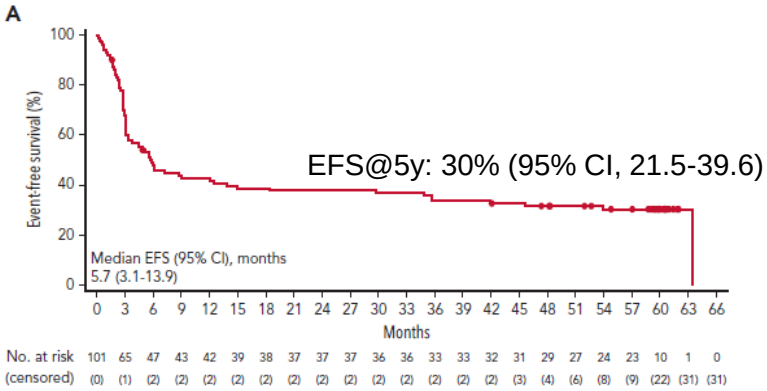
- OS, safety, and translational evaluations

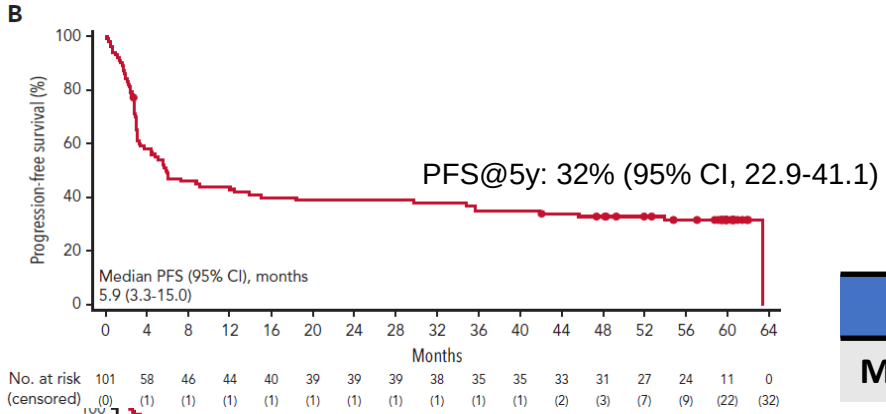


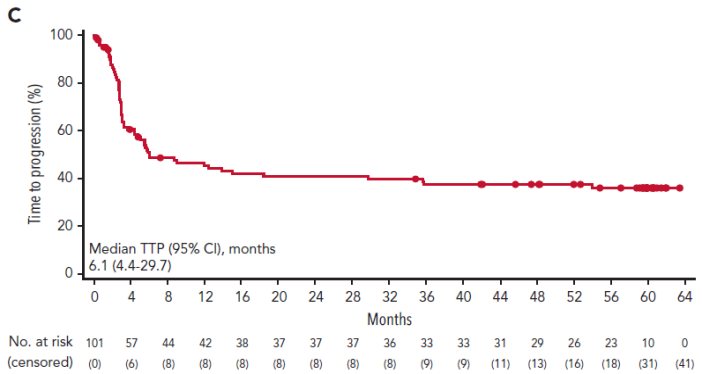
Characteristic (%)	N=101
Median age, years (range)	58 (23–76)
≥65 years	24 (24)
IPI score 3–4	46 (46)
Disease type	
DLBCL	*77 (76)*
PMBCL	8(8)
TFL	16 (16)
Disease stage III or IV	86 (85)
Prior HSCT	25 (25)

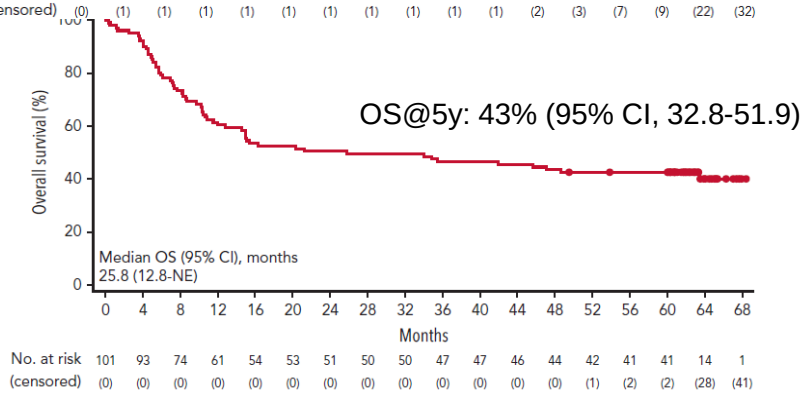
Neelapu et al, *N Engl J Med* 2017
Neelapu et al, *Blood* 2022

ZUMA-1: response and survival







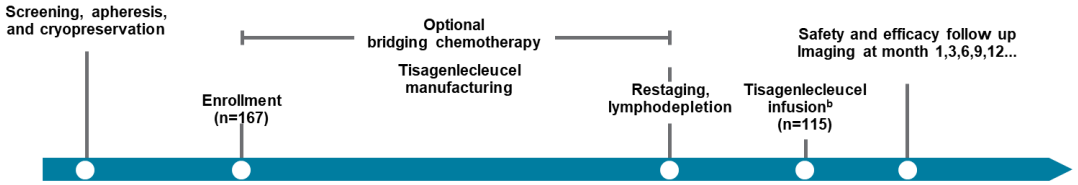


	N=101
Median follow-up, months (range)	63.1 (58.9–68.4)
ORR/CR	84 (83)/59 (58)
Median DOR, months (95% CI)	11.1 (4.2–51.3)
Patients with ongoing response, %	31

Curative potential of axi-cel >2L for responding patients who are alive at 5 years

Neelapu et al, *N Engl J Med* 2017
Neelapu et al, *Blood* 2022

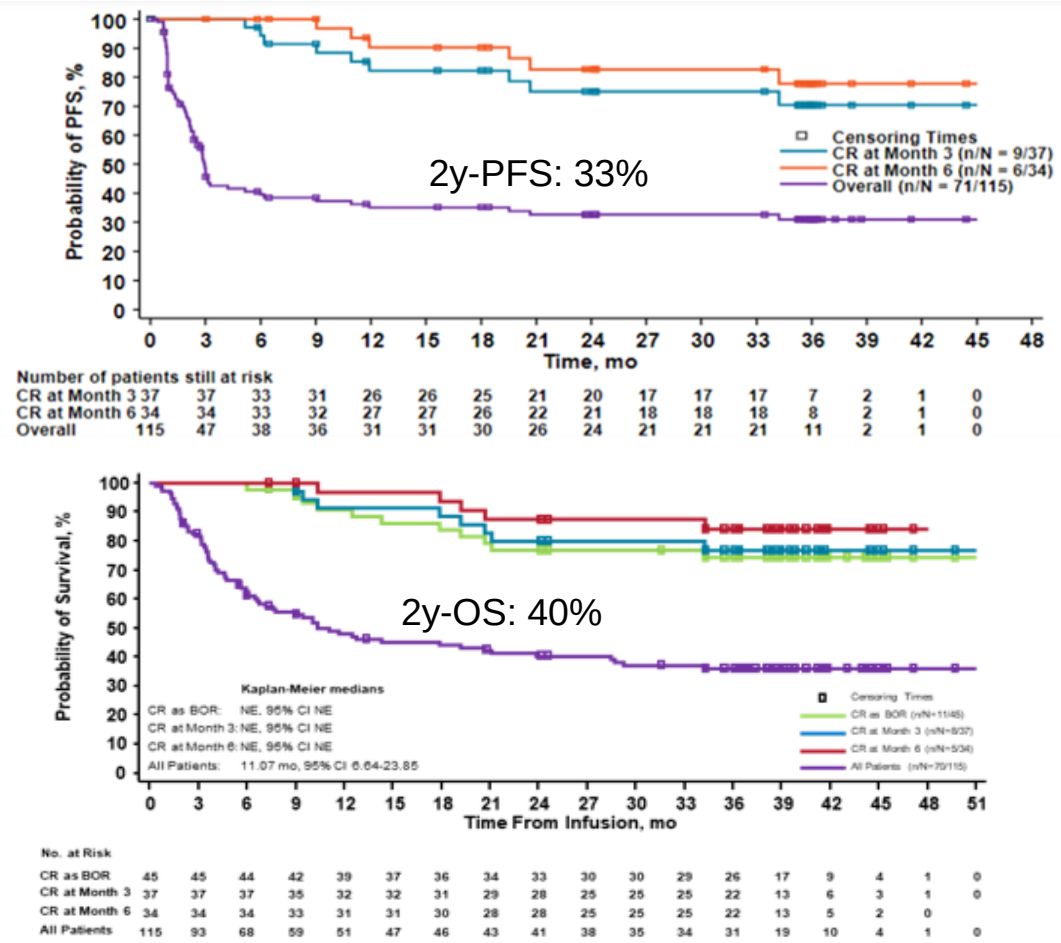
JULIET: tisa-cel in LBCL>2L



Key eligibility criteria	Study treatment	End points
• ≥ 18 years • Relapsed/refractory DLBCL - previously received ≥ 2 lines including rituximab and an anthracycline - Had either relapsed after or were ineligible for autologous transplant • No Previous anti-CD19 therapy, any gene therapy or allogeneic transplant • NO Active CNS involvement	Tisagenlecleucel dose range (single IV infusion) 0.5-6×10^8 CAR-positive viable T cells	**Primary:** Best ORR (CR + PR) **Secondary:** TTR, DOR, OS, PFS, EFS, safety and cellular kinetics

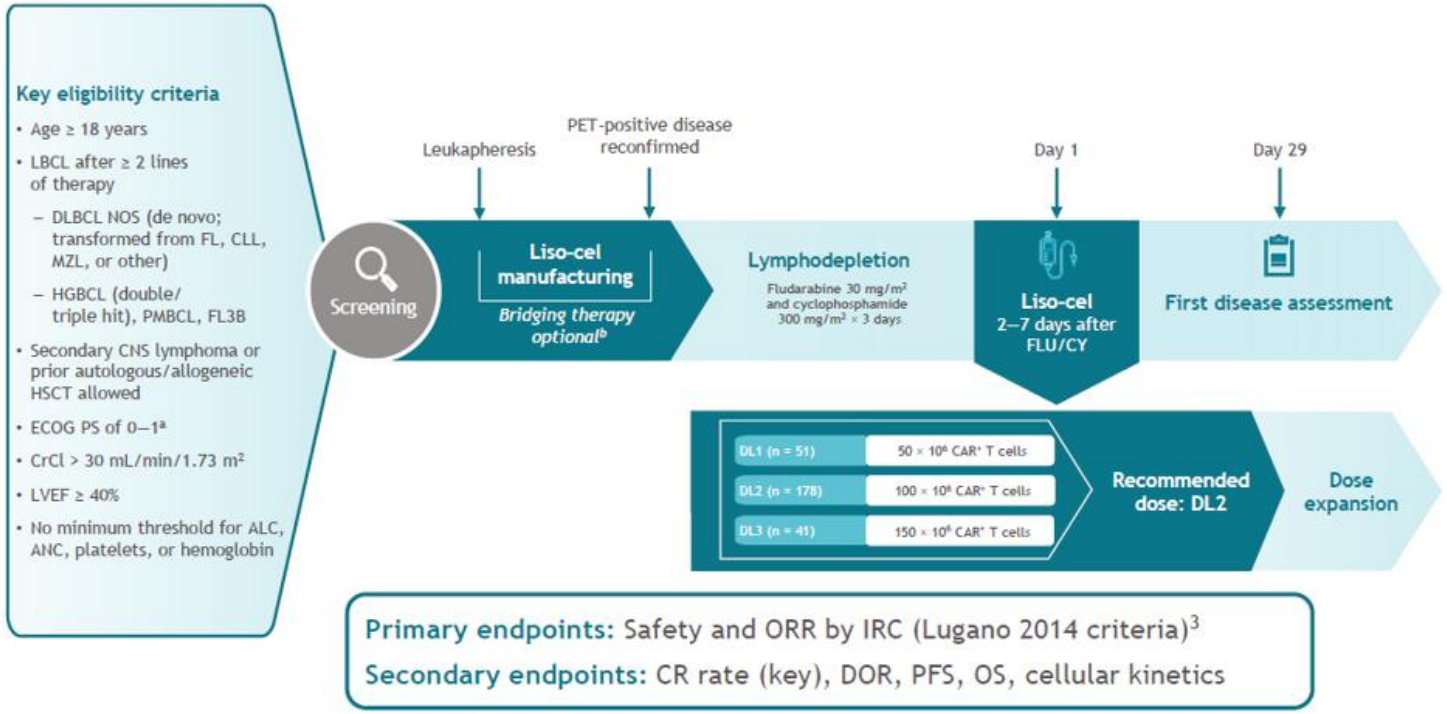
Characteristic (%)	N=115
Median age, years (range)	56 (46–64)
≥65 years	23 (20)
IPI score 2–4	84 (73)
Disease type	
DLBCL	92 (80)
TFL	23 (18)
Prior HSCT	56 (49)
Bridge therapy	104 (90)

ORR was 53% (CR 39%)



Schuster et al, *N Engl J Med* 2019
Schuster et al, *Lancet Oncol* 2021

TRANSCEND-NHL 001: liso-cel in LBCL>2L

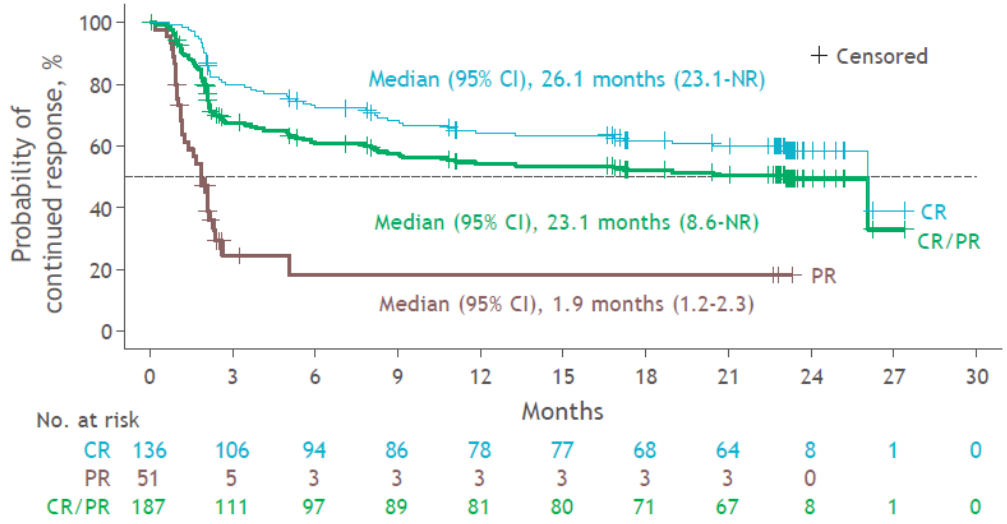


Characteristic (%)	N=270
Median age, years (range)	63 (18–86)
≥65 years, n (%)	112 (41)
Disease type	
DLBCL	137 (51)
PMBCL	15 (6)
HGBCL	36 (13)
FL3B	4 (1)
DLBCL transformed from FL/iNHL	60 (22)/18 (7)
Secondary CNS involvement	7 (3)
Median number of LOTs (range)	3 (1-8)
Prior HSCT	90 (33)
Bridge therapy	159 (59)

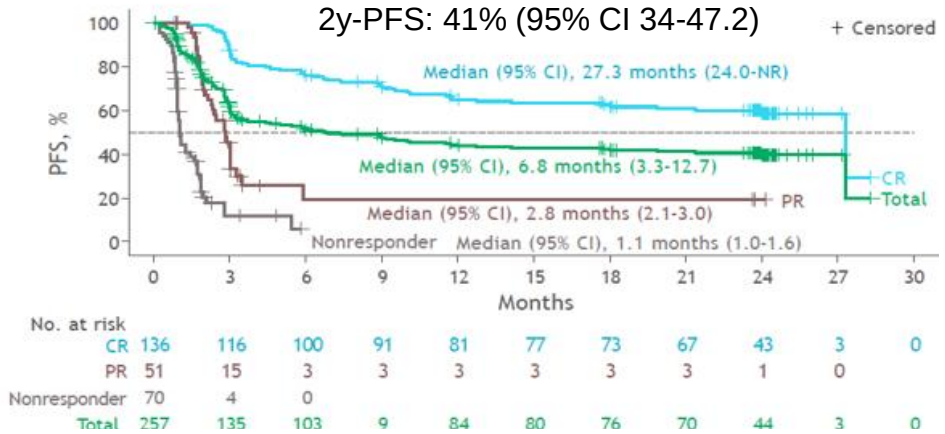
Abramson et al, Lancet 2020

TRANSCEND-NHL 001: response and survival

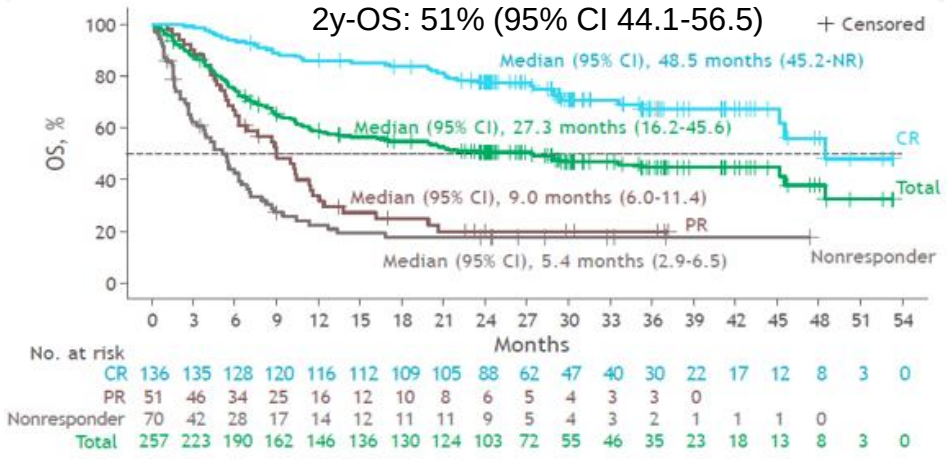
- ORR was 73% (CR 53%), being consistent across subgroups
- Probability of continued response at 2 years was 49.5%
- DOR was higher in tFL and PMBCL



2y-PFS: 41% (95% CI 34-47.2)



2y-OS: 51% (95% CI 44.1-56.5)



Abramson et al, Lancet 2020
Abramson et al, Blood 2024

From clinical trials to RWE in DLBCL>2L

Study	Product	N	Period	Median age	Median FUP	BT	NE for trials	Median V2V
CIBMTR	Axicel	1297	2017-2020	62	13 mo	22%	57%	27d
CIBMTR	Tisacel	155	2017-2020	65	12 mo	-	-	31d
CIBMTR*	Lisocel	396	2021-2022	70	7 mo	34%	53%	37d
US consortium*	Lisocel	101	2021-2023	71	10 mo	62%	30%	39d
EBMT	Tisacel	484	2018-2023	63	10 mo	-	-	51

FUP: follow-up; BT: bridge therapy; NE: non eligible
*5% (CIBMTR) and 11% (US consortium) CNS involvement

Jacobson et al. *Transplant and Cell Ther* 2022; Pasquini et al. *Blood Adv* 2020; Crombie et al. *ASH* 2023; Riedell et al. *ASH* 2023; Montoto et al. *ASH* 2024

RCTs vs RWE in LBCL>2L

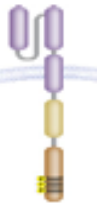
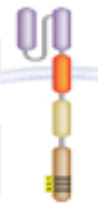
Study	Product	N	ORR/CR, %	PFS, %	OS, %	CRS overall/Gr≥3, %	ICANS overall/Gr≥3, %
ZUMA-1	Axicel	101	83/58	5y: 32	5y: 43	93/13	64/28
JULIET	Tisacel	115	53/39	2y: 33	2y: 51	57/23	20/11
TRANSCEND	Lisocel	270	73/53	2y: 41	2y: 38	42/2	30/10

Study	Product	N	ORR/CR, %	PFS, %	OS, %	CRS overall/Gr≥3, %	ICANS overall/Gr≥3, %
CIBMTR	Axicel	1297	73/56	1y: 47	1y: 62	83/8	55/24
CIBMTR	Tisacel	155	62/40	1y: 26	1y: 56	45/5	18/5
CIBMTR	Lisocel	396	76/63	1y:51	1y:66	51/3	30/11
US consortium	Lisocel	101	81/63	6-mo: 62	6-mo: 79	49/3	26/10
EBMT	Tisacel	484	62/42	2y: 36	2y: 47	67/9	18/6

Neelapu et al, *Blood* 2022; Schuster et al, *Lancet Oncol* 2021; Abramson et al, *Blood* 2024; Jacobson et al. *Transplant and Cell Ther* 2022; Pasquini et al. *Blood Adv* 2020; Crombie et al. *ASH* 2023; Riedell et al. *ASH* 2023; Montoto et al. *ASH* 2024

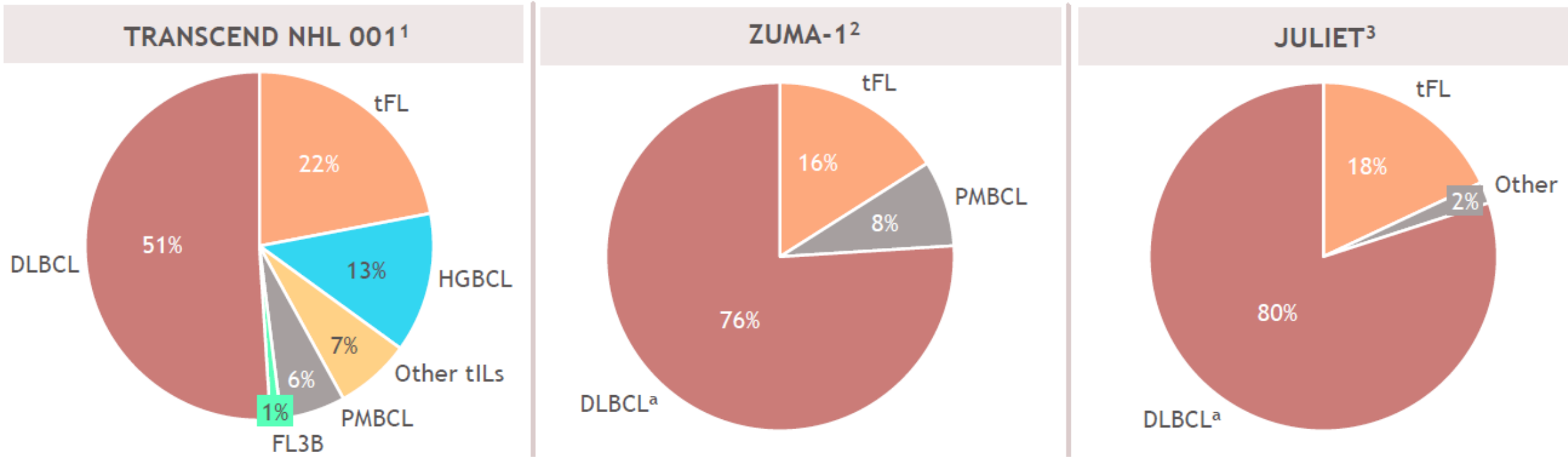
Pick up the winner

Unfair comparisons?

	Axicabtagene ciloleucel ZUMA-1[4]	Tisagenlecleucel JULIET[2,10,11]	Lisocabtagene maraleucel TRANSCEND[6]
CAR	 α CD19	 α CD19	 α CD19
Transmembrane domain	CD28	CD8	CD28
Co-stimulatory domain	CD28	4-1BB	4-1BB
T-cell activation domain	CD3ζ	CD3ζ	CD3ζ
Leukapheresis	Fresh product direct to manufacturing (within US)	Cryopreserved product (could be stored before manufacturing)	Fresh product direct to manufacturing (within US)
Conditioning therapy	Cyclophosphamide-fludarabine (500 mg/m^2, 30 mg/m^2 daily × 3 days)	Cyclophosphamide-fludarabine (250 mg/m^2, 25 mg/m^2 daily × 3 days) or Bendamustine (90 mg/m^2 daily × 2 days)[a]	Cyclophosphamide-fludarabine (300 mg/m^2, 30 mg/m^2 daily × 3 days)
CAR-T cell target dose	2 × 10^6/kg; max dose was 2 × 10^8/kg	0.1 × 10^8 to 6 × 10^8 flat dose	0.5 × 10^8 to 1.5 × 10^8 each of CD4+ and CD8+ CAR-T cells at 1:1 dose ratio
CNS disease	No history of, or active, CNS disease allowed	No active CNS disease allowed	Secondary CNS allowed
Prior anti-CD19 therapy	Not allowed	Not allowed	Allowed, if CD19+ tumor present
Bridging therapy	Not permitted	Permitted[b] **90%**	Permitted[b] **59%**
Outpatient administration	Not allowed	Allowed	Allowed
Patients enrolled, n	119	167	344
Patients infused, n	7 (phase 1) 101 (phase 2)	99 (main cohort) 16 (Cohort A)	294[c]
Manufacturing failure, n	1	12	2

Westin et al. *Am J Hematol* 2021

“Confounding” factors?



Abramson et al, *Lancet* 2020; Neelapu et al, *Blood* 2022; Schuster et al, *N Engl J Med* 2019

Axicel vs tisacel in LBCL >2L

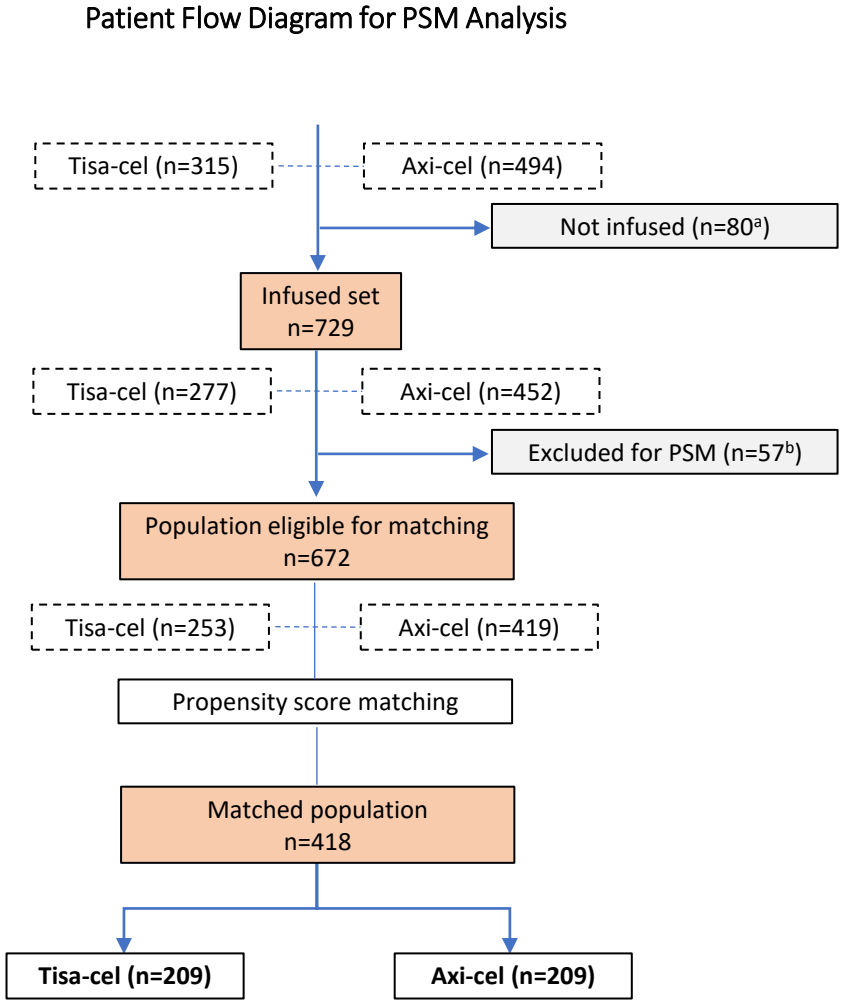
	All infused patients N=261	Axi-cel infused N=134	Tisa-cel infused N=127	P
CRS, N (%) CRS grade ≥3, N (%)	211 (81) 19 (7)	118 (88) 11 (8)	93 (73) 8 (6)	**0.003** 0.637
CRS onset day, median (range)	2 (0-10)	3 (0-10)	2 (0-10)	0.154
CRS duration days, median (range)	5 (1-35)	5 (1-15)	5 (1-35)	0.574
CRS treatment, N (%) Tocilizumab Steroids	 120 (46) 52 (20)	 81 (60) 41 (31)	 39 (31) 11 (9)	 **<0.001** **<0.001**
ICANS, N (%) ICANS grade ≥3, N (%)	78 (30) 30 (11)	57 (42) 24 (18)	21 (16) 6 (5)	**<0.001** **0.001**
ICANS onset day, median (range)	7 (2-65)	7 (2-65)	6 (2-35)	0.214
ICANS duration days, median (range)	4.5 (1-83)	4 (1-44)	7 (1-83)	0.119
ICANS treatment, N (%) Tocilizumab Steroids Anakinra Siltuximab	 2 (1) 65 (25) 15 (6) 14 (5)	 2 (1) 48 (36) 12 (9) 11 (8)	 0 (0) 17 (13) 3 (2) 3 (2)	 **<0.001** **<0.001** **<0.001** **<0.001**
Hospitalization days, median (IQR)	20 (17-27)	22 (20-29)	18 (14-22)	**<0.001**
ICU admission, N (%) median stay, days (IQR)	49 (18) 3 (2-7)	30 (22) 4 (2-7)	19 (15) 3 (1-5)	0.154 **<0.001**
Infections during first 6 months, N (%)	83 (32)	51 (38)	32 (25)	**0.033**
Persistent cytopenias by day 28, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 53 (24) 95 (43)	 31 (28) 49 (47)	 22 (19) 46 (40)	 0.082 0.278
Persistent cytopenias by day 90, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 12 (10) 18 (15)	 6 (10) 10 (16)	 6 (10) 8 (13)	 1.000 0.799
Persistent cytopenias by day 180, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 2 (3) 4 (6)	 1 (3) 3 (8)	 1 (3) 1 (3)	 1.000 0.625
Non-relapse mortality, N (%)	13 (5)	9 (7)	4 (3)	0.298

	CRS grade 3	
	OR (95% CI)	P
ECOG PS at LD, 2-3 *vs.* 0-1	3.528 (1.021-12.186)	0.046
R-IPI at LD, 0-2 *vs.* >2	1.530 (0.419-5.590)	0.520
LDH at LD, >UNL *vs.* normal	2.978 (0.580-15.284)	0.191
	ICANS grade 3	
	OR (95% CI)	**P**
CAR T type axi-cel *vs.* tisa-cel	3.545 (1.156-10.870)	0.027
Number prior lines, >2 *vs.* 2	2.000 (1.150-3.503)	0.015
ECOG PS at LD, 2-3 *vs.* 0-1	1.812 (0.418-7.878)	0.427
R-IPI at LD, 0-2 *vs.* >2	2.414 (0.868-6.711)	0.091

No differences in PFS and OS between axicel and tisacel

Kwon, et al. *Haematologica 2022*

Axicel vs tisacel in LBCL >2L



Inclusion period: Dec 2019 – Oct 2021

Outcome	Axi-cel n=209	Tisa-cel n=209
ORR, % (95% CI)	**80.4 (74.3–85.5)**	**66.0 (59.2–72.4)**
CR, % (95% CI)	**60.3 (53.3–67.0)**	**42.1 (35.3–49.1)**
1y-PFS, % (95% CI)	**46.6 (38.5–54.3)**	**33.2 (25.7–40.8)**
DOR, % (95% CI)	53.8 (44.7–62.1)	41.8 (31.3–51.9)
OS, % (95% CI)	**63.5 (55.0–70.8)**	**48.8 (39.7–57.2)**

- Higher CRS of any grade with axicel but no difference for Grade ≥3 CRS
- Higher ICANS of any grade and ≥3 with axicel
- Hematological toxicity was also significantly more frequent and more severe with axi-cel than with tisa-cel

Bachy, et al. *Nature Med 2022*

Axicel vs tisacel in LBCL>2L

Inclusion period: Nov 2019 – Dec 2023

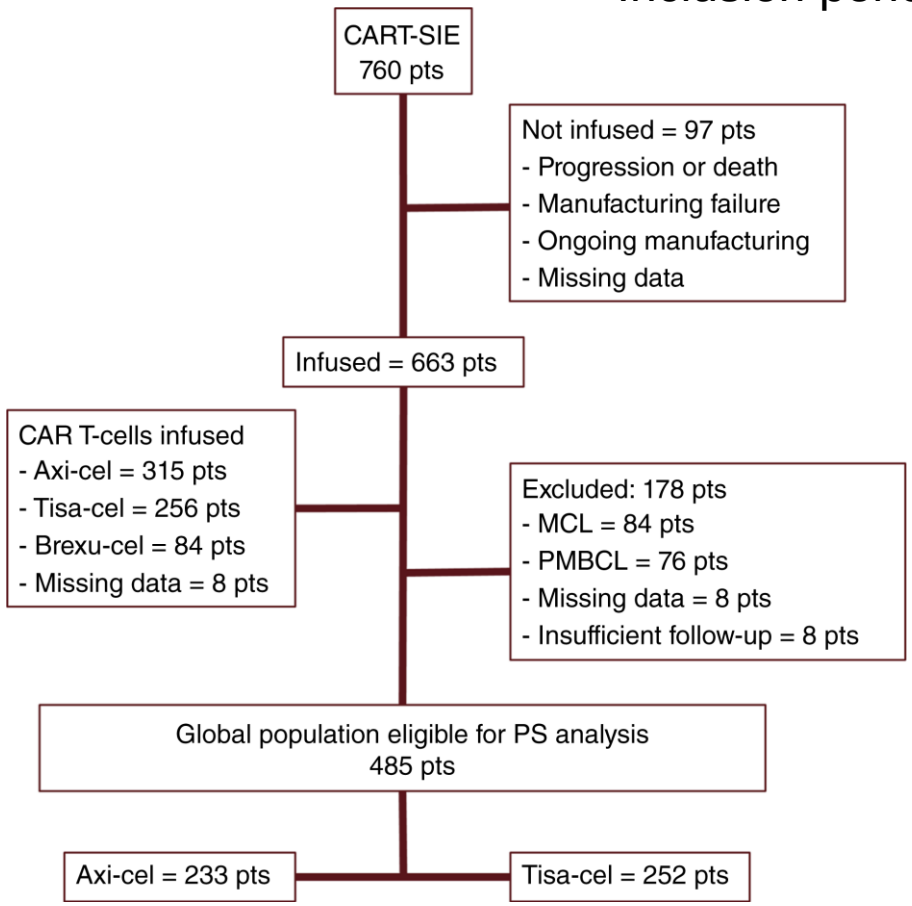


Table 3. Stabilized inverse PS weighting: patient characteristics before and after weighting.

	Before weighting = 485 pts			After weighting = 367.1 pts		
	Tisa-cel *n* = 252	Axi-cel *n* = 233	SMD[a]	Tisa-cel *n* = 184.6	Axi-cel *n* = 182.5	SMD[a]
Age, mean (SD)	58.7 (10.7)	56.7 (12.1)	0.177	57.8 (11.3)	58 (11.3)	0.012
Sex, male	153 (60.7%)	155 (66.5%)	0.121	118 (64%)	117 (64.3%)	0.007
Histology, HGBL	81 (32.1%)	62 (26.6%)	0.122	53.2 (28.8%)	53.6 (29.4%)	0.012
Disease status, relapse (%)	84 (33.3%)	60 (25.8%)	0.167	53.1 (28.8%)	51.6 (28.2%)	0.012
Stage, III-IV	190 (75.4%)	163 (50%)	0.122	133.8 (72.5%)	133.3 (73%)	0.010
IPI ≥3	110 (43.7%)	92 (39.5%)	0.085	75.8 (41.1%)	75.1 (41.1%)	0.002
Extranodal combo			0.223			0.034
<2	81 (32.1%)	74 (31.8%)		62.3 (33.7%)	60.7 (33.3%)	
≥2	44 (17.5%)	59 (25.3%)		40.6 (22.0%)	39.1 (21.4%)	
No	118 (46.8%)	96 (41.2%)		77.1 (41.8%)	78.7 (43.1%)	
Missing	9 (3.6%)	4 (1.7%)		4.7 (2.5%)	4 (2.2%)	
Bulky disease	77 (30.6%)	88 (37.8%)	0.153	62 (33.6%)	62.4 (34.2%)	0.012
Normalized LDH (LDH/ULN), mean (SD)	21.14 (51.15)	1.13 (1.27)	0.009	1.16 (1.20)	1.14 (1.28)	0.009
CRP, mean (SD)	27.14 (40.79)	24.18 (49.4)	0.065	26.97 (39.76)	26.76 (54.57)	0.004
N° prev. treatment, mean (SD)	2.44 (0.78)	2.5 (0.85)	0.071	2.47 (0.8)	2.46 (0.81)	0.019
Previous ASCT	73 (29%)	61 (26.2%)	0.062	48.8 (26.4%)	48.6 (26.6%)	0.004
Bridging response			0.067			0.010
No bridge	45 (17.9%)	47 (20.2%)		32.2 (17.5%)	31.3 (17.2%)	
No response	139 (55.2%)	128 (54.9%)		105 (57.5%)	105.3 (57.1%)	
Response	68 (27%)	58 (24.9%)		47 (25.5%)	46.3 (25.3%)	
Vein to vein time mean (SD)	2.3 (1.68)	1.75 (1.05)	0.396	1.89 (0.78)	1.84 (1.16)	0.051

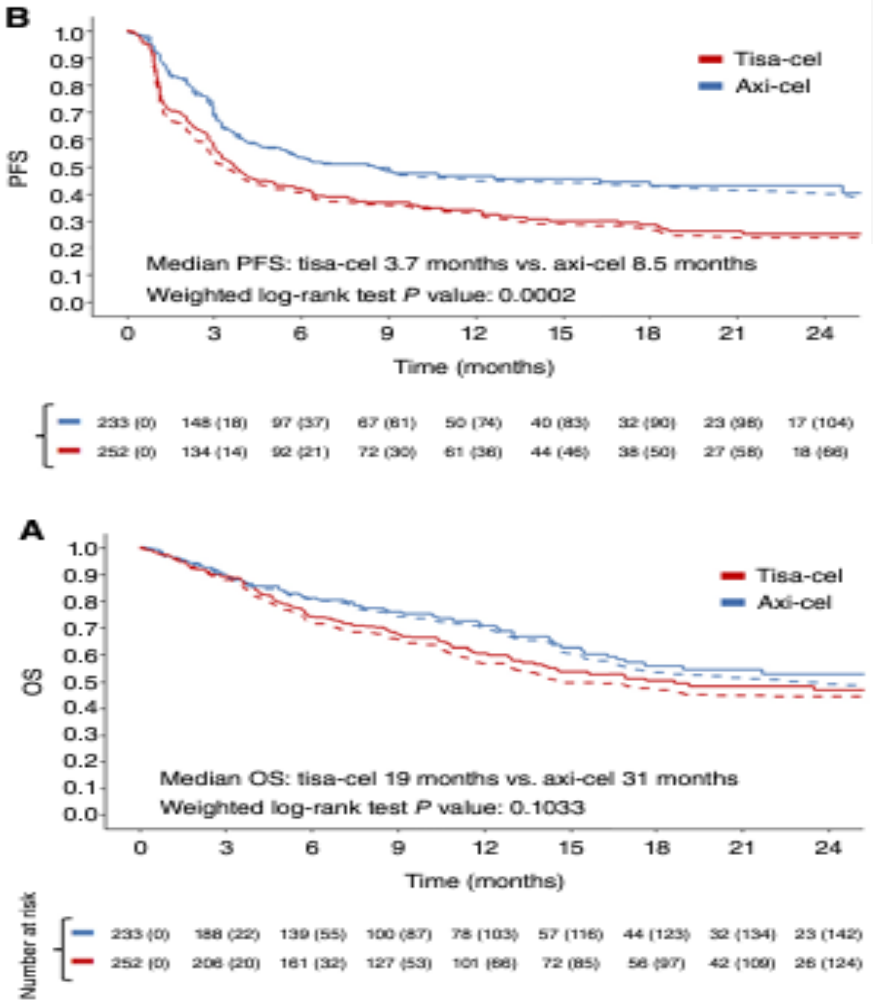
Abbreviation: pts, patients.
[a]SMD, standardized mean difference: assesses the balance in covariates between treatment groups, with a lower value indicating improved equivalence and reduced bias.

Stella, et al. *Blood Cancer Discov 2024*

Axicel vs tisacel in LBCL>2L

Outcome	Axi-cel n=233	Tisa-cel n=252
ORR, %	59%	48%
CR, %	75%	61%

- Higher CRS and ICANS of any grade with axicel
- No difference for Grade ≥3 CRS or ICANS
- No significant differences for long-term hematological toxicity



Stella, et al. *Blood Cancer Discov 2024*

Axicel vs lisocel in LBCL>2L

Dana-Farber Cancer Institute

Cohorts

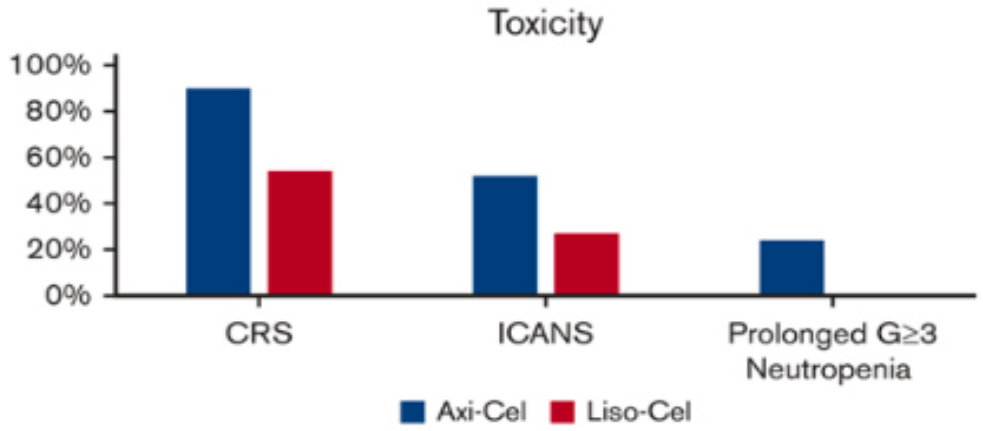
Axi-cel: 50 patients, median age 62 yrs

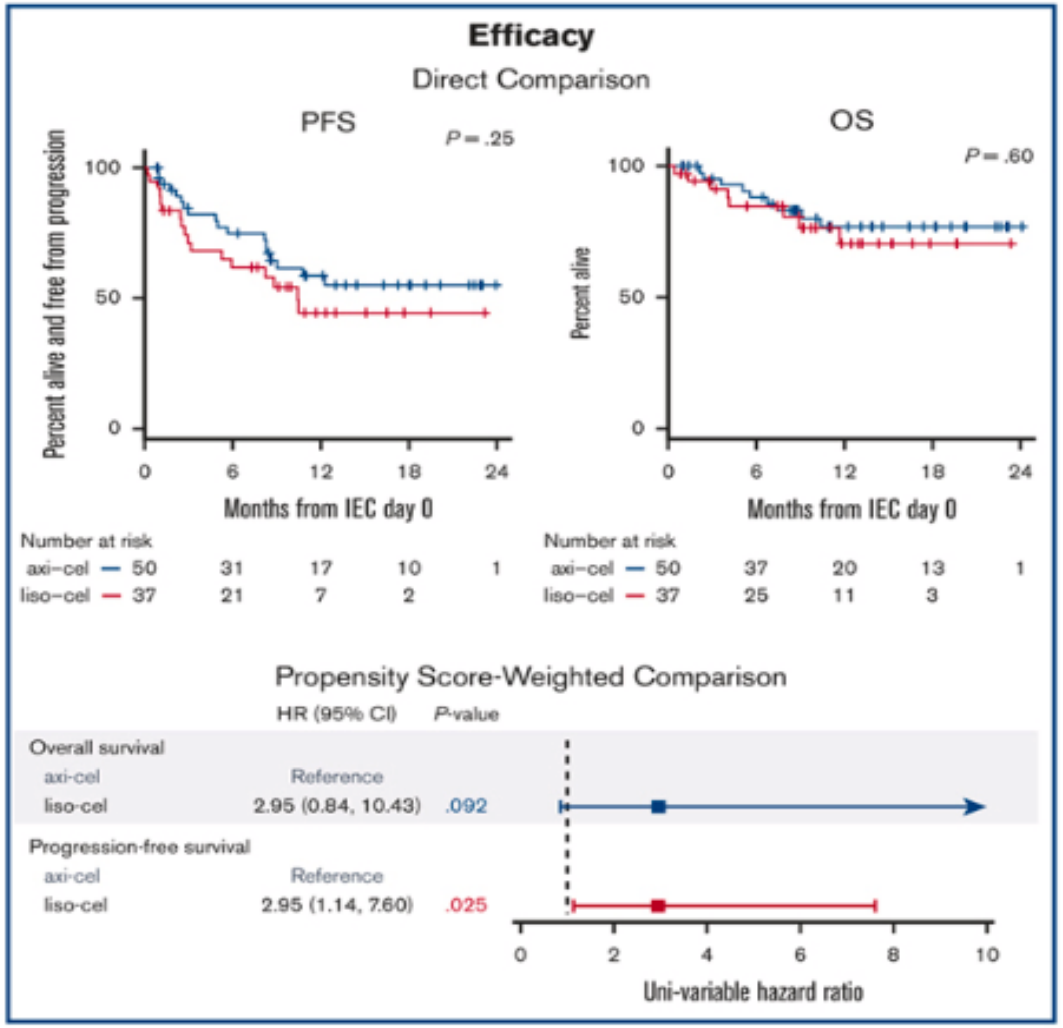
Liso-cel: 37 patients, median age 73 yrs

Time from Referral to Treatment

Axi-cel: 57 days

Liso-cel: 81 days



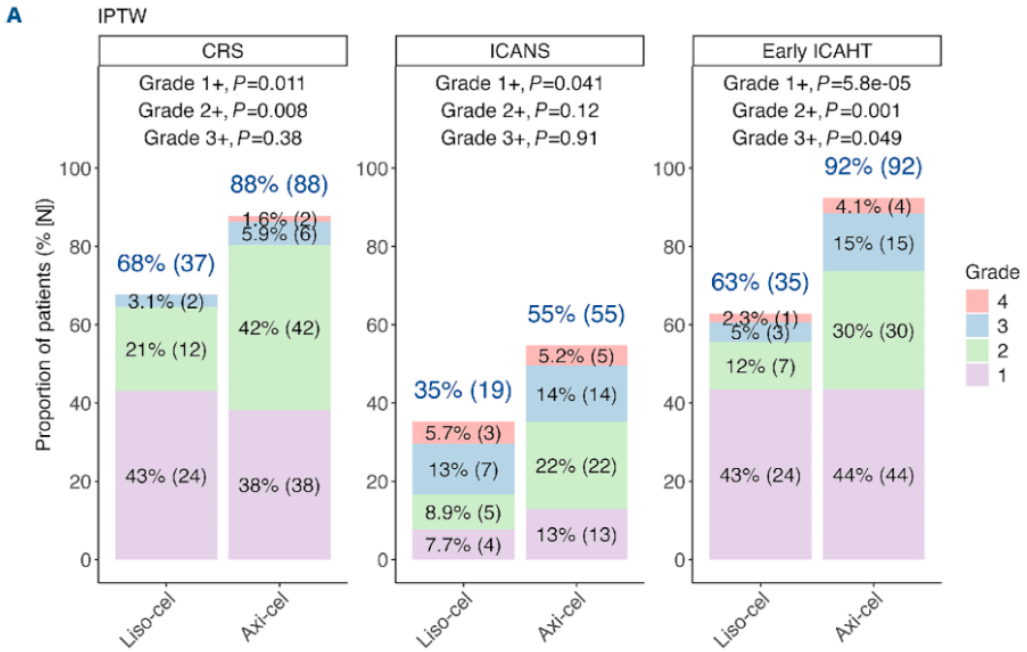


Looka et al. *Blood Adv 2025*

Axicel vs lisocel in LBCL>2L

Fred Hutch Cancer Center

Toxicities

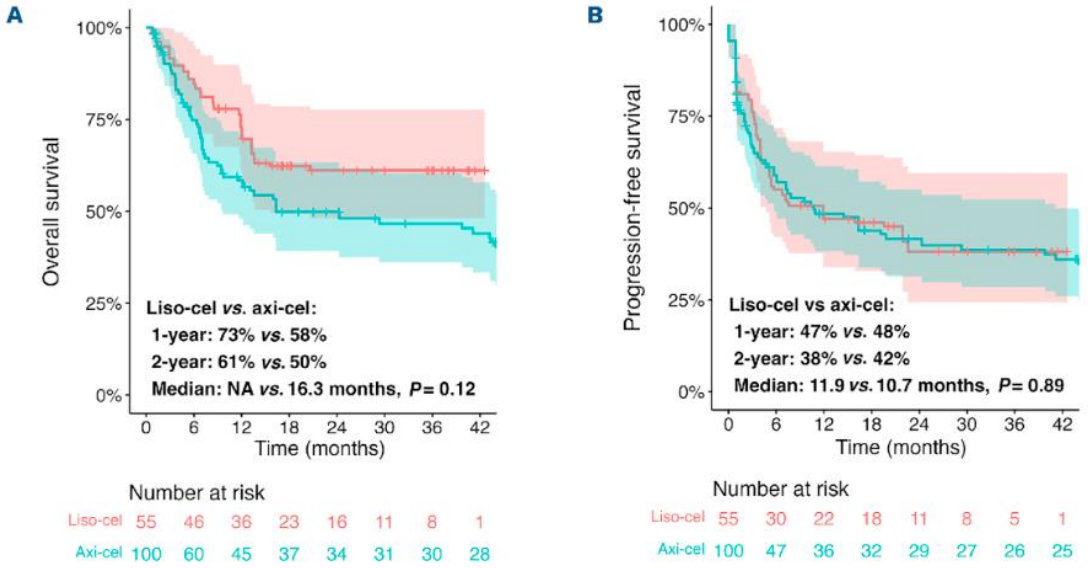


Lower incidence of toxicities with lisocel

V2V 34 (liso) vs 27 days (axi)

ORR 76% with Liso (CR 49%) vs 77% with axi (CR 48%)

Survival outcomes

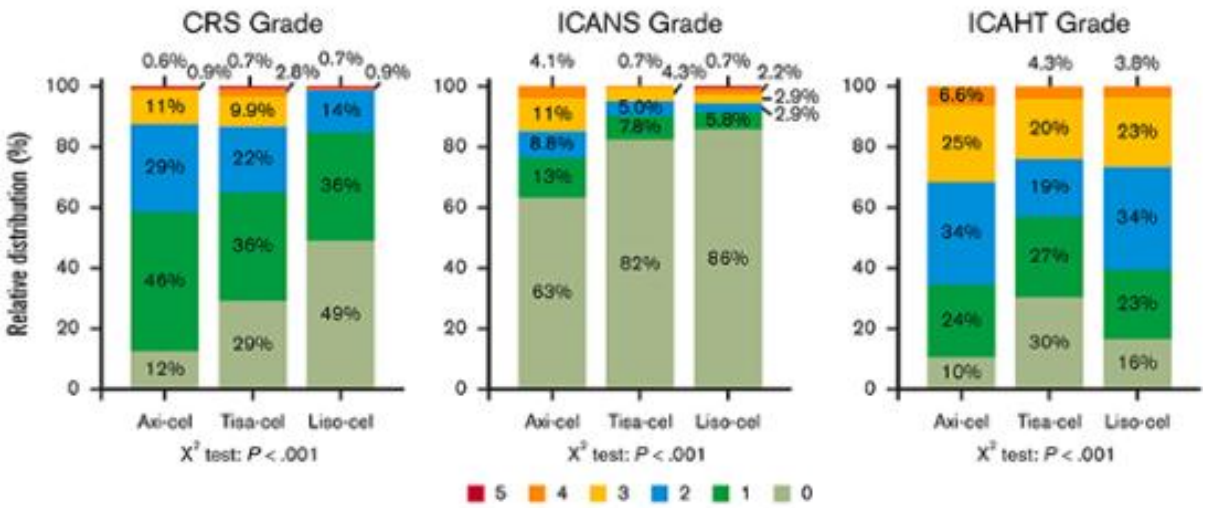


No differences for PFS and OS

Portuguese et al. *Haematologica 2025*

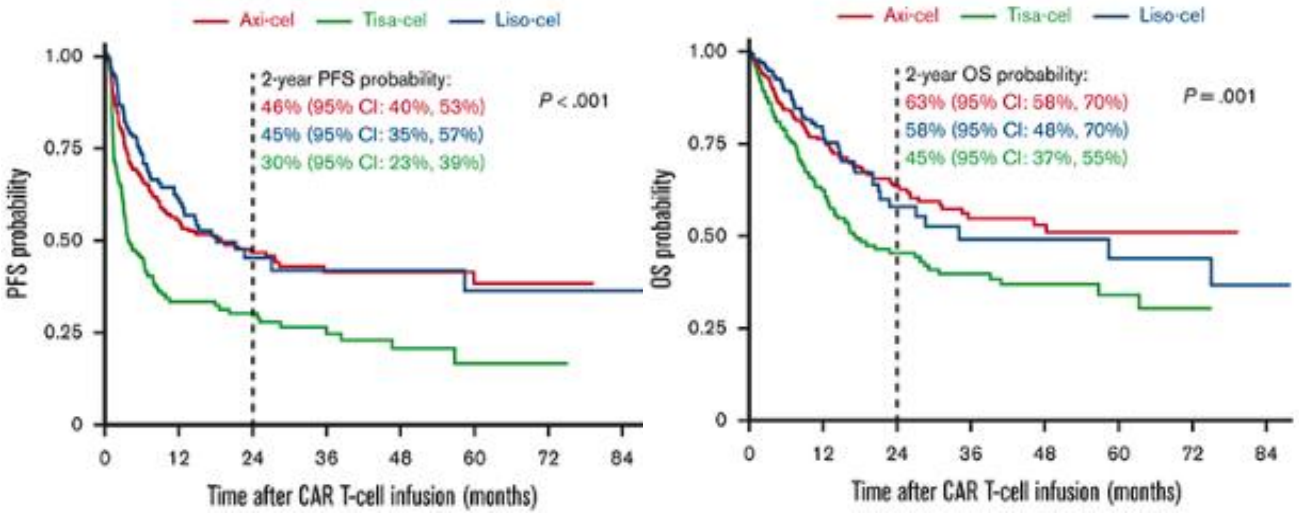
Comparing all products in LBCL>2L

Toxicities



Lisocel exhibits the most favorable toxicity profile → fewer resources for the management of post-infusion toxicities

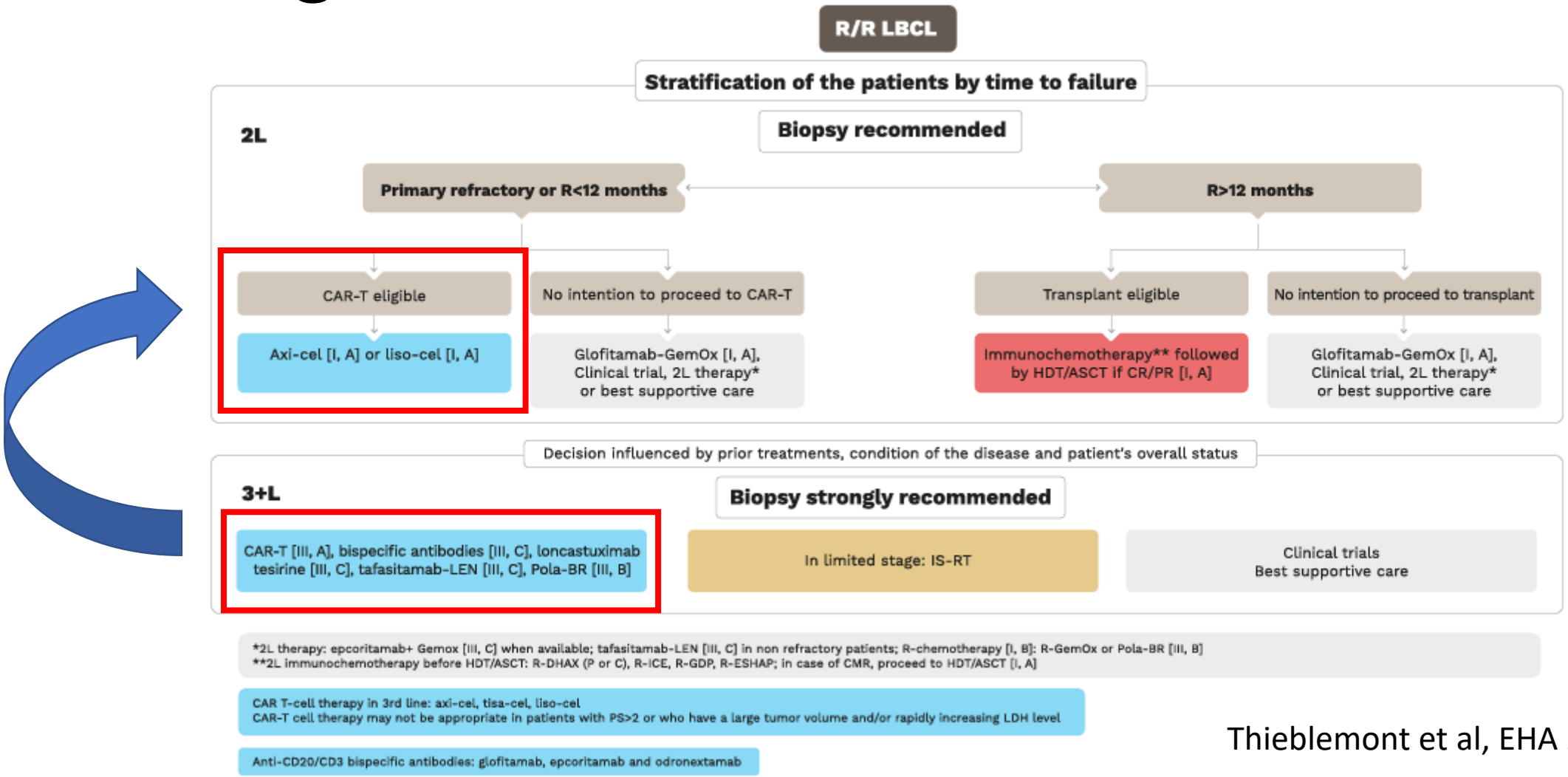
Survival outcomes



Tisacel associated with lower efficacy
Axi- and lisocel associated to similar survival

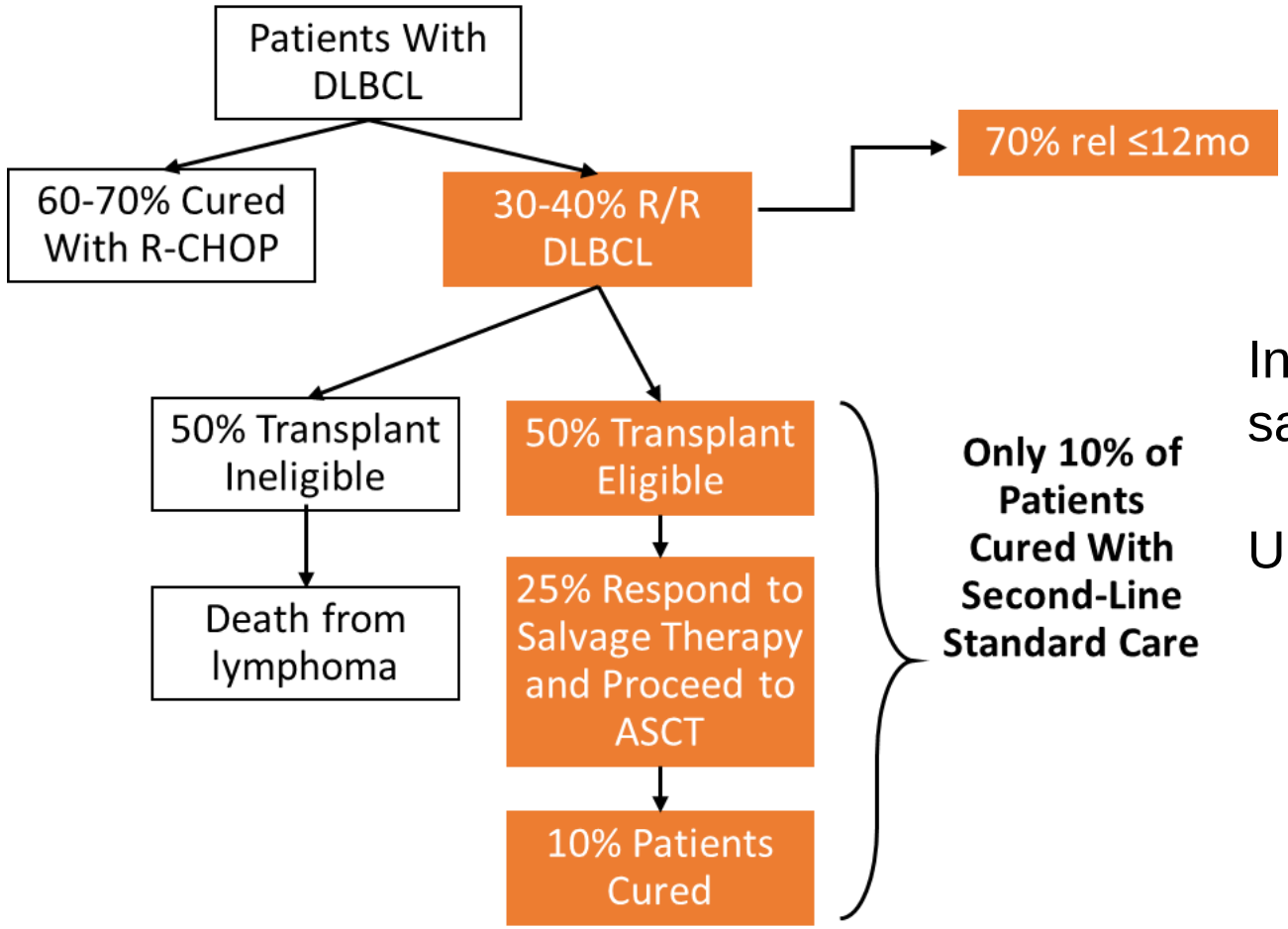
Deschenes-Simard et al. *Blood Adv 2025*

Moving CAR-T to earlier lines



Thieblemont et al, EHA 2025 guidelines

Why CAR-T in earlier lines for LBCL?



In R/R LBCL, treatment was initially based on salvage CHT + auto-HSCT

Unmet medical need:

- Many patients are ineligible for auto-HSCT
- Patients relapsing ≤12 months face poor prognosis

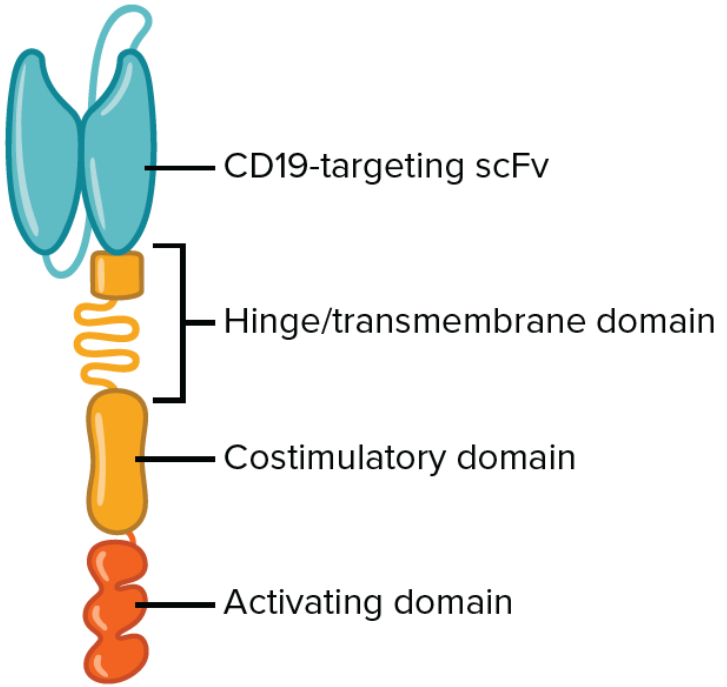
Adapted from Friedberg, *ASH* 2011; Zahid, et al. *Curr Hematol Malig Rep* 2017; Gisselbrecht, et al. *J Clin Oncol* 2010

Pivotal CAR-T trials in LBCL 2L

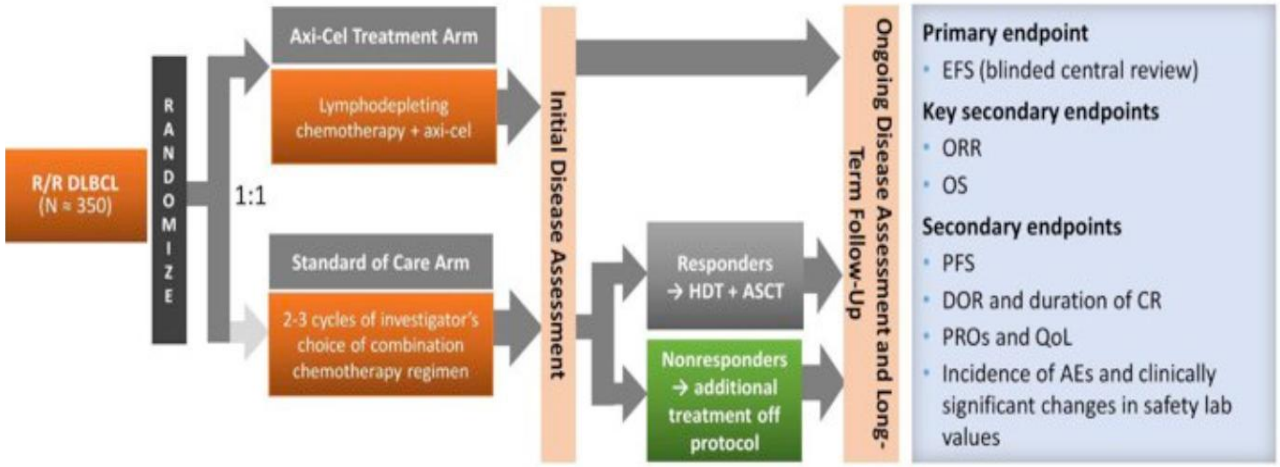
ZUMA-7 (axi-cel) ✓

BELINDA(tisa-cel) ✗

TRANSFORM (liso-cel) ✓



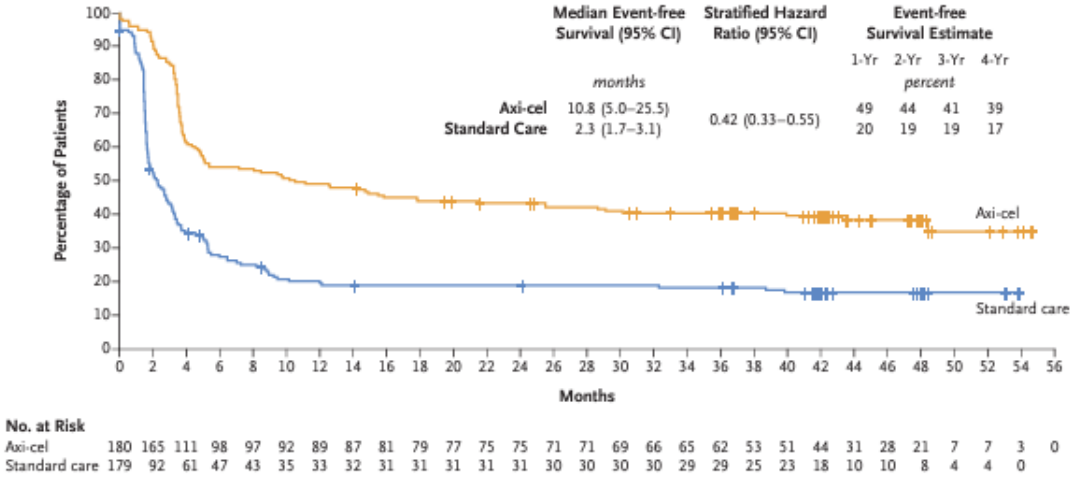
ZUMA-7: axi-cel vs SOC in DLBCL 2L



Characteristic (%)	Axi-cel (n=180)	SOC (n=179)
Median age, years (range)	58 (21-80)	60 (26-81)
Stage IV	139 (77)	146 (82)
sAAIPI 2-3	82 (46)	79 (44)
Primary refractory	133 (74)	131 (73)
Relapse ≤12 mo	47 (26)	48 (27)

3-fold patients received CAR-T (n=170) vs SOC (n=72)
Vein-to-vein time: 29 days (27-34) (delivery in 18 days)
ORR: 83% (65% CR) vs 50% (32% CR); p<0.0001
ORR and EFS results consistent across subgroups
Tumor burden correlated with safety and efficacy outcomes
Bridge therapy max steroids

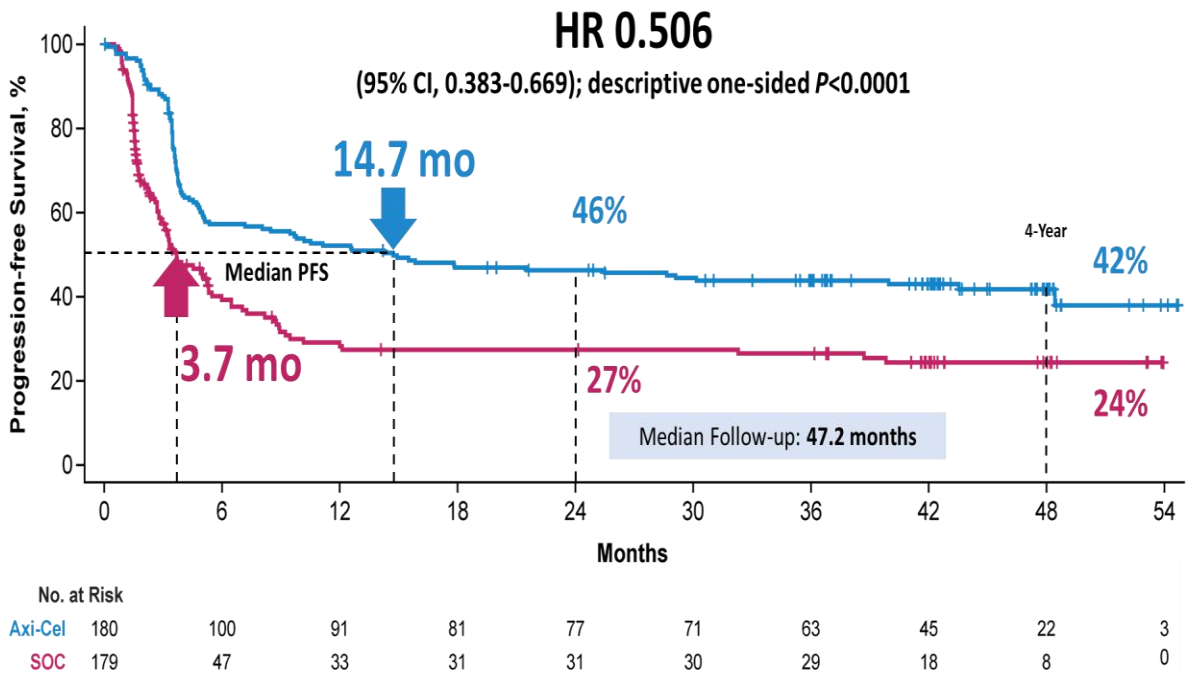
Median follow-up 47.2 months

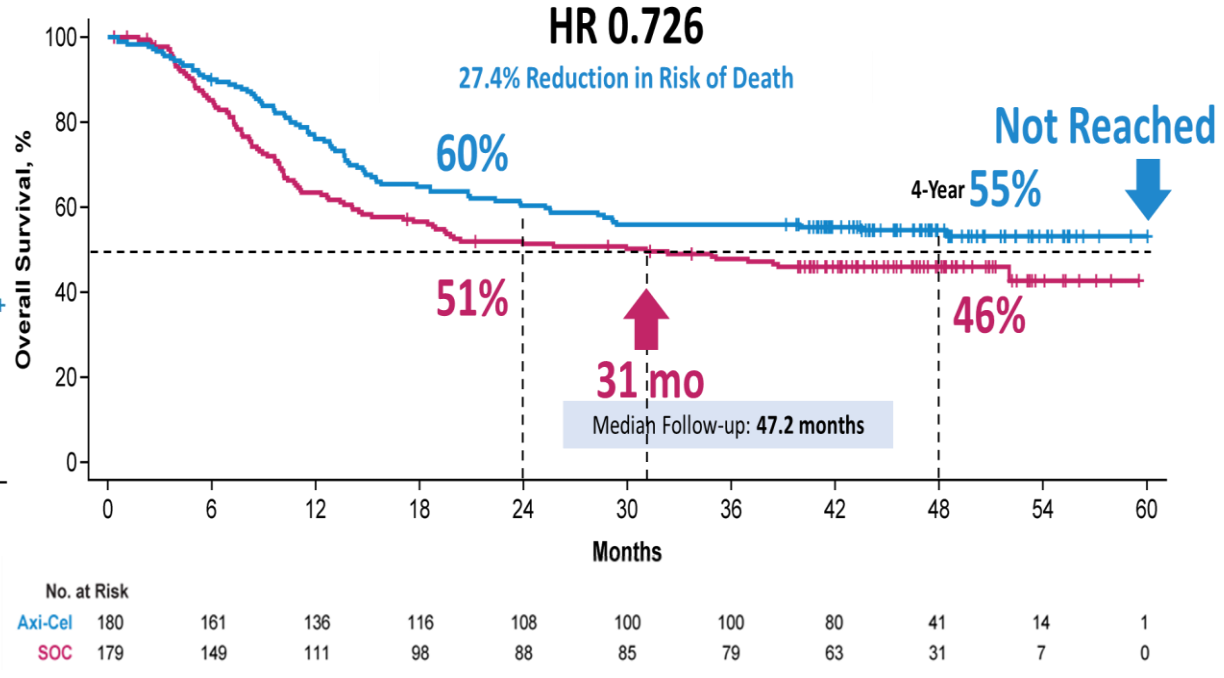


Locke FL et al. *N Engl J Med*. 2021
Westin et al. *N Engl J Med*. 2023

ZUMA-7: survival

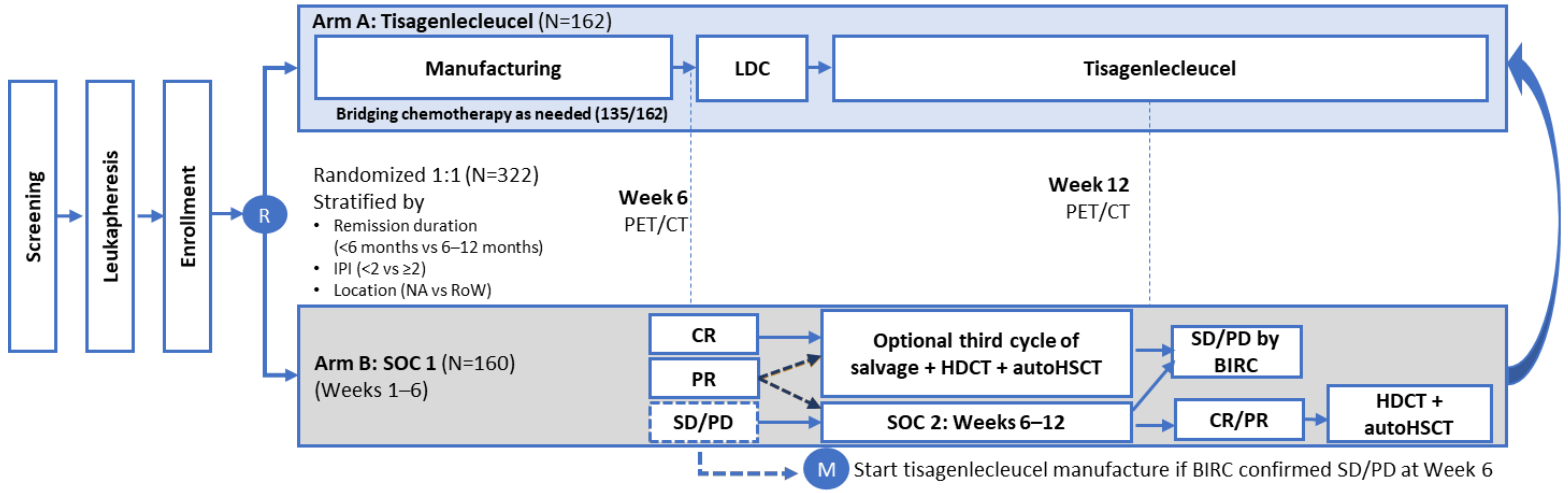
57% of SOC patients received subsequent cellular immunotherapy (off protocol)





Westin et al. *N Engl J Med*. 2023

BELINDA: tisacel vs SOC in DLBCL 2L



Safety and efficacy follow-up

- Week 6 for treatment decision
- Week 12 ± 1 week for disease assessment
- Every 3 months up to Month 12
- Every 6 months up to Month 24
- Annually to Month 60

Crossover allowed if BIRC SD/PD confirmed at/after Week 12, up to 1 year after HSCT

Endpoints

Primary: EFS (defined as time to SD or PD by BIRC at/after Week 12 [±1 week] or death at any time)

Secondary: OS, ORR and BOR rate, safety, cellular kinetics

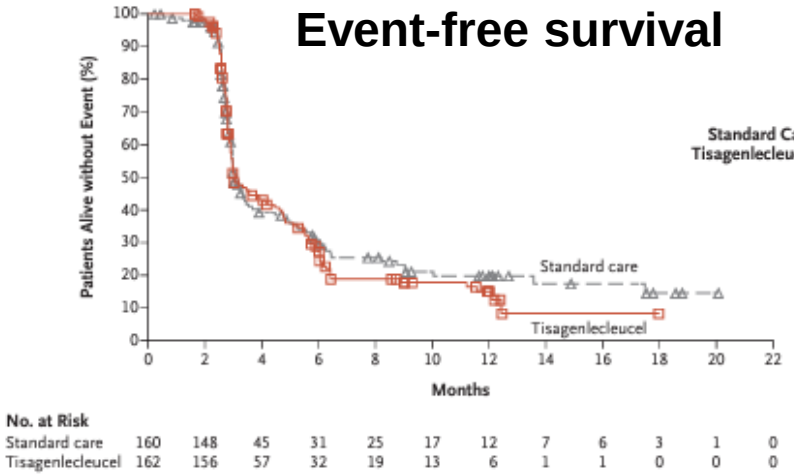
Characteristic (%)	Tisa-cel (n=162)	SOC (n=160)
Median age, years (range)	51 (19-79)	58 (19-77)
Stage IV	139 (77)	146 (82)
IPI ≥2	106 (65)	92 (58)
Primary refractory	107 (66)	107 (67)
Relapse ≤12 mo	55 (34)	53 (33)

ORR: 46% (28% CR) vs 42% (28% CR)

A higher proportion of PD prior to infusion (26%) vs SOC (14%)

Median vein-to-vein time: 52 days

Event-free survival

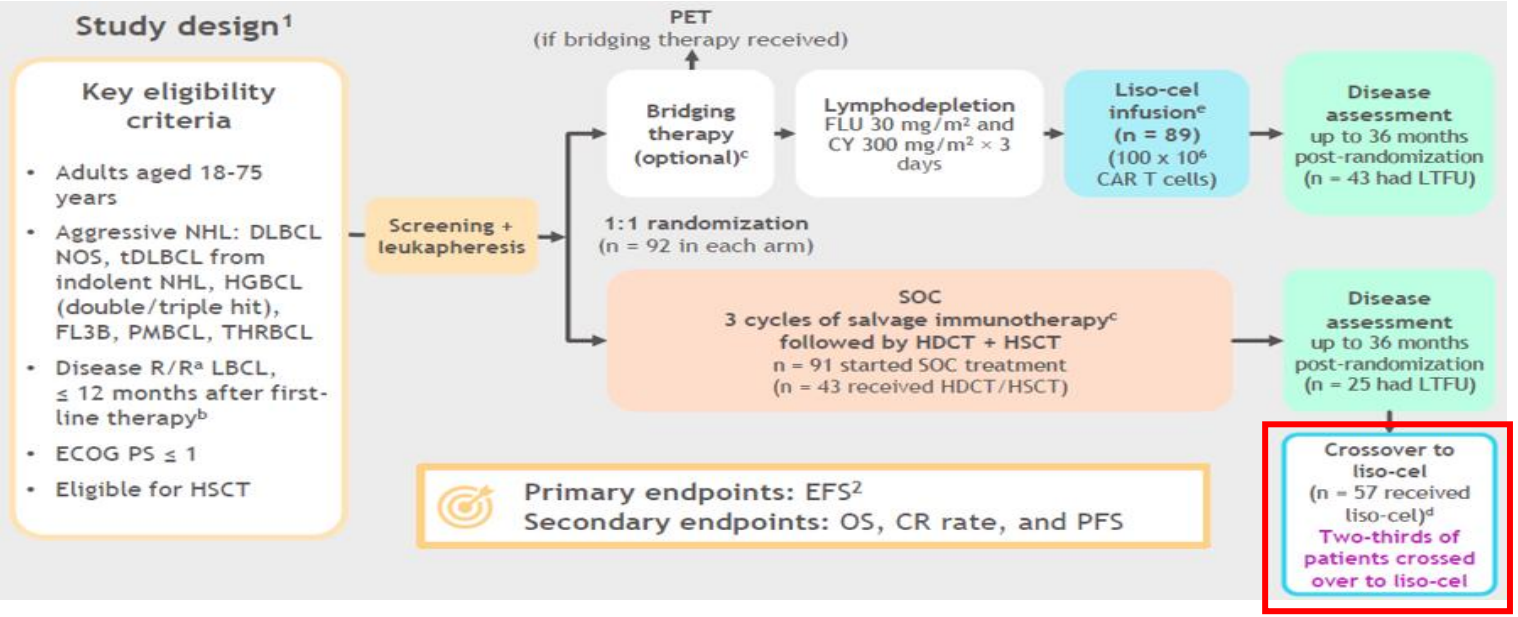


	No. of Patients	No. of Events	Median Event-free Survival (95% CI) mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

Bishop et al. *N Engl J Med*. 2022

TRANSFORM: liso-cel in 2° line DLBCL



CNS+ Included

Characteristic (%)	Liso-cel (n=92)	SOC (n=92)
Median age, years (range)	60 (20-74)	58 (26-75)
Stage IV	50 (54)	50 (54)
sAAIPI 2-3	36 (39)	37 (40)
Primary refractory	67 (73)	70 (76)
Relapse ≤12 mo	25 (27)	22 (24)
Secondary CNS lymphoma	1 (1)	3 (3)

97% received liso-cel vs 47% in SOC (n=72)

63% bridge therapy

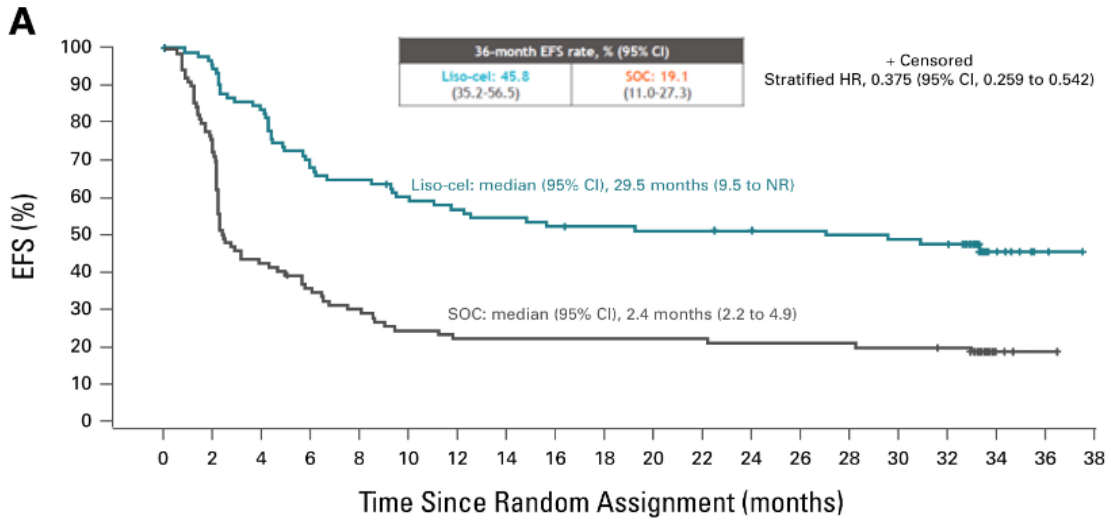
ORR: 87% (74% CR) vs 49% (43% CR)

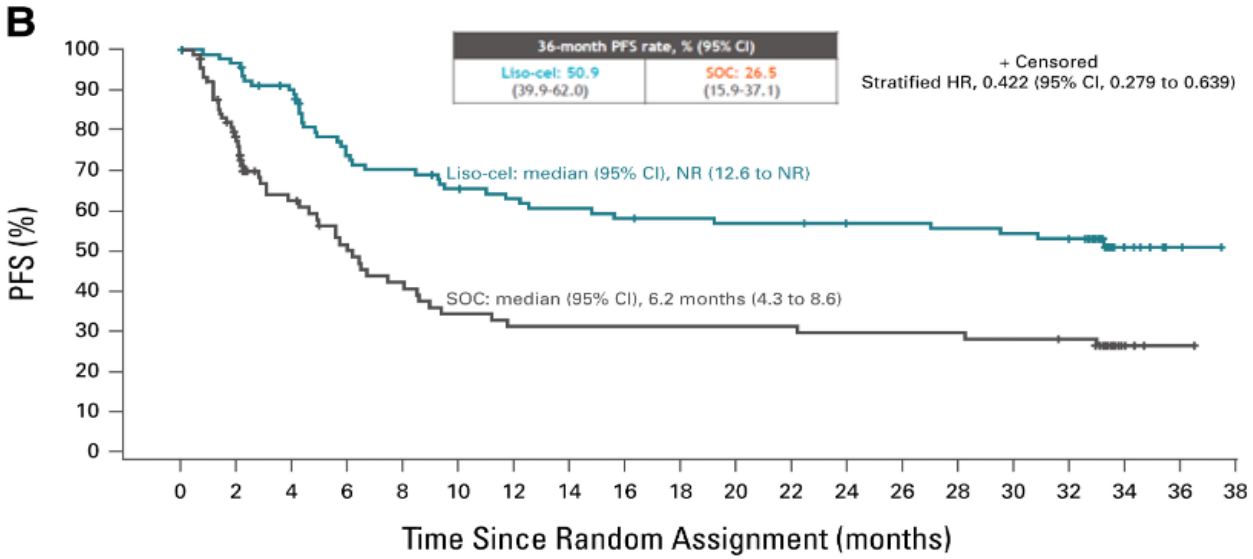
Consistent results across subgroups

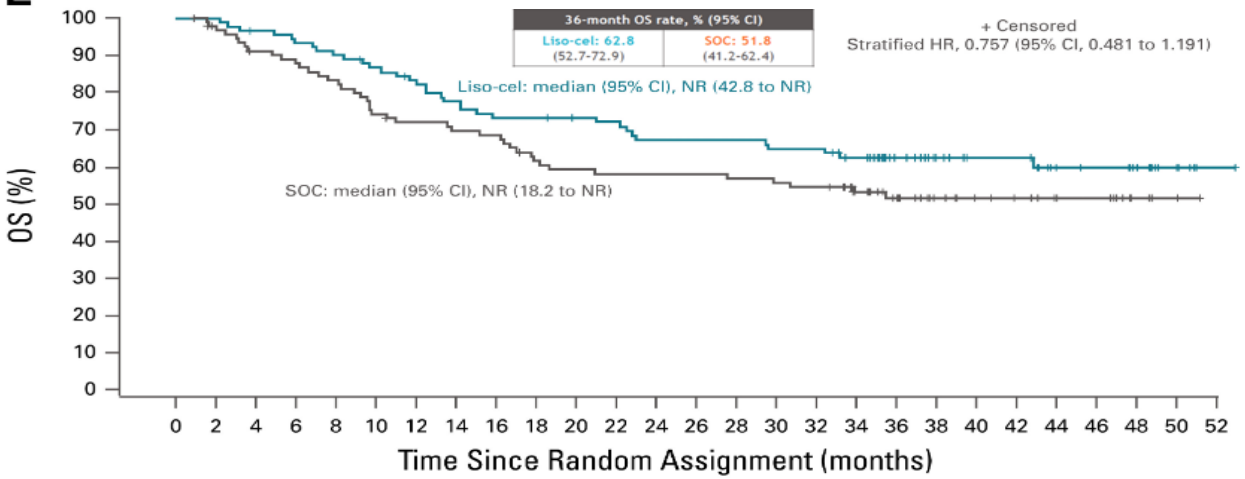
62% SOC arm underwent crossover → 64% ORR (53% CR)

Abramson et al. Blood 2023

TRANSFORM: survival







62% of SOC patients received subsequent cellular immunotherapy (crossover), with 64% ORR (53% CR)

When taking into account crossover effect, potential benefit of liso-cel for OS

Kamdar et al. *J Clin Oncol* 2025

From clinical trials to RWE in DLBCL 2L

Study	Product	N	Period	Median age	Median FUP	BT	NE for trials	Median V2V
DESCART	Axicel	201	2022-2023	61	3 mo	88%	-	36d
UK	Axicel	346	2023-2024	62	9.5 mo	98%	-	36d
CIBMTR	Axicel	442	2022-2023	64	12 mo	66%	49%	29d
CIBMTR	Lisocel	156	2022-2024	72	6 mo	72%	67%	-

FUP: follow-up; BT: bridge therapy; NE: non eligible

Brisou et al *ASH* 2023; Kuhnl et al *ASH* 2024; Lee et al *ASH* 2024; Bobillo et al *ASH* 2024

RCTs vs RWE in DLBCL 2L

Study	Treatment	N	ORR/CR, %	EFS, %	PFS, %	OS, %	CRS overall/Gr≥3, %	ICANS overall/Gr≥3, %
ZUMA-7	Axicel SOC	180 179	83/65 50/32	4y: 39 4y: 17	4y: 42 4y: 24	4y: 55 4y: 46	92/6 -	60/21 -
BELINDA	Tisacel	162 160	46/28 42/28		-	-	61/5	10/2
TRANSFORM	Lisocel SOC	92 92	87/74 49/43	3y: 46 3y:19	3y: 51 3y: 27	3y: 63 3y:52	49/1 -	11/4 -

Study	Product	N	ORR/CR, %	EFS, %	PFS, %	OS, %	CRS overall/Gr≥3, %	ICANS overall/Gr≥3, %
DESCART	Axicel	201	88/66	-	-	-	93/5	43/13
UK	Axicel	346	87/61	-	12-mo: 51	12-mo: 71	98/5	48/18
CIBMTR	Axicel	442	79/64	1y: 53	-	1y: 71	87/5	50/22
CIBMTR	Lisocel	156	84/70	6-mo: 61	-	6-mo: 87	45/1	20/6

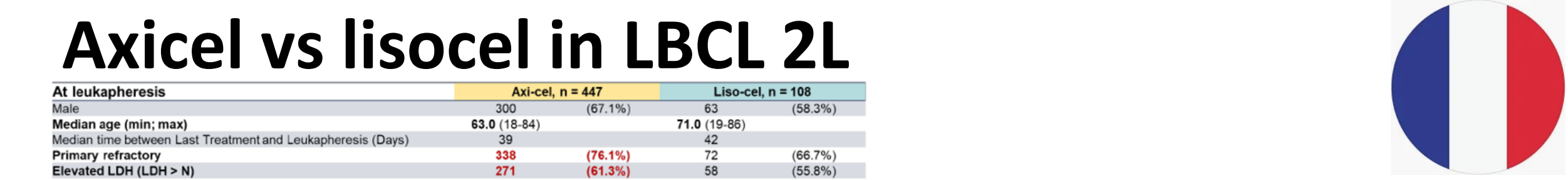
Westin et al. *N Engl J Med*. 2023; Bishop et al. *N Engl J Med*. 2022; Abramson et al. *Blood* 2023; Kuhnl et al. *ASH* 2024; Lee et al. *ASH* 2024; Bobillo et al. *ASH* 2024

Pick up the winner

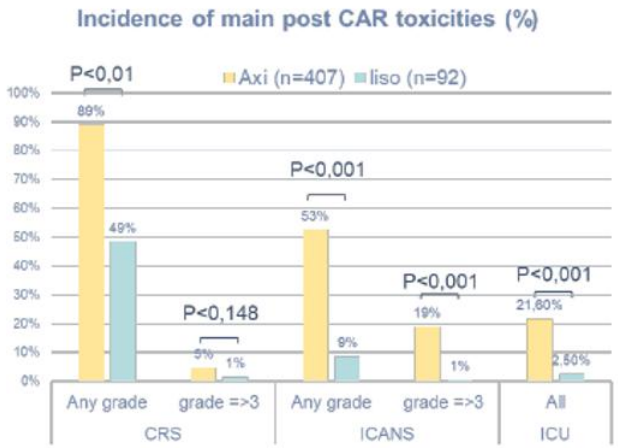
Axicel vs lisocel in LBCL 2L

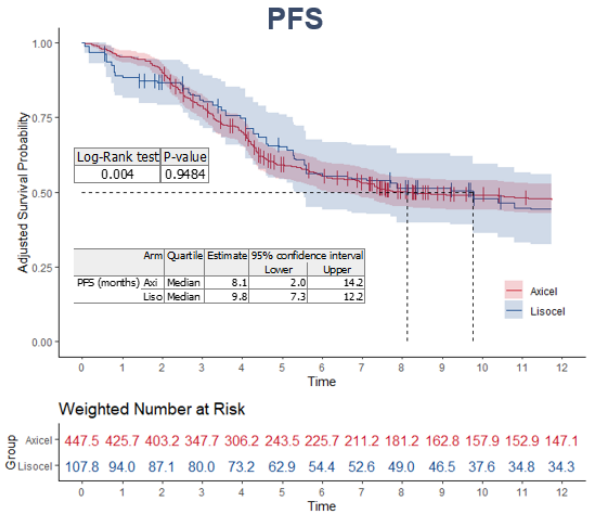
At leukapheresis	Axi-cel, n = 447		Liso-cel, n = 108	
Male	300	(67.1%)	63	(58.3%)
Median age (min; max)	**63.0** (18-84)		**71.0** (19-86)	
Median time between Last Treatment and Leukapheresis (Days)	39		42	
Primary refractory	**338**	**(76.1%)**	72	(66.7%)
Elevated LDH (LDH > N)	**271**	**(61.3%)**	58	(55.8%)
ECOG ≥ 2	45	(11.4%)	**22**	**(22.4%)**
Ann Arbor Stage III/IV	**349**	**(84.5%)**	77	(75.5%)
LBCL	366	(81.9%)	87	(80.6%)
HGBL	**27**	**(6.0%)**	2	(1.9%)
Transformed Indolent	54	(12.1%)	19	(17.6%)

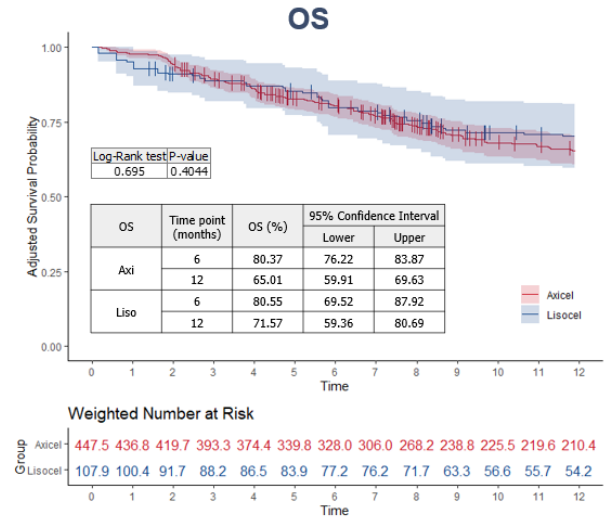
At infusion	Axi-cel, n = 410		Liso-cel, n = 93	
Median time between Last Treatment and Infusion (Days) (Q1-Q3) including vein-to-vein time	87.5 (62-188)		**113 (78-260)**	
CRP > 30mg/L	**94**	**(24.9%)**	15	(17.9%)
LDH > Upper Limit	153	(41.7%)	37	(42.5%)
Response After Bridging				
No Bridge	28	(7.3%)	3	(3.7%)
CR /PR	173	(44.8%)	**42**	**(50.6%)**
SD/PD	185	(47.9%)	38	(45.8%)



Baseline differences reveal selection bias regarding CAR-T choice, with liso-cel being more often proposed to older, frailer patients, able to wait longer for infusion.

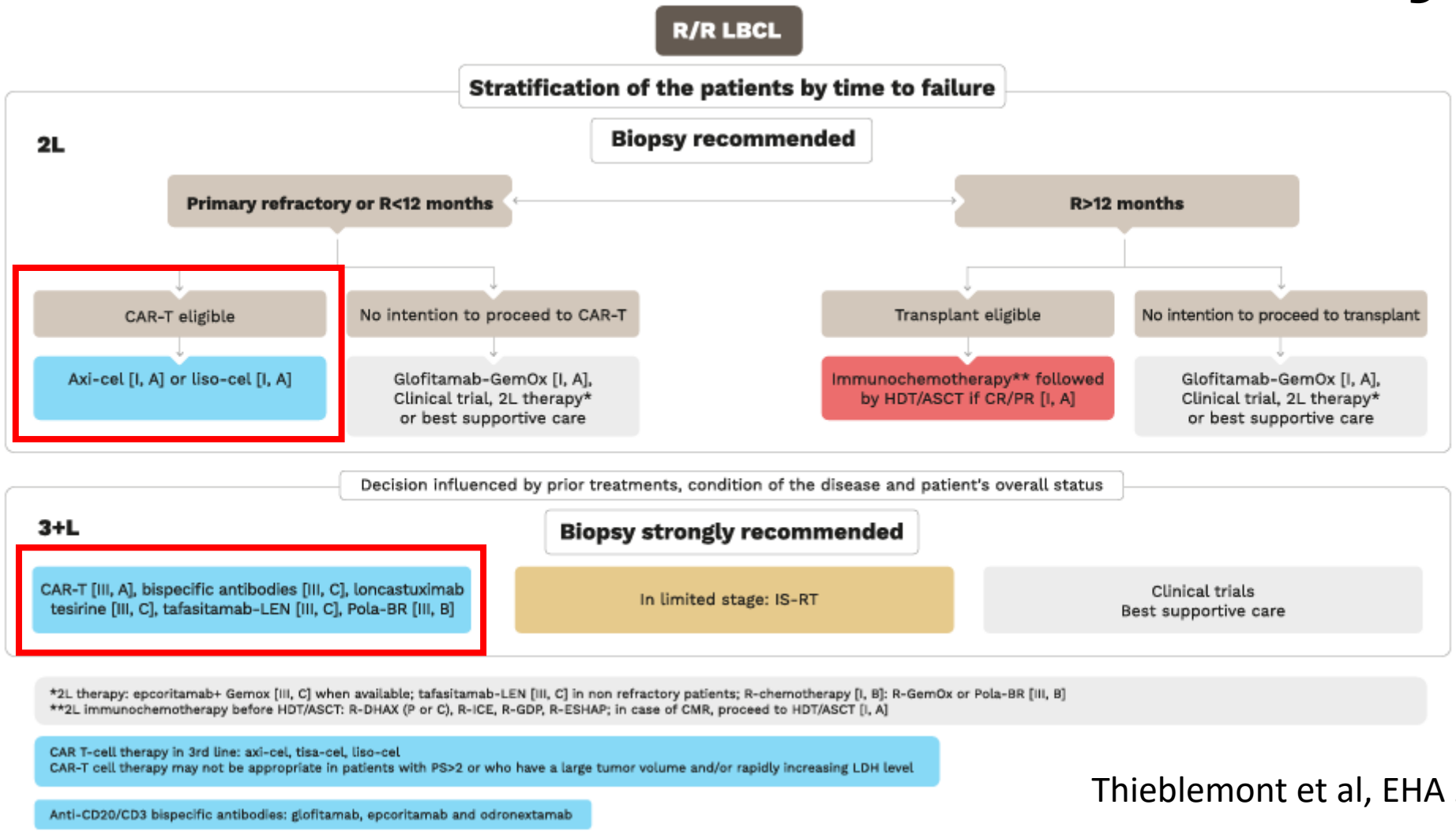






Brisou et al. ASH 2025

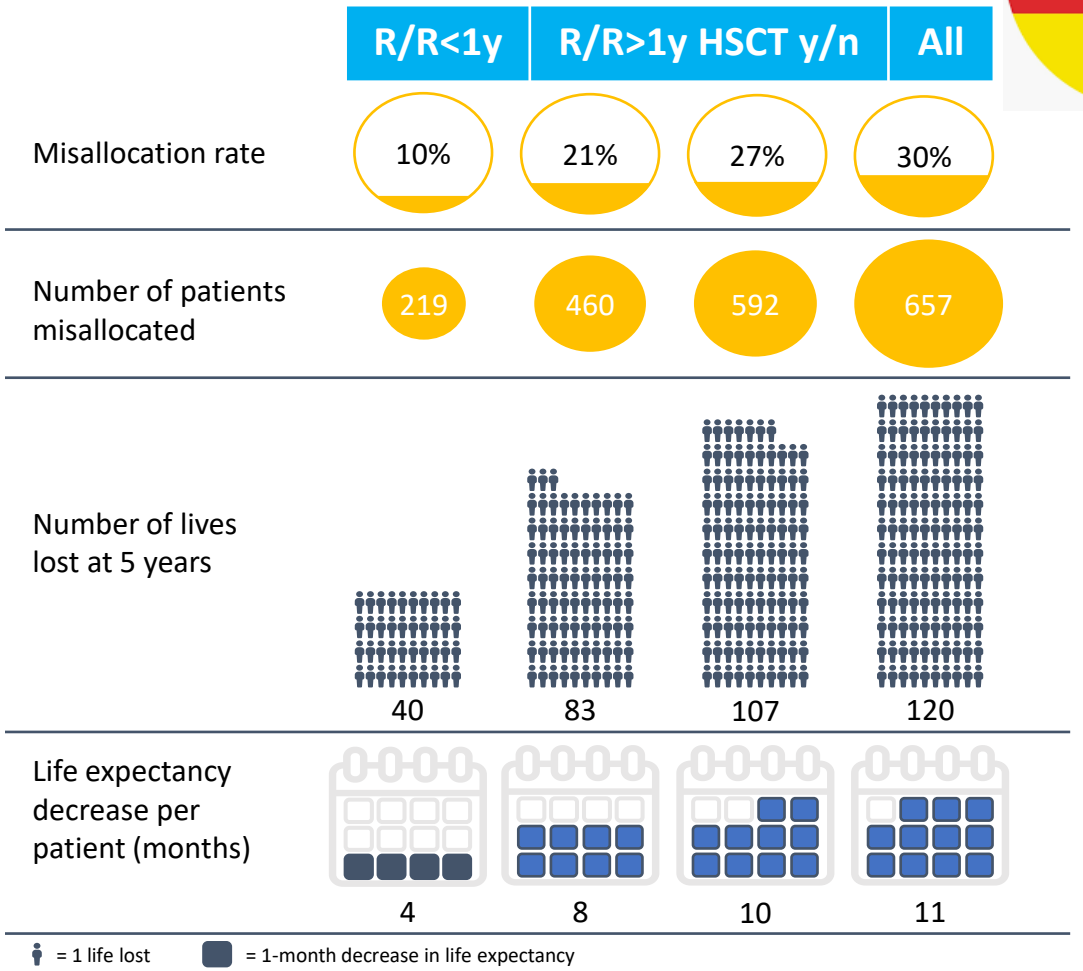
Earlier or later: how to choose wisely



Thieblemont et al, EHA 2025 guidelines

CAR-T misallocation consequences

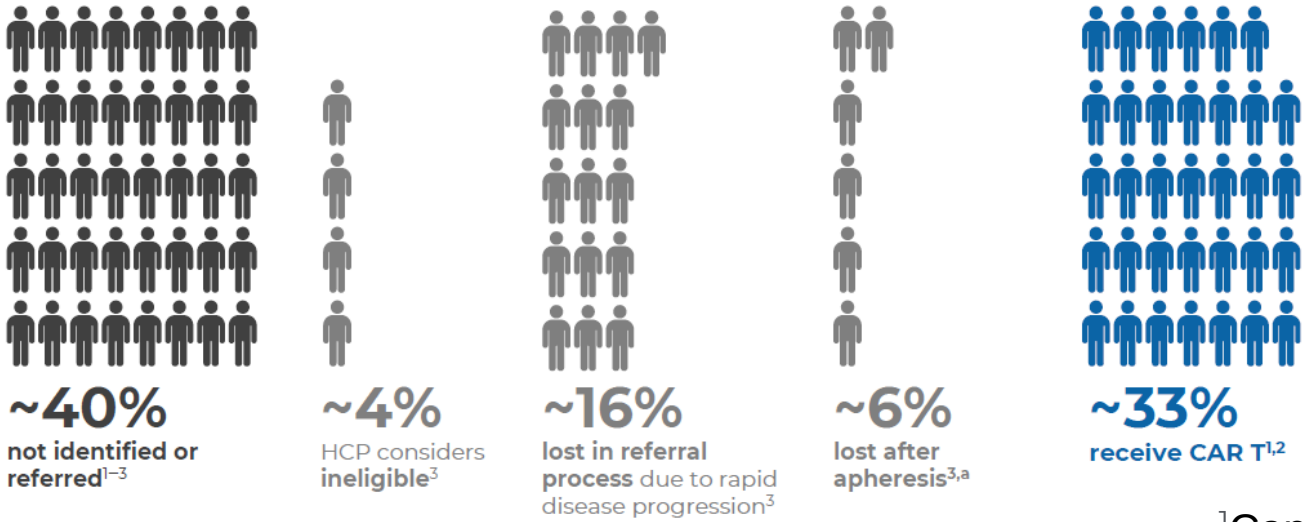
- Simulation modelling to examine the impact of misallocation of CAR-T eligibility due to clinical and non-clinical reasons
- Patients received alternative sequences of treatments likely to reduce the overall survival, resulting in suboptimal outcomes at the population level.
- **Greater efforts are needed to ensure that CAR-T eligible patients are identified systematically, and referral pathways are optimized to ensure all eligible patients receive CAR-T therapy.**



Buecklein et al, ASH 2024

The gap between eligibility and access

- Despite their curative potential, CAR T aren't reaching enough patients
  - In Europe, only ~33% of eligible LBCL patients receive CAR T-cell therapy
  - In the US, even after 7 years, only ~20% of eligible LBCL patients access CAR T



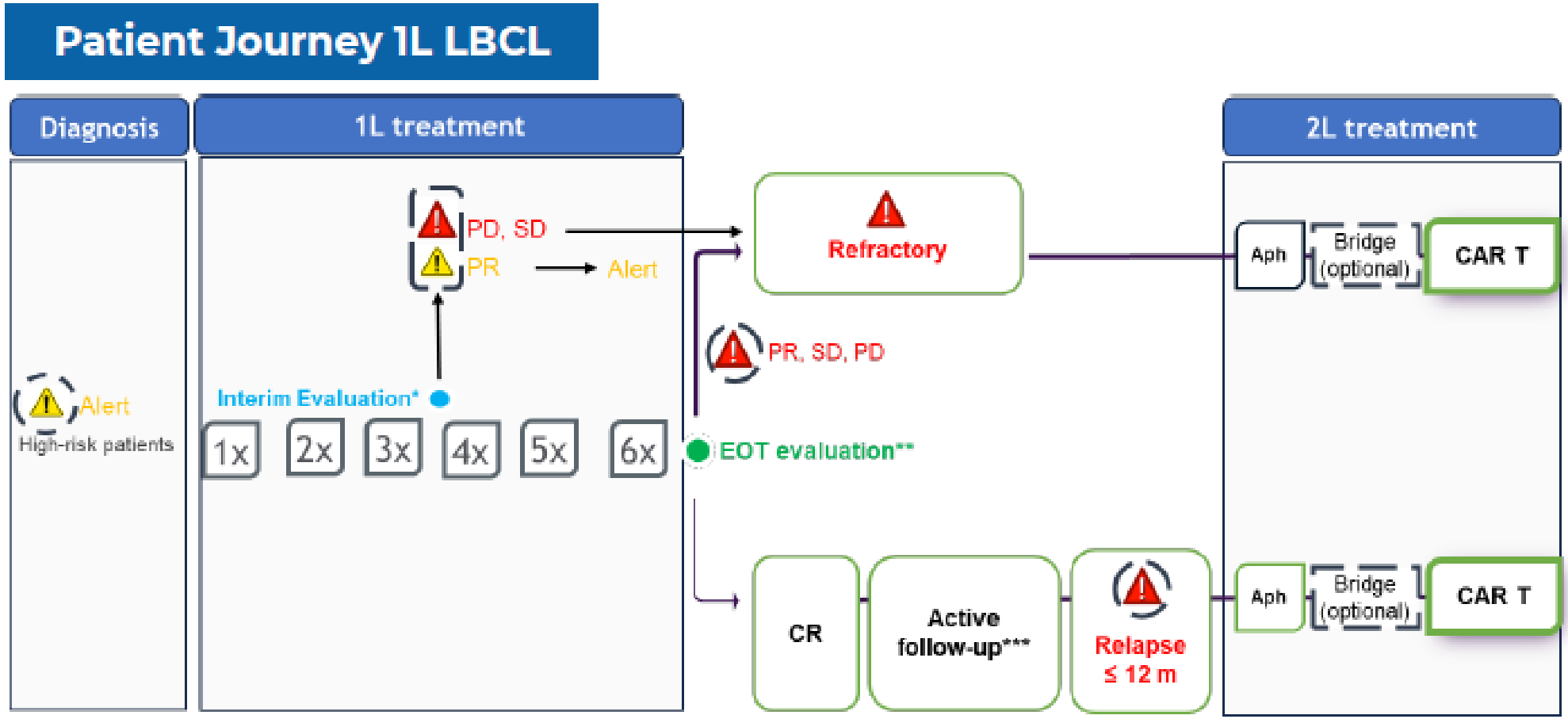
Patient journey **optimization** through **early** and **effective identification and referral** are essential to ensuring more eligible patients finally receive treatment CAR-T

[1]Canales Albendea et al. Front Med (Lausanne) 2023
[2]Hopfinger et al. MEMO 2023
[3]Spanjaart et al. Cancers (Basel) 2023

Time matters

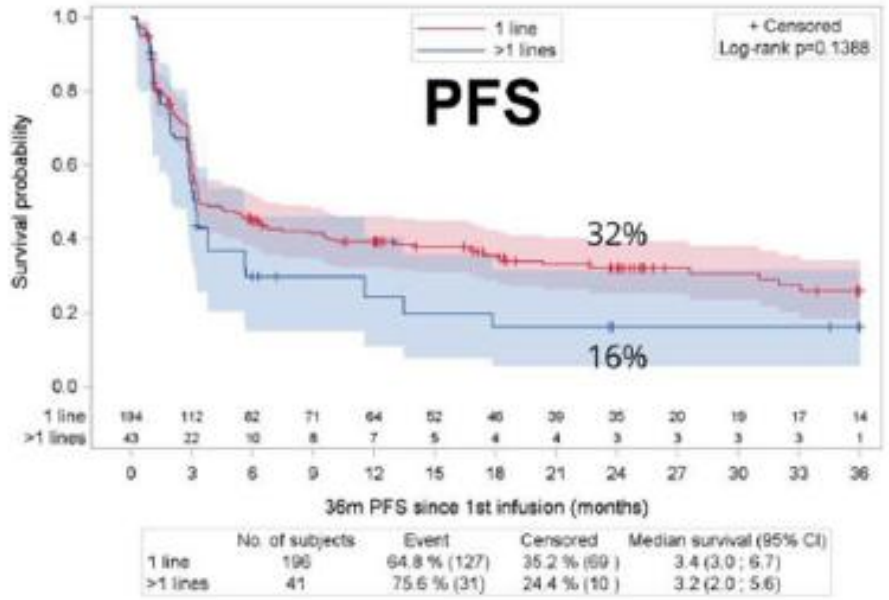
Don’t wait the perfect moment, act early

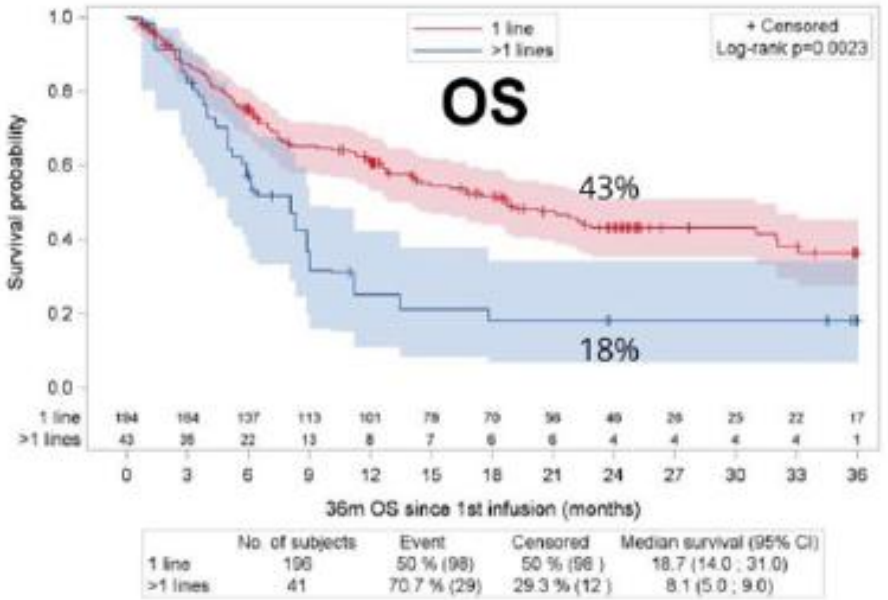
Anticipating Treatment Failure



Luminari et al, *Cytotherapy* 2025

BT: caution, don’t cumulate, don’t delay



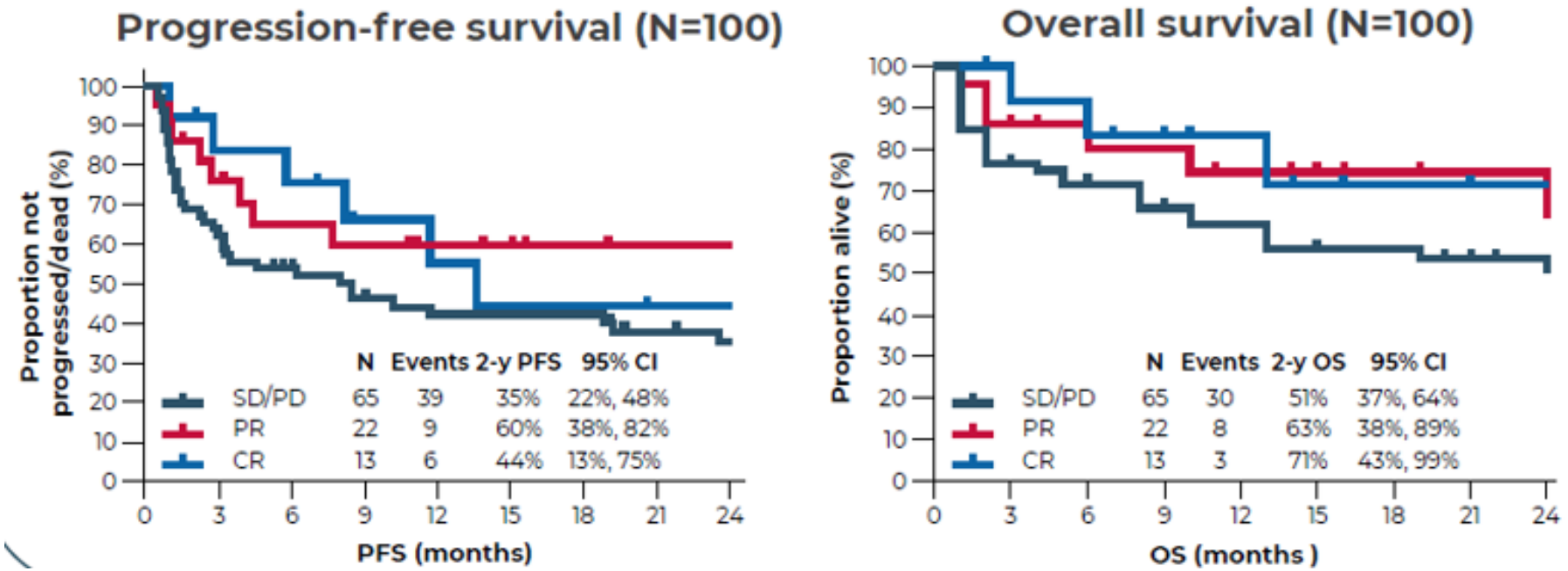


Administering >1BT line led to higher rates of persistent hematotoxicity and inferior OS compared to a single BT line, even in patients with PD after initial BT. While additional BT lines may improve disease status at infusion in a minority of patients, delaying CAR T-cell infusion for this purpose does not appear to improve survival

Manson et al, *ASH* 2025

No need to wait for deeper responses

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®



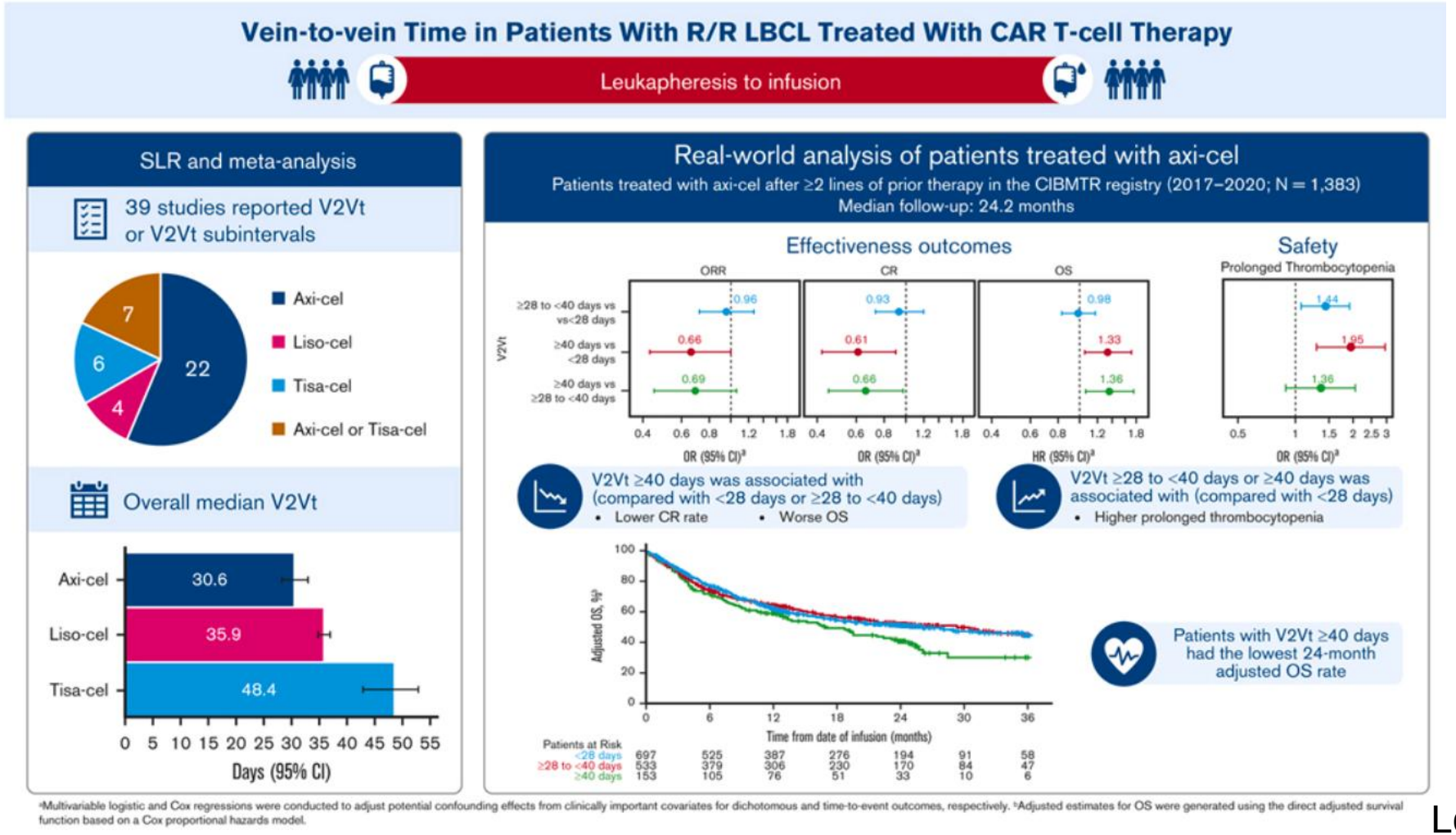
No clear impact of disease status at infusion?.....

.....Results should be interpreted with caution given sample size and heterogeneity

Case-by-case evaluation of SD/PD patients

Jallouk et al, *Haematologica* 2023

V2V time matters

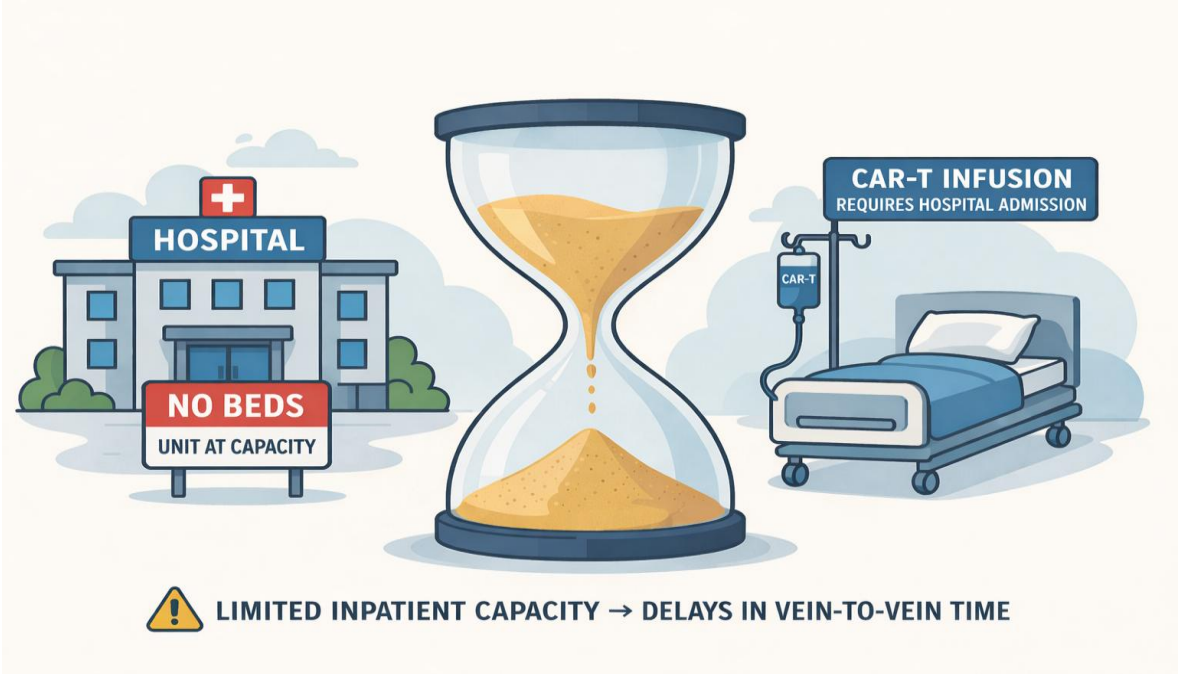


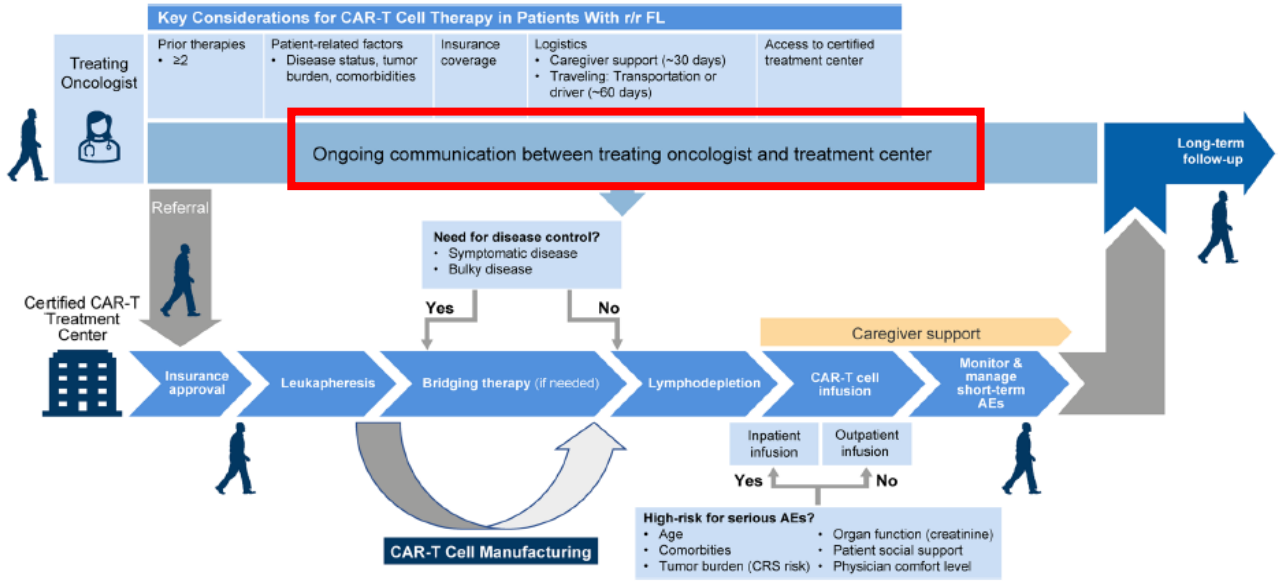
[a]Multivariable logistic and Cox regressions were conducted to adjust potential confounding effects from clinically important covariates for dichotomous and time-to-event outcomes, respectively. [b]Adjusted estimates for OS were generated using the direct adjusted survival function based on a Cox proportional hazards model.

Better CR and OS if axi-cel V2Vt <28 days or 28-40 days compared with ≥40 days

Locke et al, *Blood Adv* 2025

When timing meets reality





Fowler NH et al, *Target Oncol* 2024

Barriers to CAR-T eligibility

Older patient age

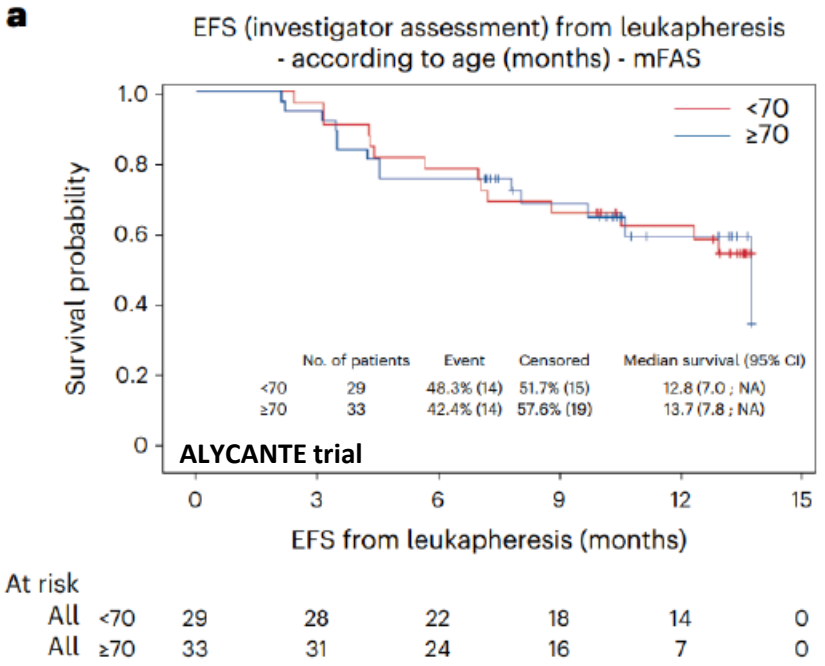
Safety concerns

Comorbidities

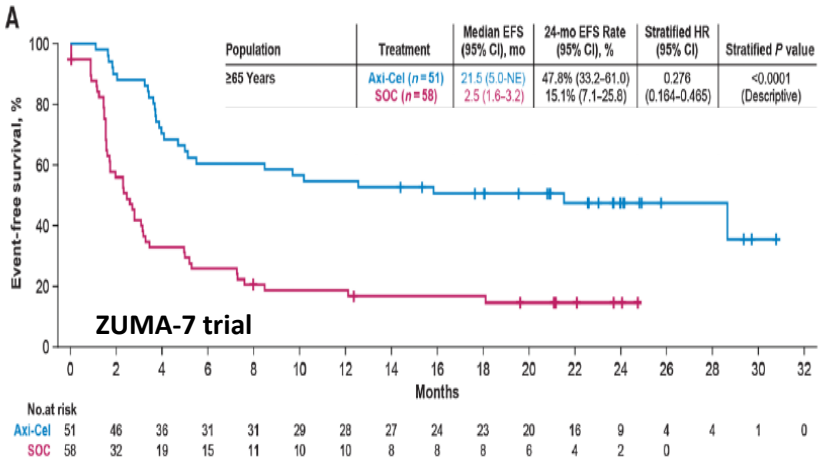
Barriers or perceived barriers?

AIFA AGENZIA ITALIANA DEL FARMACO

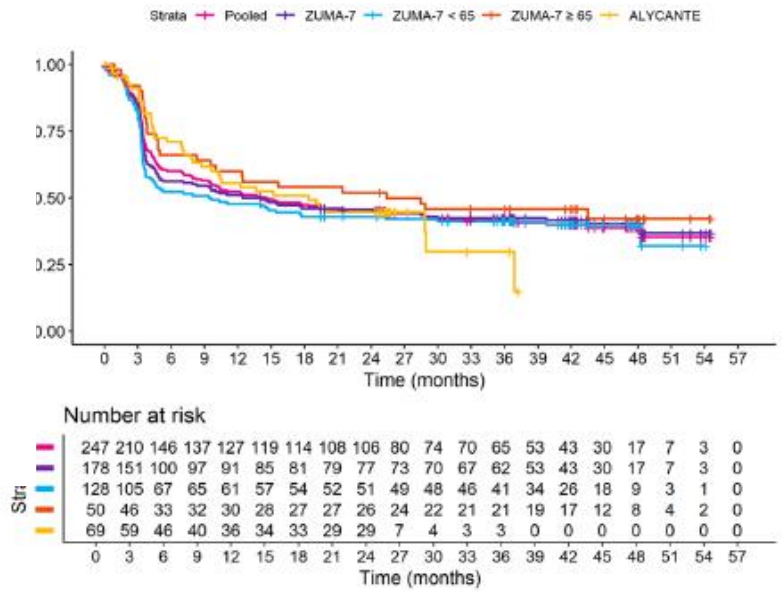
Age is not a contraindication for CAR-T



Houot et al. *Nat Medicine* 2023



Westin et al. *Clin Cancer Res* 2023



Houot et al. *ASH* 2025

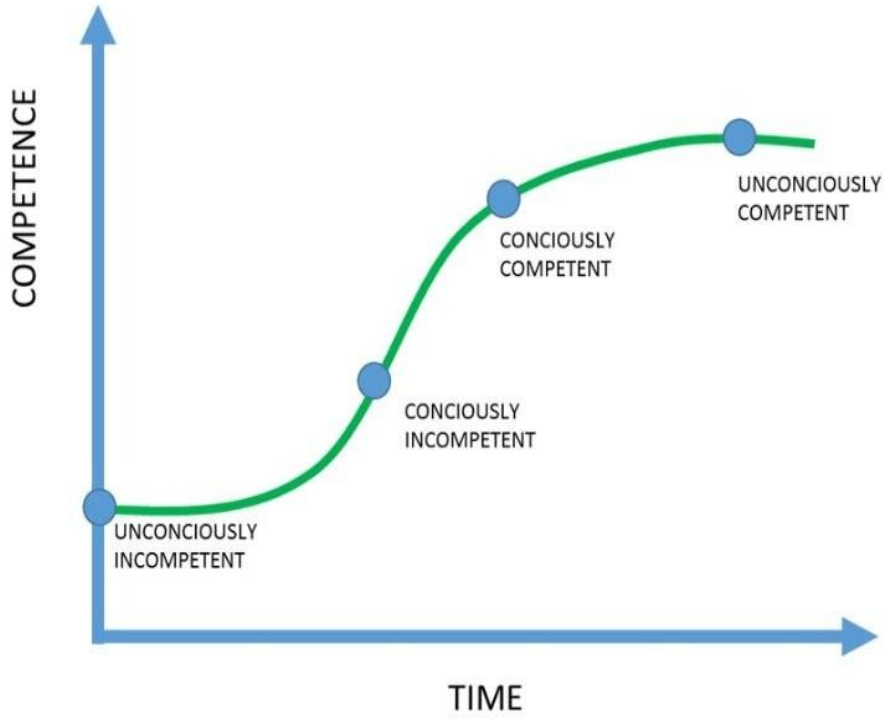
In a RWE subanalysis with axicel (< or ≥65 y), elderly patients had favorable efficacy outcomes with axicel despite higher rates of CRS and ICANS (Jacobson et al, *Transplant Cell Ther* 2022)

Other potentially reversible barriers

Age	ZUMA-7 and real world data suggest no age-related survival differences with axi-cel[1-2] Only reimbursement restriction should be considered for age limits[3]
ECOG PS	ZUMA-7 showed axi-cel survival benefit over chemotherapy in patients with ECOG PS 0-1[1] When considering ECOG PS for CAR T eligibility assessment, ensure it is not related to patient's disease
Comorbidities including compromised organ function	In real-world analyses of patients with 2L R/R LBCL and comorbidities infused with axi-cel, no significant associations were found between hepatic, pulmonary or infection comorbidities and any effectiveness outcome[4,5]
Ineligible for transplant	In ALYCANTE trial, axi-cel demonstrated survival benefit in patients with R/R LBCL deemed ASCT-ineligible, suggesting the curative potential of axi-cel for patients with limited treatment pathways[6]

Kersten et al, *ASH* 2023; Lee et al, *EHA* 2025; Locke et al, ASH 2021; Houot et al, *Nat Med* 2023

CAR-T toxicities: a learning curve



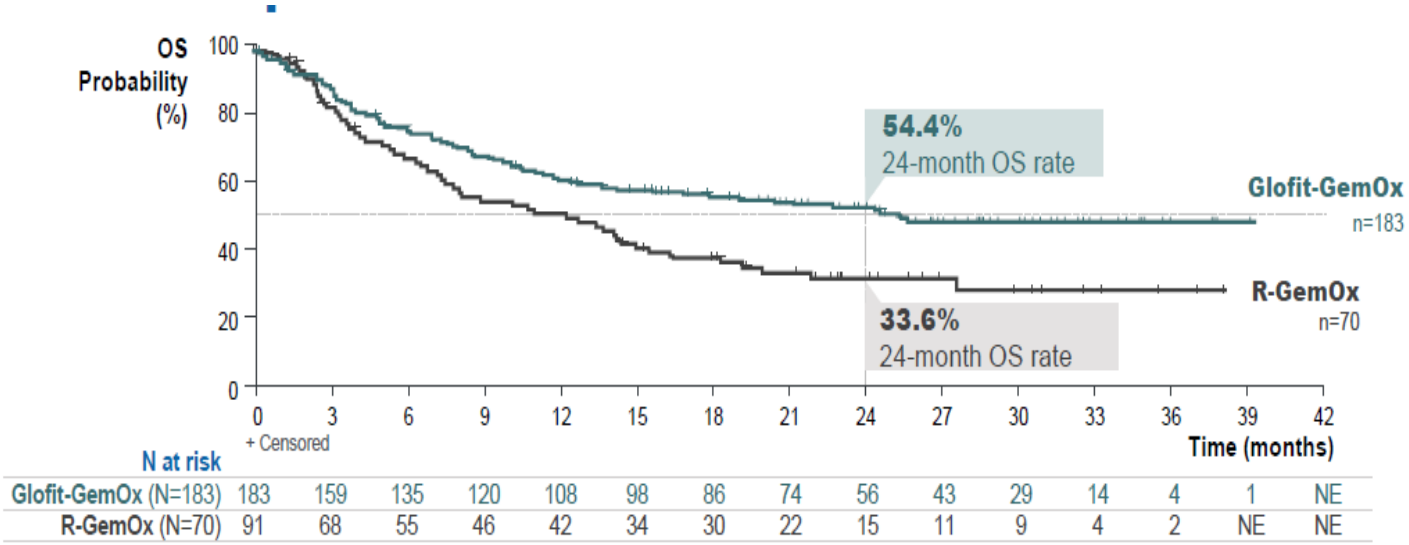
- Analysis of patients with R/R LBCL who received >2L axicel in real-world settings in the USA
- Improvements were observed in CAR T-cell–related toxicities over time
  - Decreases in incidence of Grade ≥3 CRS and duration of any grade CRS
  - Decreases in incidence and duration of any grade ICANS
- Evolving clinical practices were identified
  - Increased use of bridging therapy
  - Increased use of anakinra for treatment of CRS/ICANS

Wang et al, *ASH* 2024

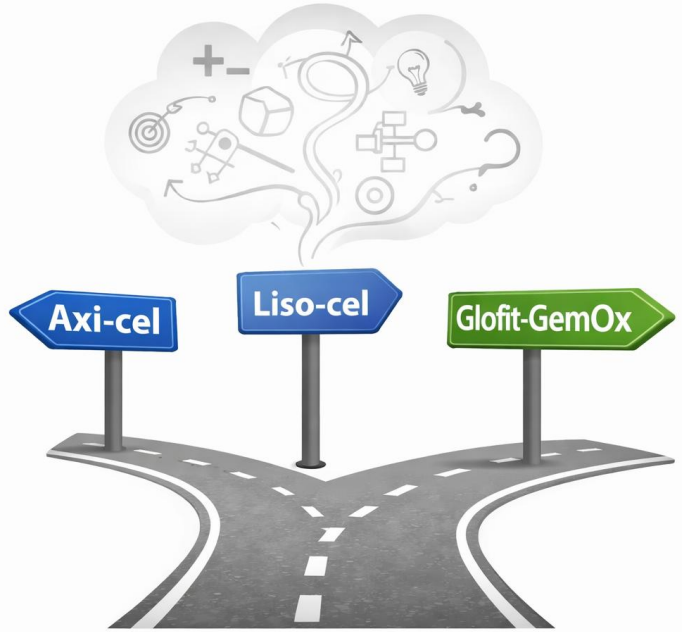
Conclusions

- CAR-T is now a **standard of care in 2L R/R LBCL**
- CAR-T should be delivered **as early as possible** to maximize survival outcomes
- Early and accurate identification of eligible patients is essential to **avoid misallocation**
- **Not ready to finally picking up a winner**: to be fully defined in real-world settings
- **Timing is crucial**: delays in referral and infusion may compromise outcomes
- **Eligibility should be reconsidered**: age and comorbidities should not automatically exclude patients

Future landscape is evolving



Much remains to be learned



- Glofit-GemOx upcoming
- Making comparisons is difficult
- Potential alternative for transplant or CAR-T ineligible patients?

Abramson et al, *Lancet* 2024

CAR-T team – Programma Trapianti AOU Federico II – Direttore Prof. Fabrizio Pane

Unità Clinica
Serafina Barbato
Raffaella Iannotta
Giorgia Battipaglia
Carlangela Causa, Roberta Russo, Pierpaolo Santopadre (AIF)
Alessia Salemme (psicologa)

Unità Aferesi
Claudia Andretta
Pasqualino Correale
Ermanno Badi
Antonio Leonardi

Laboratorio manipolazione
Domenica Borzacchiello
Antonella Abagnale
Antonio Feliciello