COACHES

Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

SESSION IV: NEW PERSPECTIVES IN R/R DLBCL

CAR-T cell therapy: what is the best timing?

M. Martino (Reggio Calabria)

Disclosures of Massimo Martino

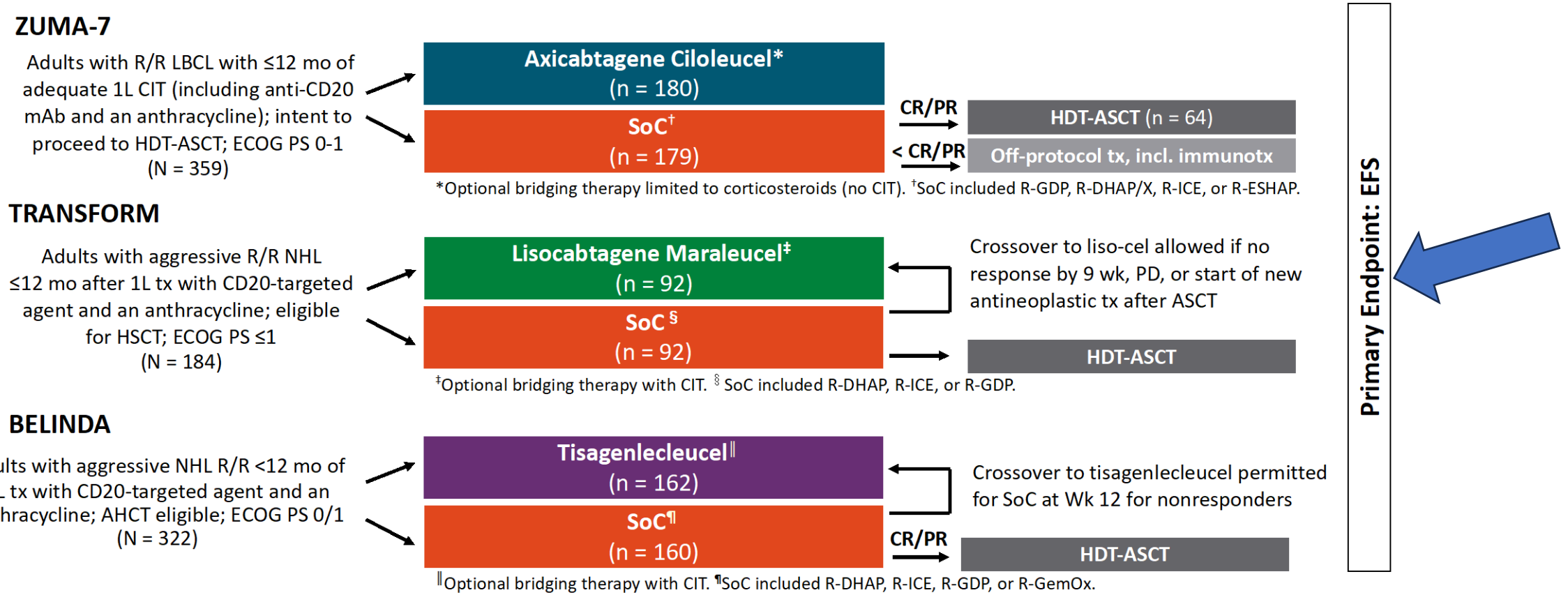
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
KITE/GILEAD					x	x	
BMS					x	x	
Novartis					x	x	
JANSENN CILAG					x	x	
PFIZER						x	
ABBVIE					x		x
SANDOZ	x						
TAKEDA						x	
MEDAC	x				x	x	
GSK						x	
AMGEN					x		
SANOFI						x	

Indications for haematopoietic cell transplantation for haematological disease, solid tumours and immune disorders: current practice in Europe, 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 CAR T-Cell Therapy in Second-line LBCL: Randomized Phase III Trials



Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. Kamdar. Lancet. 2022;399:2294.
Kamdar. ASH 2021. Abstr 91. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

ZUMA-7, TRANSFORM, BELINDA: Outcomes

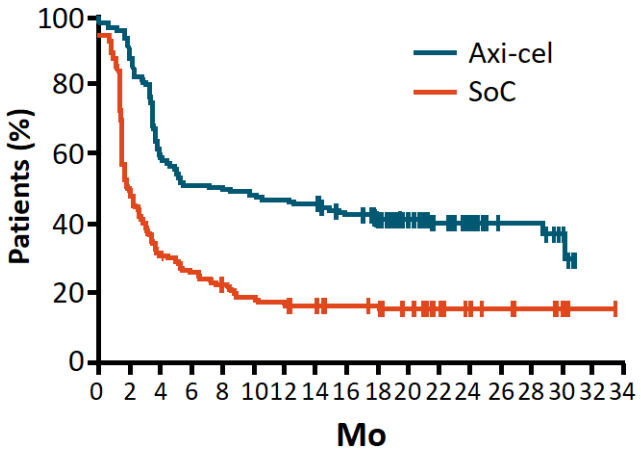
	ZUMA-7[1]	TRANSFORM[2]	BELINDA[3]
Product	Axi-cel vs SoC	Liso-cel vs SoC	Tisa-cel vs SoC
ORR, %	83 vs 50	86 vs 48	46 vs 43
CR, %	65 vs 32	66 vs 39	28 vs 28
Median EFS, mo	8.3 vs 2.0	10.1 vs 2.3	3.0 vs 3.0
EFS, %	2-yr: 41 vs 16	1-yr: 44.5 vs 23.7	--
Median PFS, mo	14.7 vs 3.7	14.8 vs 5.7	--
PFS, %	2-yr: 46 vs 27	1-yr: 52.3 vs 33.9	--
Median OS, mo	NR vs 35.1	NR vs 16.4	16.9 vs 15.3
OS, %	2-yr: 61 vs 51	1-yr: 79.1 vs 64.2	--

1. Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. 2. Kamdar. Lancet. 2022;399:2294. Kamdar. ASH 2021. Abstr 91. 3. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

ZUMA-7, TRANSFORM, BELINDA: EFS

ZUMA-7

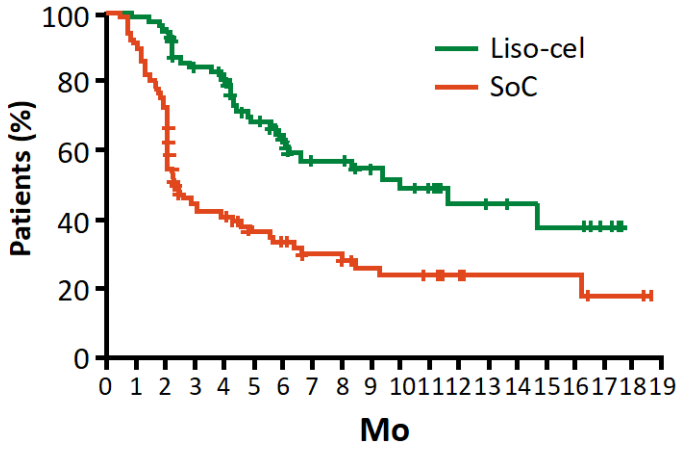
	Axi-Cel (n = 180)	SoC (n = 179)
Median, mo (95% CI)	8.3 (4.5-15.8)	2.0 (1.6-2.8)
HR (95% CI)	0.40 (0.310.51)	
P value	<.0001	



Median follow-up: 24.9 mo

TRANSFORM

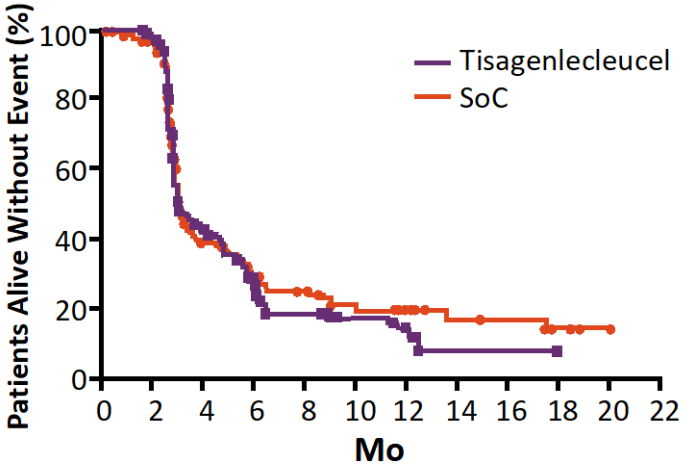
	Liso-Cel (n = 92)	SoC (n = 92)
Median, mo (95% CI)	10.1 (6.1-NE)	2.3 (2.2-4.3)
HR (95% CI):	0.349 (0.229-0.530)	
P value	<.0001	



Median follow-up: 6.2 mo

BELINDA

	Tisa-Cel (n = 162)	SoC (n = 160)
Median, mo (95% CI)	3.0 (2.9-4.2)	3.0 (3.0-3.5)
HR (95% CI)	1.07 (0.82-1.40)	
P value	.61	



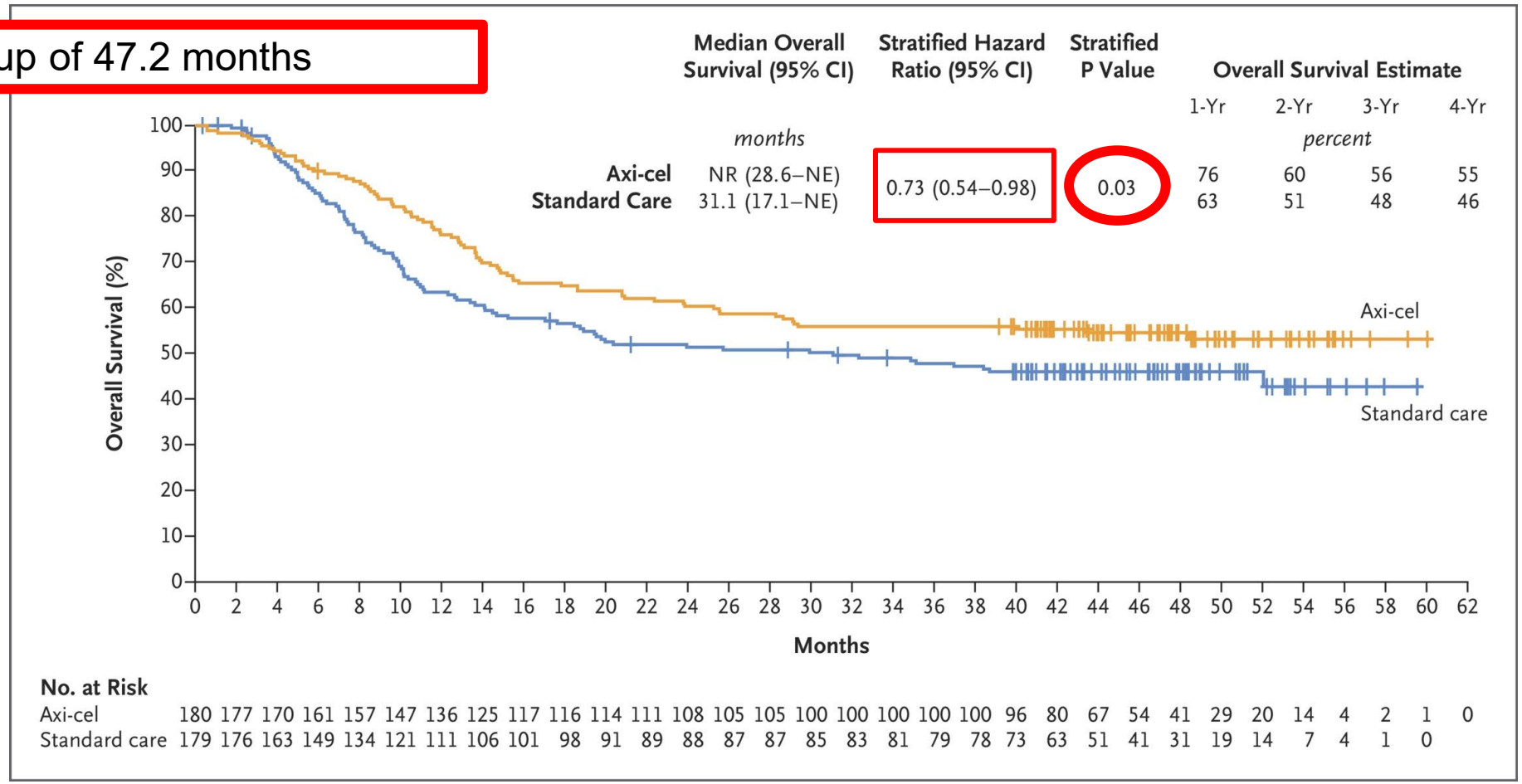
Median follow-up: 10 mo

Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. Kamdar. Lancet. 2022;399:2294.
Kamdar. ASH 2021. Abstr 91. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

	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%

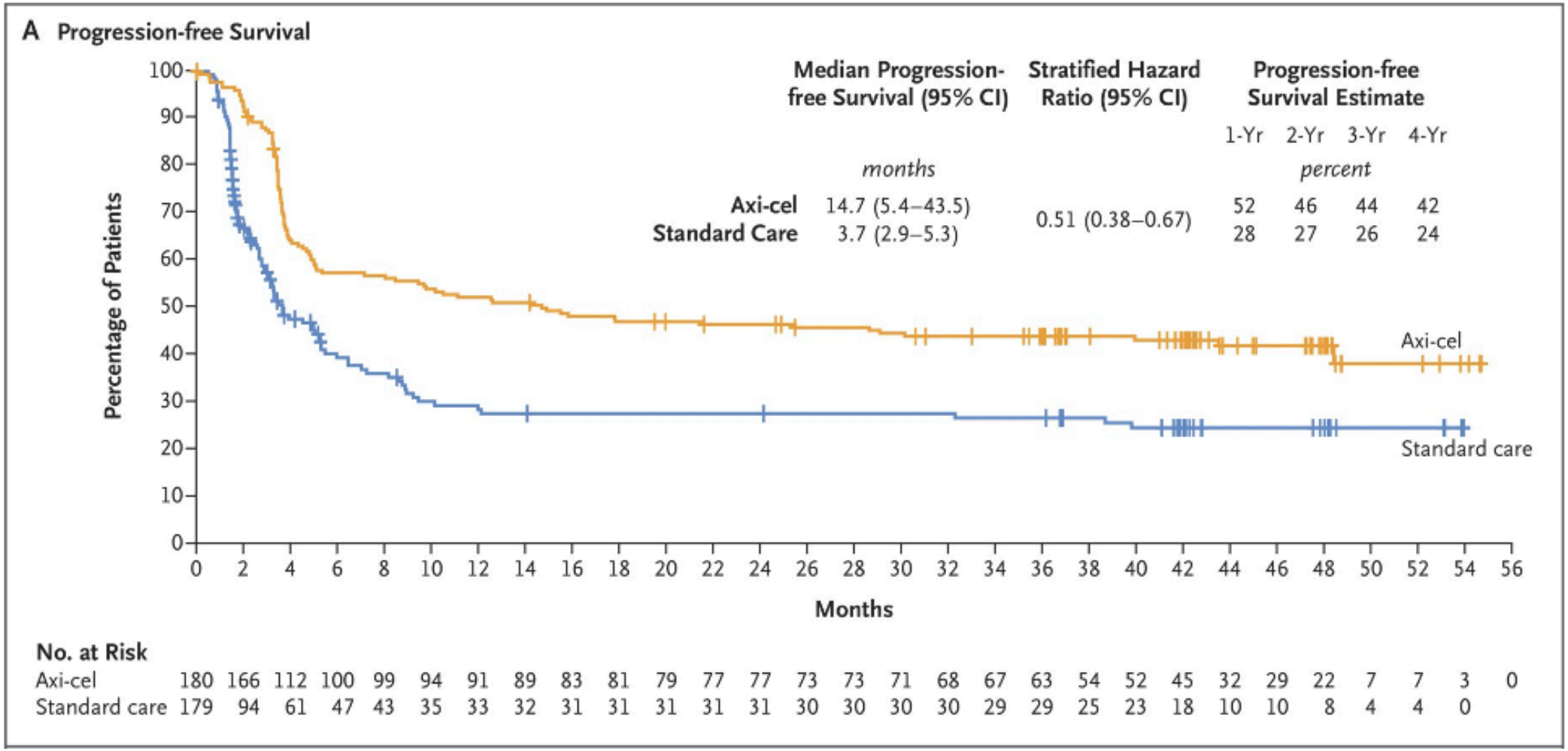
Overall Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

median follow-up of 47.2 months



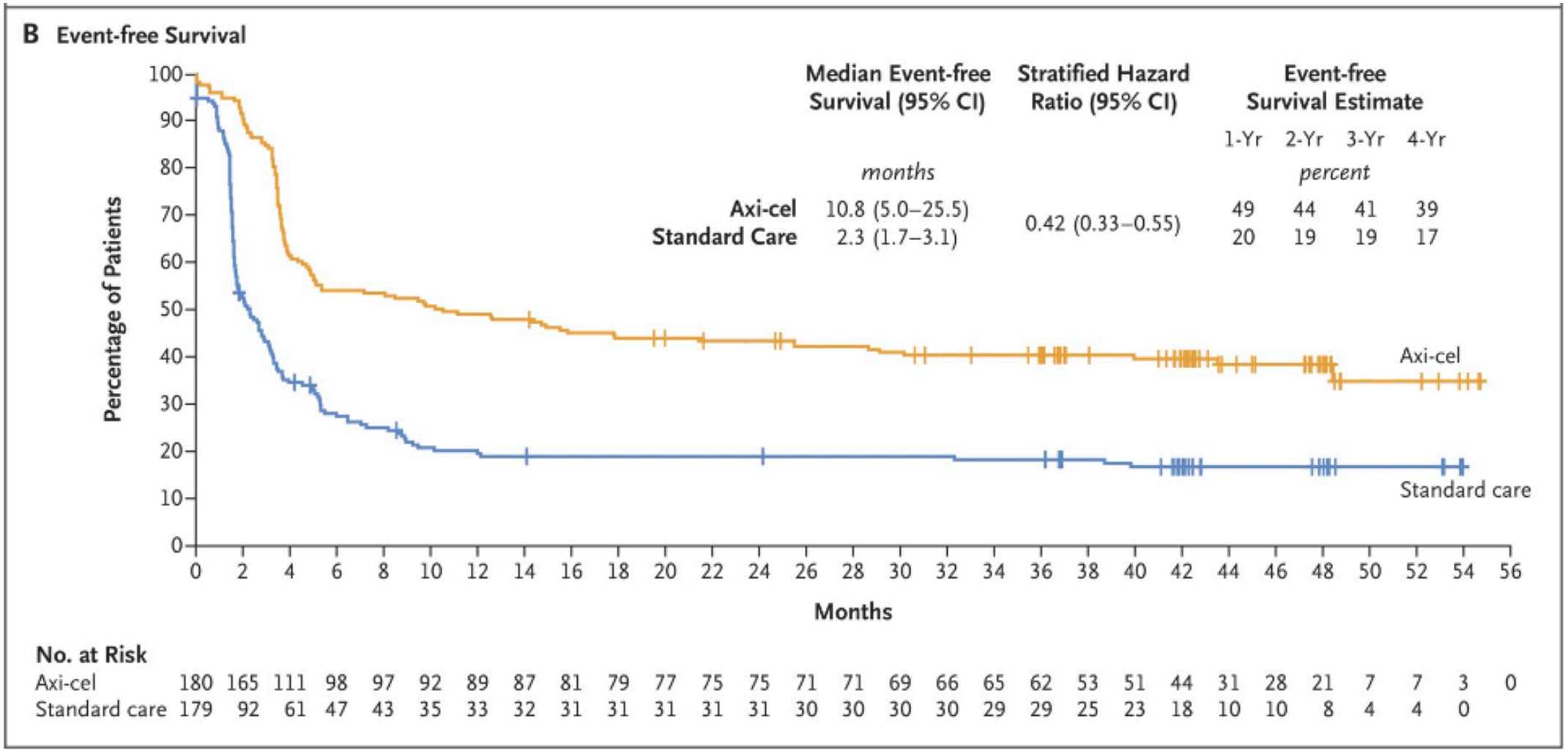
Westin JR et al. N Engl J Med Volume 389(2):148-157 July 13, 2023

Progression-free Survival



Westin JR et al. N Engl J Med Volume 389(2):148-157 July 13, 2023

Event-free Survival



Westin JR et al. N Engl J Med Volume 389(2):148-157 July 13, 2023

Deaths among Treated Patients (Safety Analysis Population).

Table 1. Deaths among Treated Patients (Safety Analysis Population).*

Death	Axi-cel (N=170)	Standard Care (N=168)
	number of patients	
Total deaths	74	91
Progressive disease	51	71
Fatal adverse event	8	2
Covid-19	2	0
Sepsis	2†	0
Acute respiratory distress syndrome	0	1‡
Cardiac arrest	0	1‡
Hepatitis B reactivation	1§	0
Myocardial infarction	1	0
Pneumonia	1	0
Progressive multifocal leukoencephalopathy	1	0
New or secondary cancer	2¶	0
Other reason‖	13	18
Covid-19	4	4
Other infection or inflammation	3	7**
Neurologic organ failure	2	0
Respiratory organ failure	1	1
Cardiac organ failure	1	0
Cardiopulmonary and neurologic organ failure	0	1
Progressive disease	1††	0
Unknown	1	5

* The safety analysis population included all the patients who had received at least one dose of axicabtagene ciloleucel (axi-cel) or standard care according to the protocol. Covid-19 denotes coronavirus disease 2019.

† One patient who died of sepsis also had ongoing grade 3 myelodysplastic syndrome at the time of death.

‡ In this patient who received high-dose chemotherapy and underwent autologous stem-cell transplantation, the cause of death was considered by the investigator to be related to high-dose chemotherapy.

§ This patient had a history of hepatitis B virus (HBV) infection with positive hepatitis B core antibody and surface antigen, but HBV was undetectable on polymerase-chain-reaction assay at enrollment, so the patient met the trial eligibility criteria. The patient was treated with antiviral therapy for hepatitis B viremia and prophylaxis, which had been started during the patient's initial treatment with first-line rituximab-containing chemotherapy. After the discontinuation of entecavir, grade 5 fulminant hepatic failure occurred because of reactivation of HBV approximately 1 year after the administration of axi-cel.

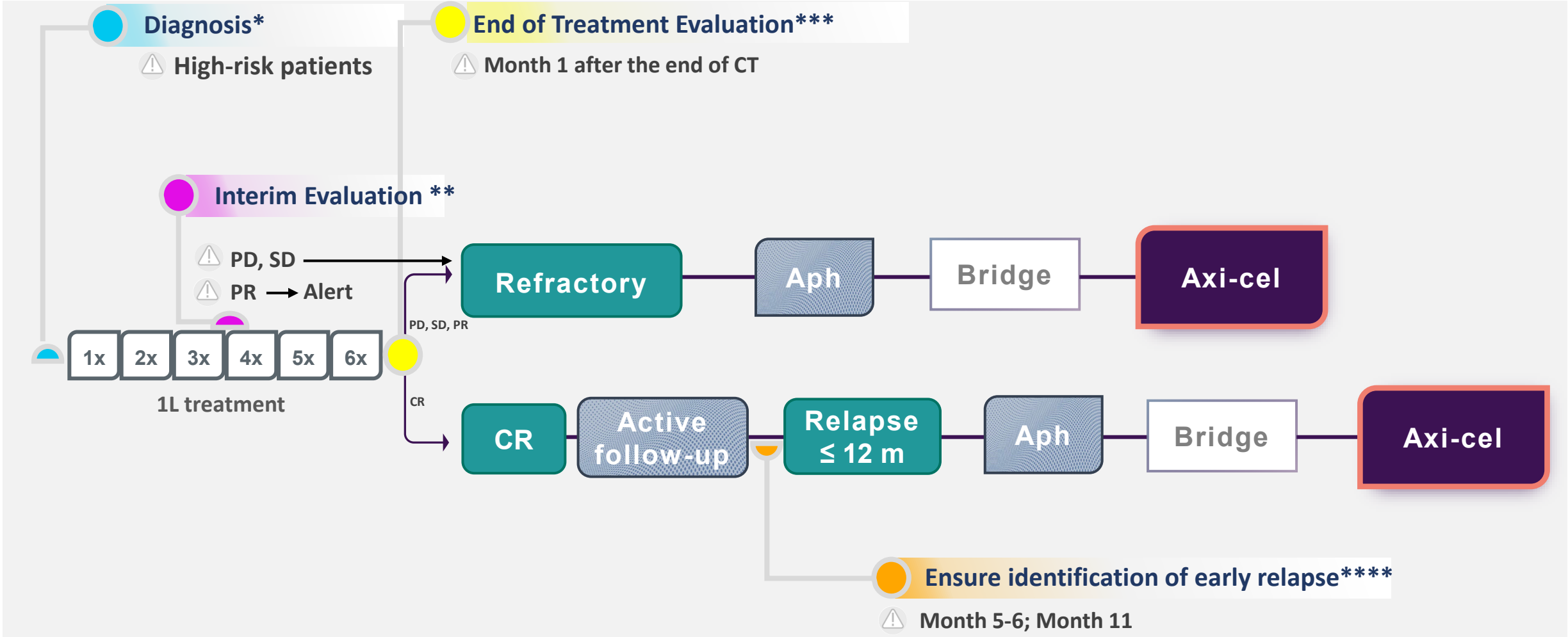
¶ One patient died of acute myeloid leukemia, and one died of lung adenocarcinoma.

‖ This category includes fatal events that occurred outside the reporting period for adverse events.

** One patient died from infection with progressive disease.

†† This patient died from euthanasia that was performed because of progressive disease.

Patient Journey to CAR-T in 2L LBCL: the «brain to vein» vision



* Rosenwald A. et al. Blood. 2018; 132(Suppl 1): 344-344; Alaggio R. et al. Leukemia. 2022 Jul;36(7):1720-1748. Epub 2022 Jun 22; Johnson NA. et al. J Clin Oncol. 2012; 30(28): 3452-3459; Fox CP et al. BR J Haematol 2024 Apr;204(4):1178-1192.
** Cheson BD. et al. J Clin Oncol. 2014 Sep 20;32(27):3059-68; Eertink JJ. Et al. Blood Adv (2021) 5 (9): 2375-2384; Dührsen U et al. J Clin Oncol 2018 Jul 10;36(20):2024-2034.
*** Cheson BD. et al. J Clin Oncol. 2014 Sep 20;32(27):3059-68; Kostakoglu L. et al. Blood Adv (2021) 5 (5): 1283-1290; Moskowitz CH. et al. J Clin Oncol. 2010 Apr 10;28(11):1896-903.
**** Cheson BD. et al. J Clin Oncol. 2014 Sep 20;32(27):3059-68; Moskowitz CH. et al. J Clin Oncol. 2010 Apr 10;28(11):1896-903; Locke FL et al. *N Engl J Med* 2022 Feb 17;386(7):640-654 ; SmPC Yescarta

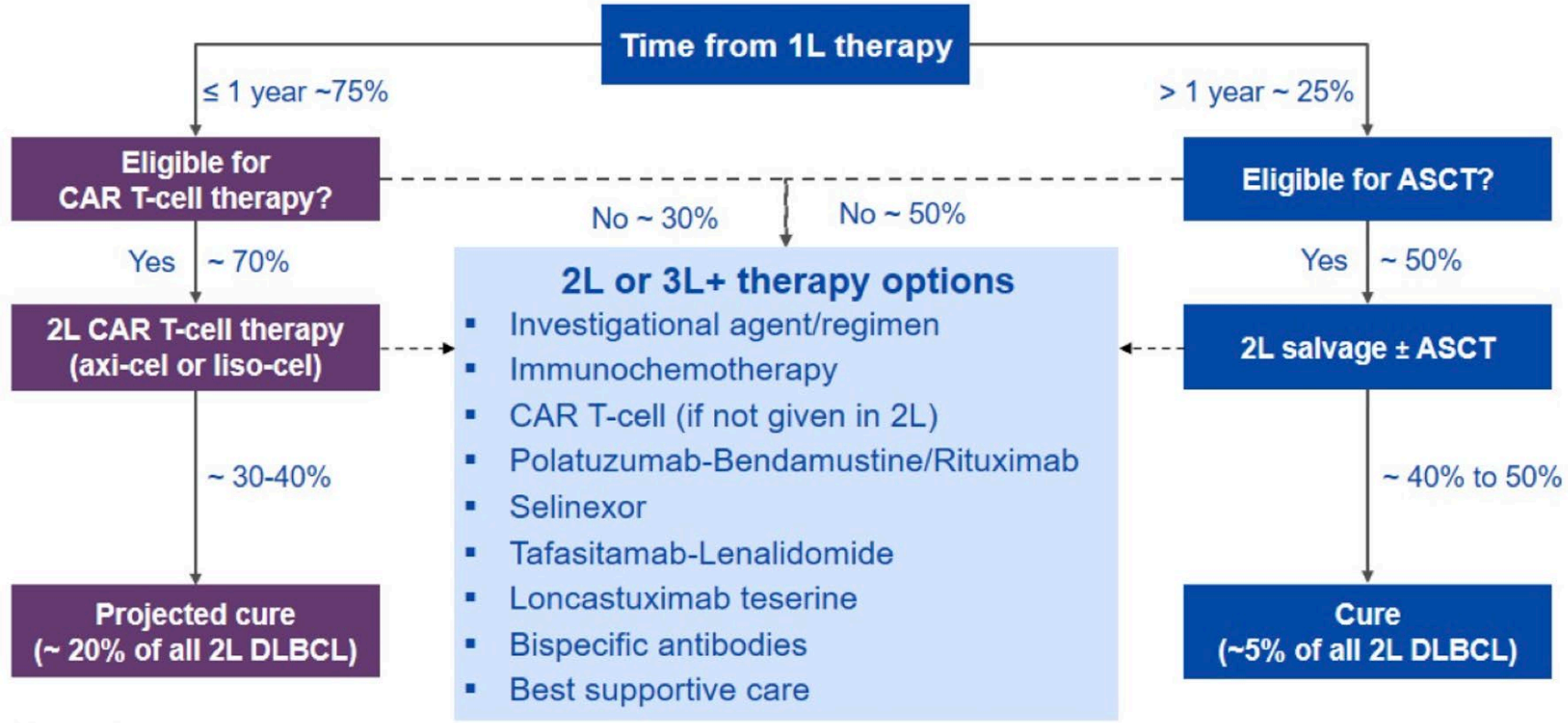
Salvage and Bridging Therapy

- **Goals of salvage therapy:** *to stabilize disease*
  - may be recommended during time between referral and consult and apheresis
  - Requires washout period before apheresis

- **Goals of bridging therapy:** reduce tumor burden, palliate symptoms, stabilize disease and QoL. *Maintain functional reserve during manufacturing period*
  - For patients with rapidly proliferating disease during time between apheresis and lymphodepletion
  - Limit CRS/ICANS severity by debulking
  - Potential impact on CAR T-cell efficacy
- Maintain frequent communication with patient, primary oncologist, and manufacturer
  - Ensure workup completed
  - Monitor patient's status
- Choose least toxic therapy, if possible, and allow hematologic recovery prior to lymphodepleting therapy
  - Real-life time from pheresis to infusion is >30 days
- Consider avoiding immunosuppressive therapy, checkpoint inhibitors, blinatumomab

Jain. Biol Blood Marrow Transpl. 2019;25:2305. Kansagra. Bone Marrow Transplant. 2019;54:1868.

Treatment Algorithm for Second-Line LBCL 2022



Available treatment options vary by region.
ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor.
Westin J, et al. Blood. 2022;139:2737-2746.

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

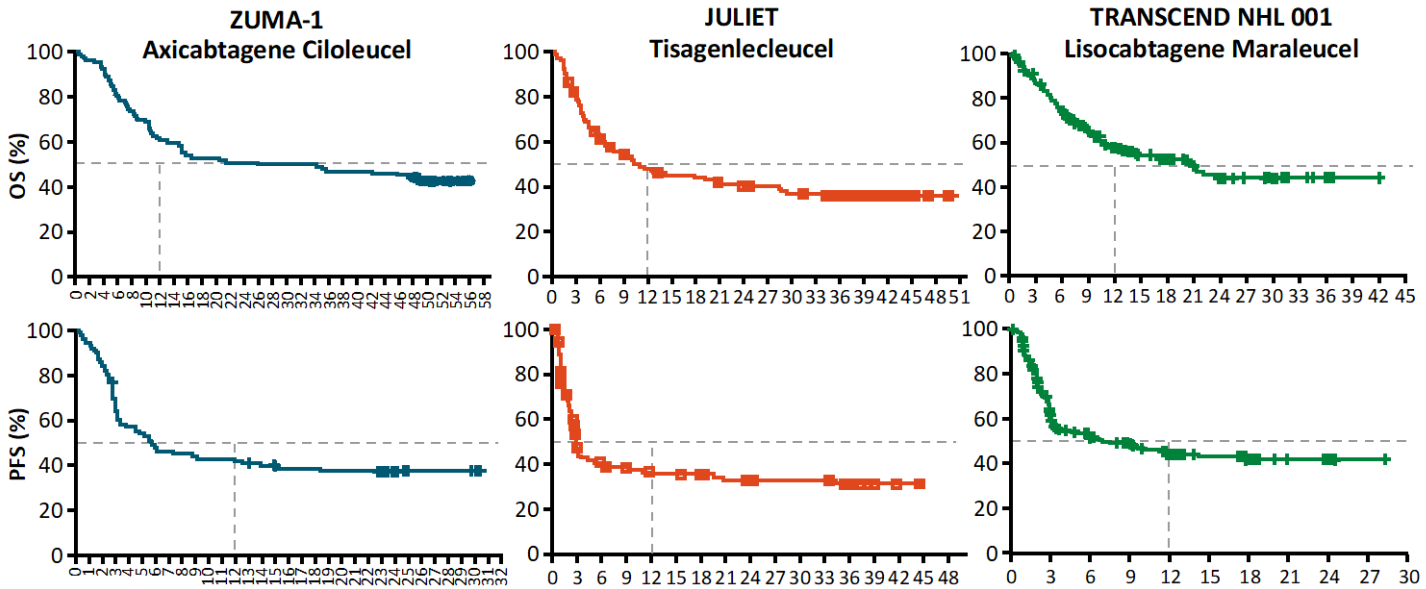
1. Neelapu. NEJM. 2017;377:2531. 2. Locke. Lancet Oncol. 2019;20:31. 3. Westin. Am J Hematol. 2021;96:1295. 4. Schuster. NEJM. 2019;380:45. 5. Abramson. Lancet. 2020;396:839.

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.

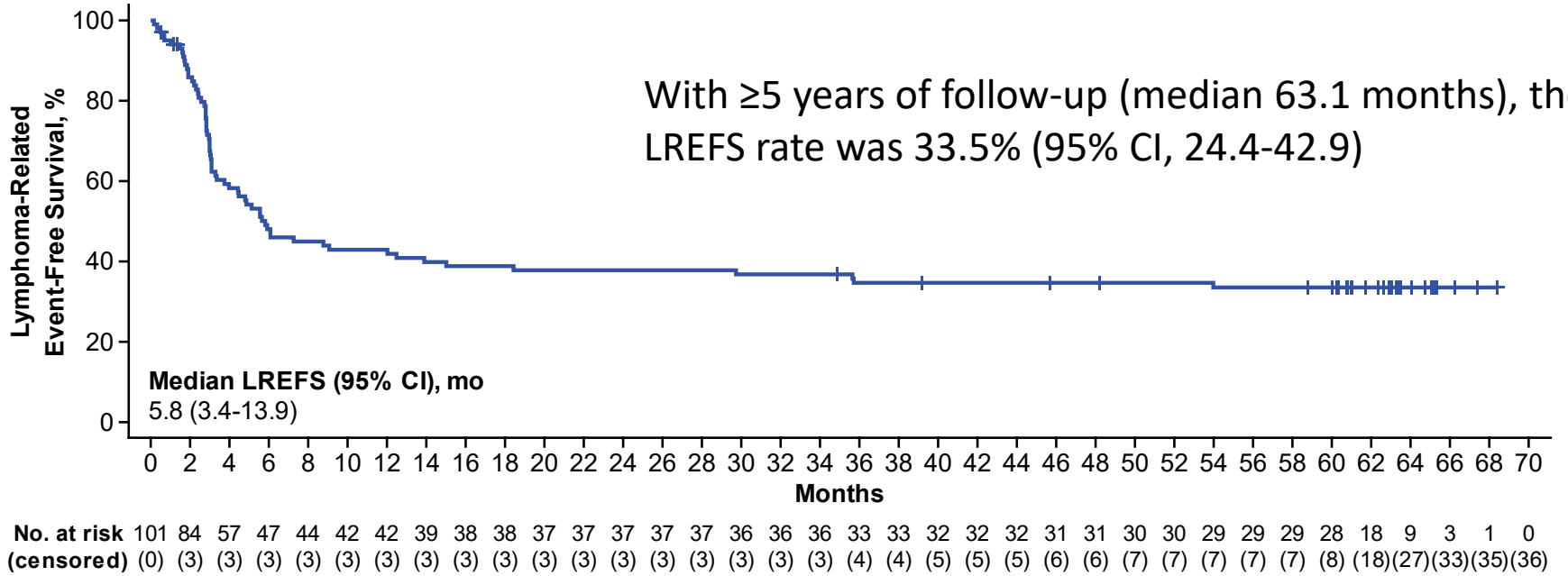
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: DLBCL



Locke. Lancet Oncol. 2019;20:31. Jacobson. ASH 2020. Abstr 1187. Jaeger. ASH 2020. Abstr 1194. Abramson. Lancet. 2020;396:839.

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

‡

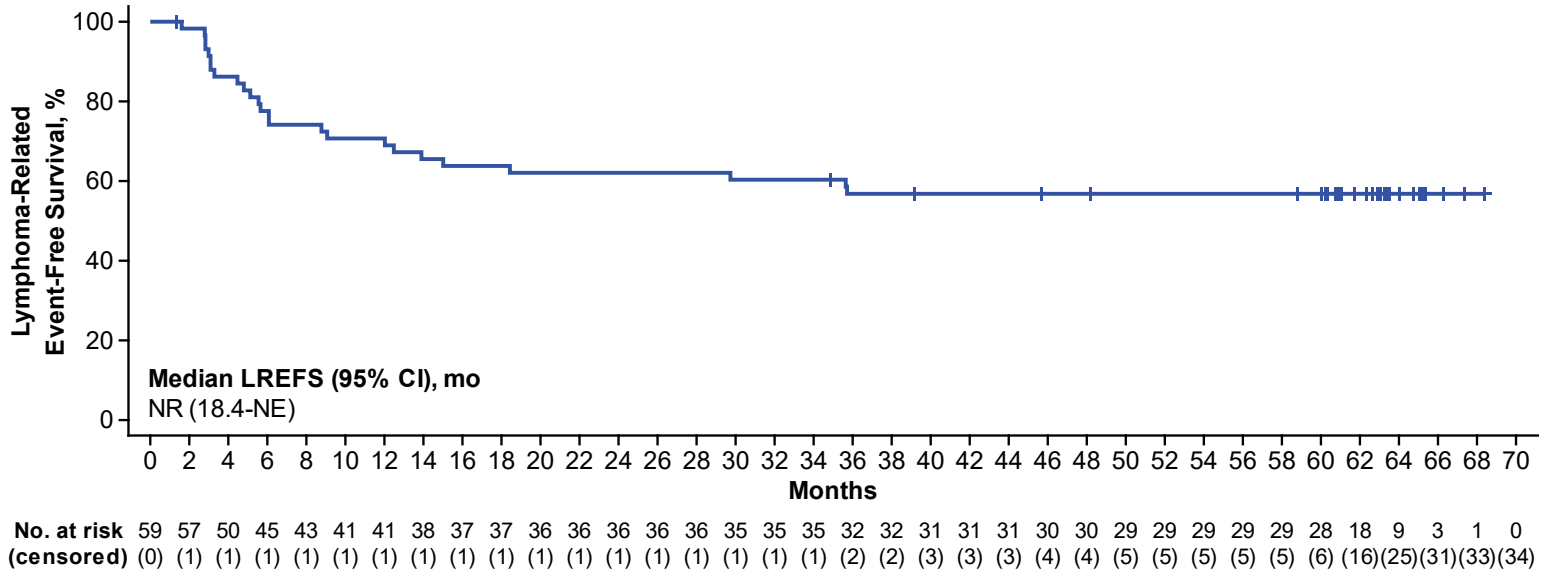


With ≥5 years of follow-up (median 63.1 months), the 5-year LREFS rate was 33.5% (95% CI, 24.4-42.9)

Lymphoma-Related Event-Free Survival (LREFS)

Neelapu et al. ASH 2023 Abstract # 4864

Lymphoma-Related Event-Free Survival Among Patients Who Achieved CR



Among patients with a CR, the 5-year LREFS rate was 56.8% (95% CI, 43.1-68.4), with a plateau emerging in the curve by Month 36

Neelapu et al. ASH 2023 Abstract # 4864

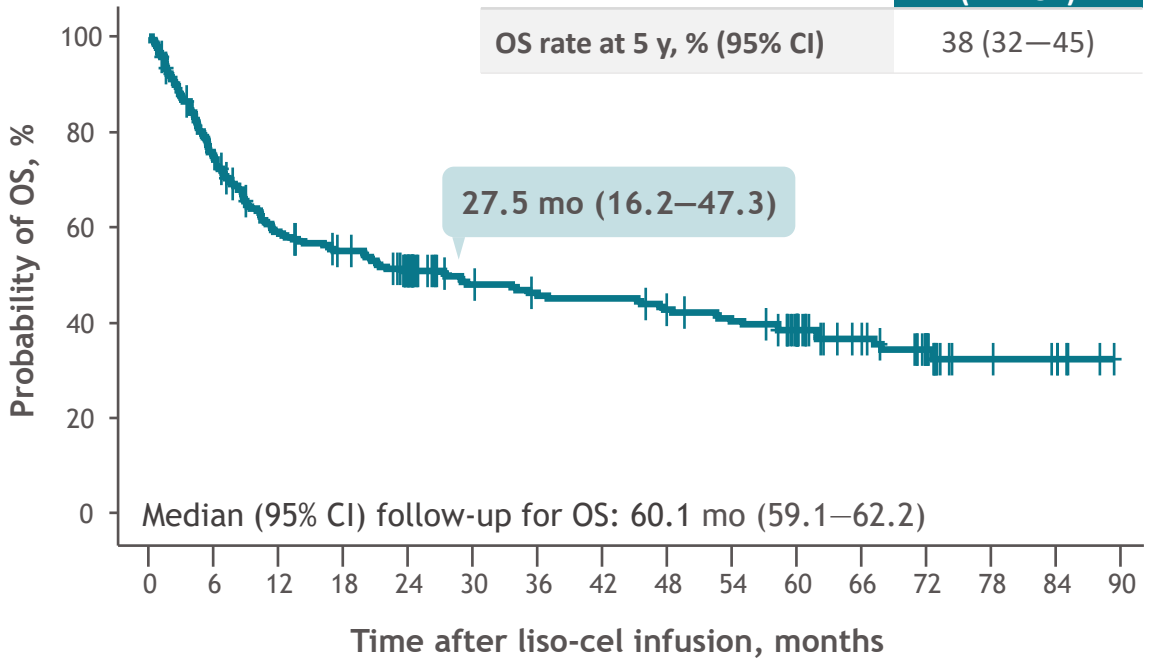
Five-Year Survival of Patients (pts) from Transcend NHL 001 (TRANSCEND) Supports Curative Potential of Lisocabtagene Maraleucel (liso-cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL)

Abramson et al Blood (2024) 144 (Supplement 1): 3125.

Overall survival

(A)

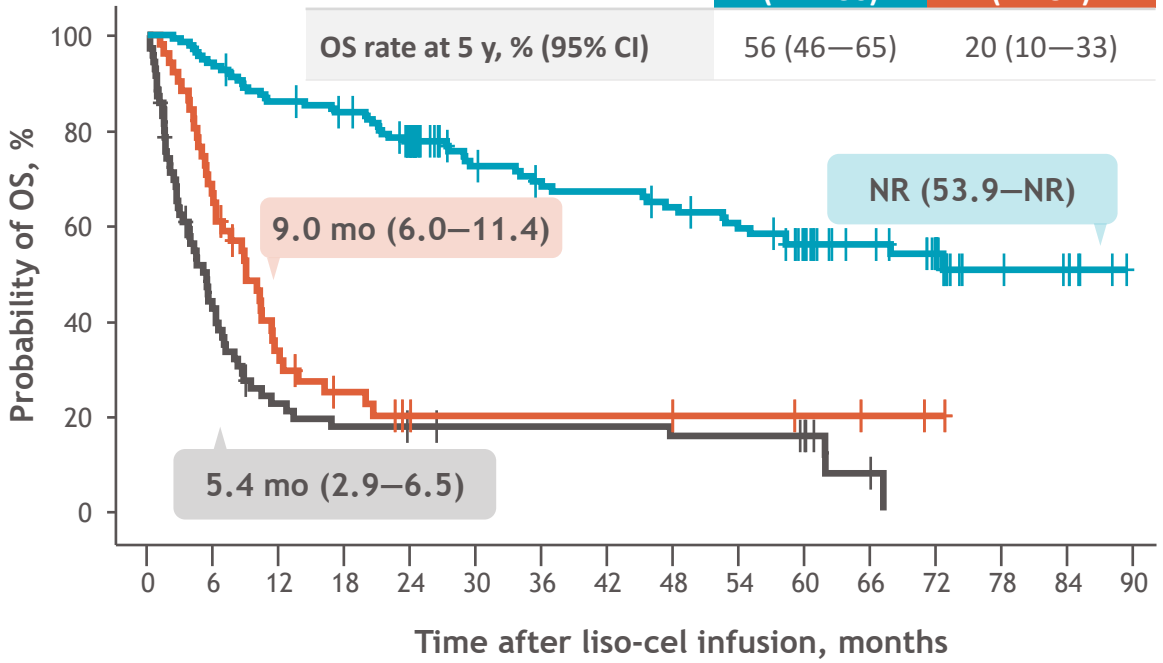
	Total (n = 257)
OS rate at 5 y, % (95% CI)	38 (32—45)



Total	257	190	146	132	111	83	77	76	70	65	51	35	23	8	6	0

(B)

	Patients with CR (n = 136)	Patients with PR (n = 51)
OS rate at 5 y, % (95% CI)	56 (46—65)	20 (10—33)



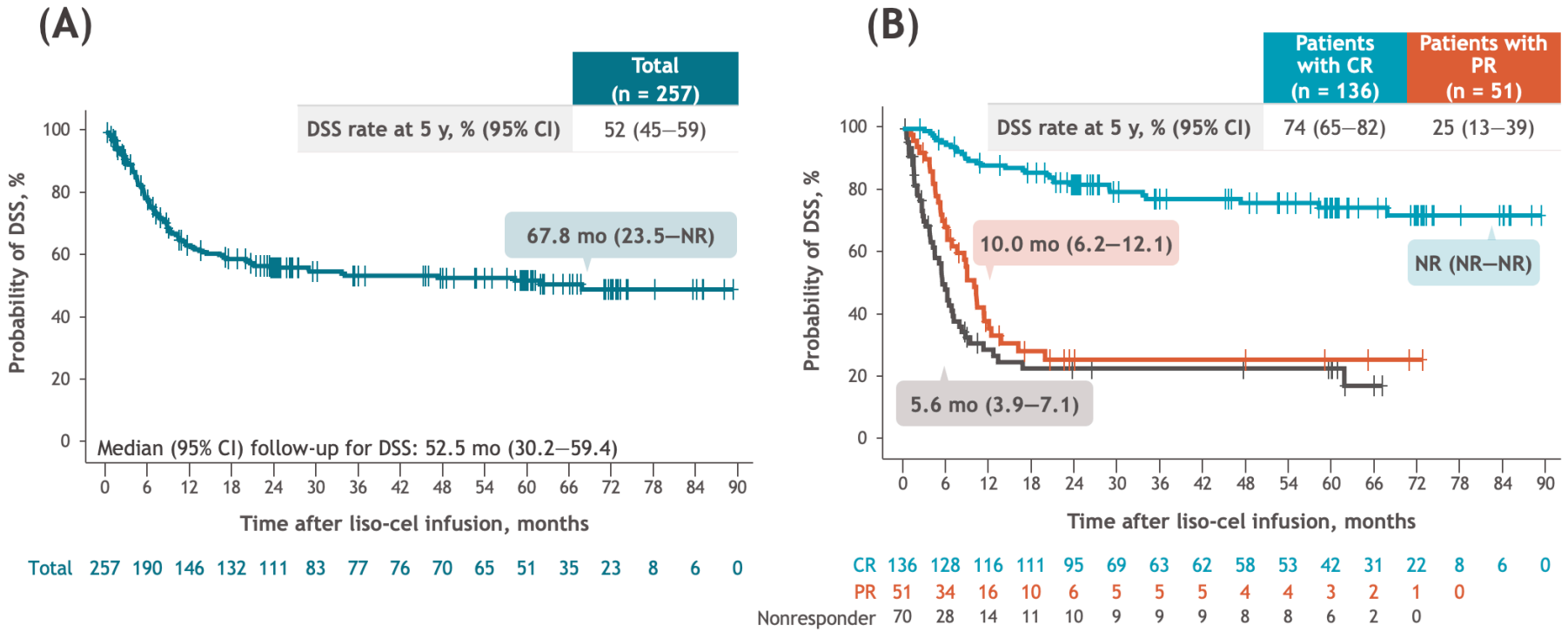
CR	136	128	116	111	95	69	63	62	58	53	42	31	22	8	6	0
PR	51	34	16	10	6	5	5	5	4	4	3	2	1	0		
Nonresponder	70	28	14	11	10	9	9	9	8	8	6	2	0			

Five-Year Survival of Patients (pts) from Transcend NHL 001 (TRANSCEND) Supports Curative Potential of Lisocabtagene Maraleucel (liso-cel) in Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL)

Abramson et al Blood (2024) 144 (Supplement 1): 3125.

TRANSCEND NHL 001 5-yr FU

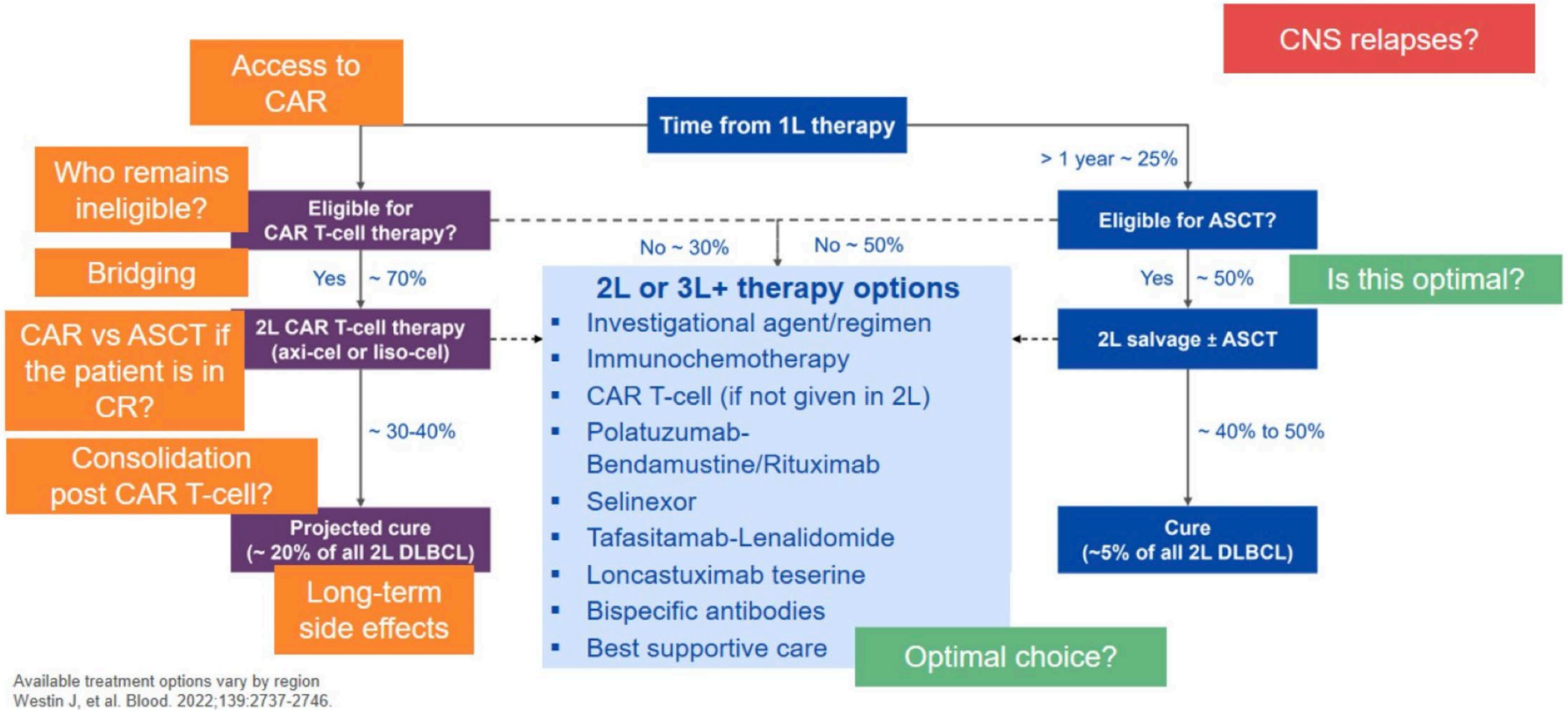
Disease-specific survival



Data on KM curves are expressed as median (95% CI). The nonresponder group included patients with a best response of stable disease or PD. [a]Only deaths due to disease progression were considered events; all other deaths were censored; 1 additional patient was determined to have died of PD after the data cutoff date and is not accounted for in the KM curve.

Treatment Algorithm

OPEN QUESTIONS



Available treatment options vary by region
Westin J, et al. Blood. 2022;139:2737-2746.

Transplant Eligibility

Patient-Related Health Criteria

- Organ functions and comorbidities: cardiac, renal, lung, neurological, …
- Performance status

Patient-Related Social Criteria

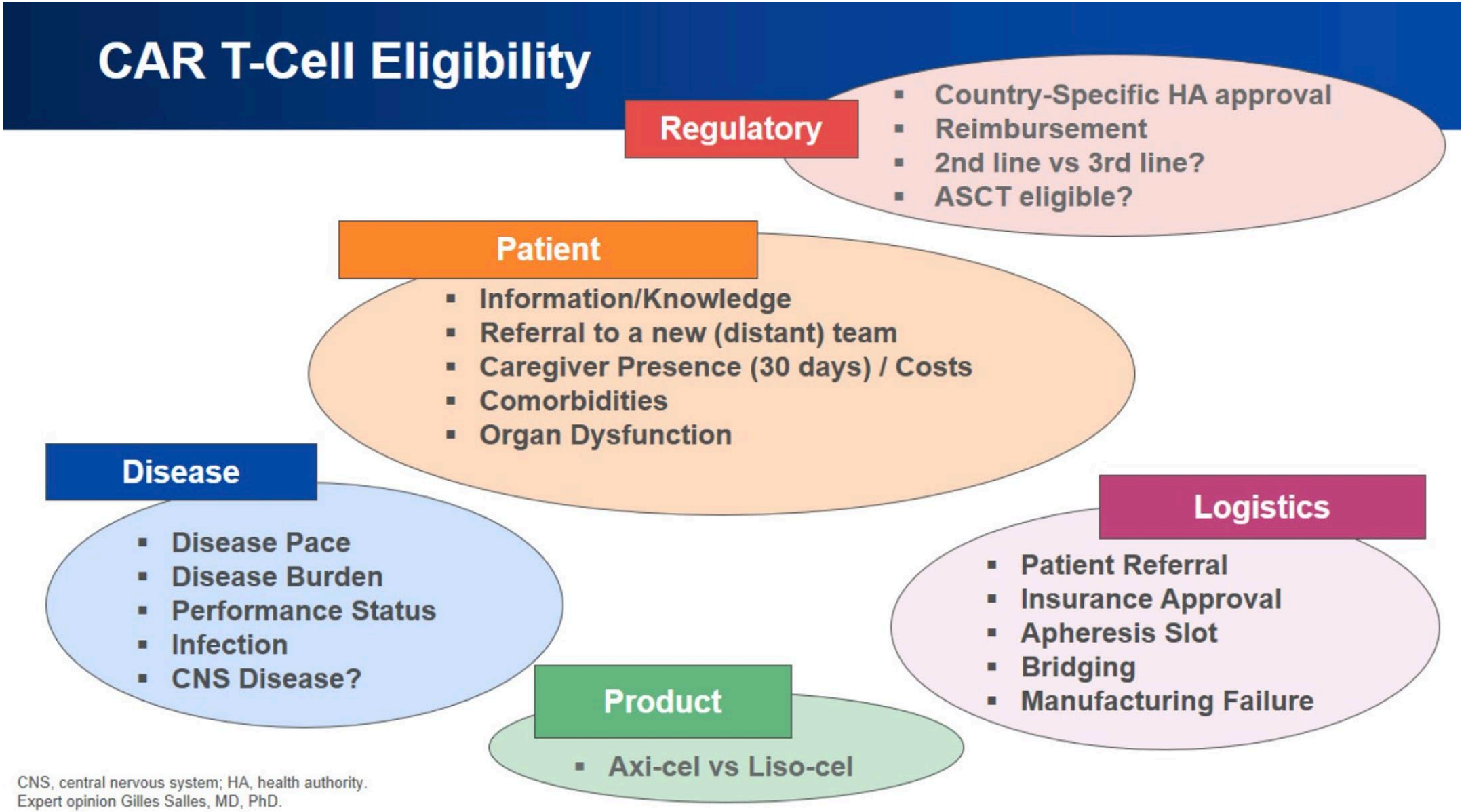
- Familial or social constraints
- Caregiver support
- Distance from the transplant center
- Costs

Disease-Related Criteria

- Chemosensitivity / Response to salvage therapy
- Timing of disease progression after 1L line therapy (< or > 12 months)
- Success of peripheral blood progenitor mobilization

Expert opinion Gilles Salles, MD, PhD.

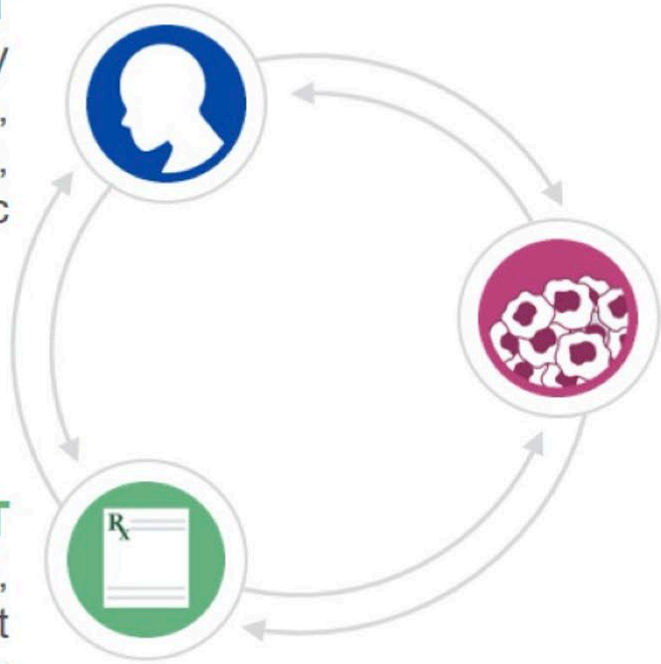
CAR T-Cell Eligibility



CNS, central nervous system; HA, health authority.
Expert opinion Gilles Salles, MD, PhD.

Patient-Centered Care for DLBCL
Factors Impacting Treatment Choice

PATIENT
Fitness, comorbidities, family circumstances, personal preference, treatment cost, comorbidities, other medicines, etc



DISEASE
IPI score, stage, bulk, double hit lymphoma, etc

TREATMENT
Prior treatment, optimal sequencing, integrating novel treatments, treatment toxicities, impact on quality of life, etc

DLBCL, diffuse large B-Cell lymphoma, IPI, International Prognostic Index.
Expert opinion Wendy Osborne, MBBS (Hons), MRCP, FRCPath.

Physician and Patient Outcome Measurements

Physician Perspective

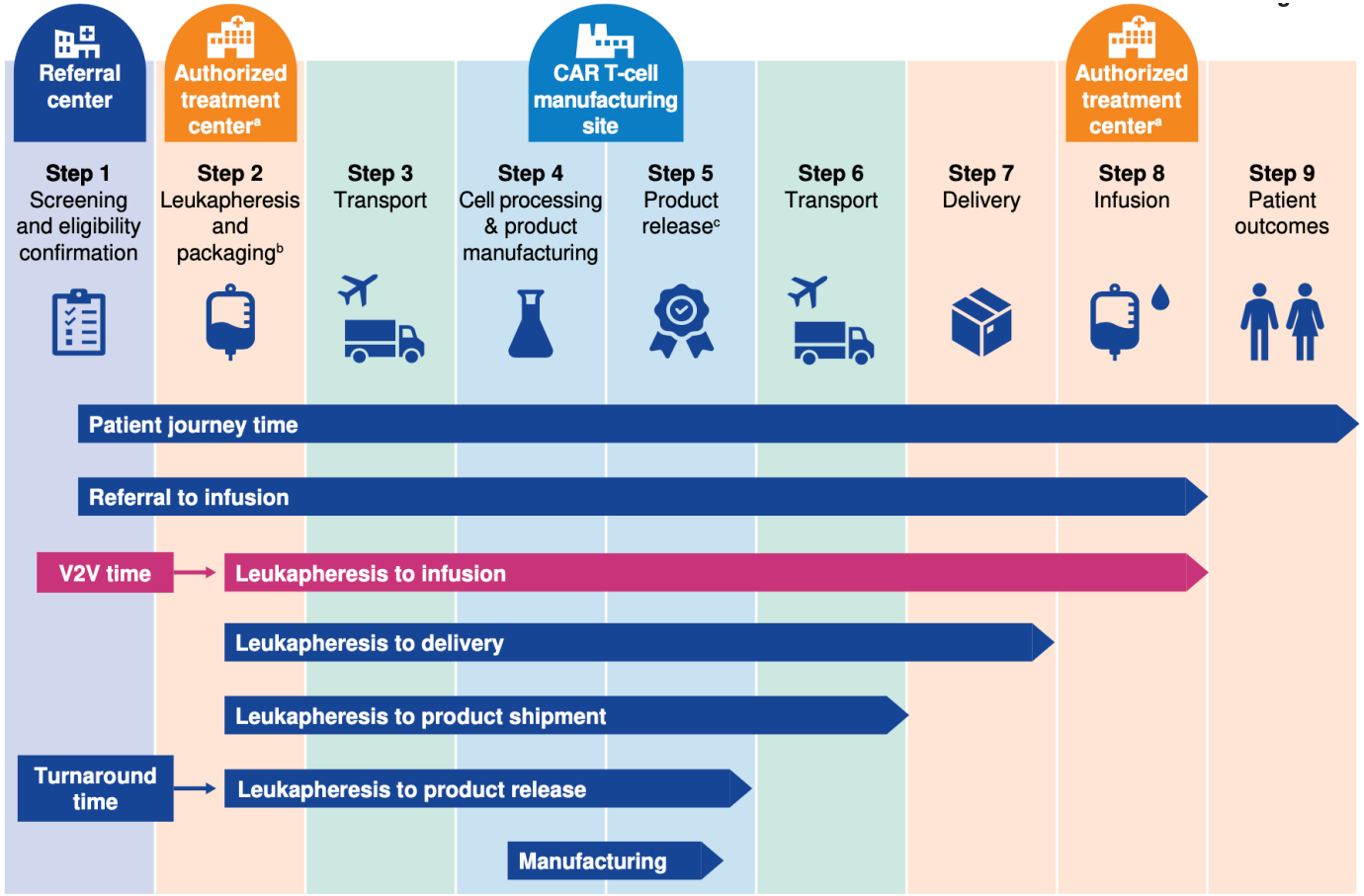
- Overall survival
- Progression free survival
- Time to next treatment
- Event free survival
- Toxicities

Patient Perspective

- Multiple admissions to the hospital
- Frequent visits to the hospital
- Side effects
- Late effects

«vein-to-vein» vision

Locke FL, et al. Blood Advances 2024



- Time from leukapheresis to infusion, known as vein-to-vein time (V2Vt)
- Impact on clinical outcomes
- adult patients with R/R LBCL who had received ≥1 prior line of therapy before treatment with axi-cel, tisa-cel, or liso-cel. Clinical trials or observational studies, including prospective and retrospective studies, were included.
- A noninterventional post-authorization safety study (PASS) was facilitated using the CIBMTR registry, which prospectively enrolled patients treated with commercial axi-cel in the US after ≥2 lines of prior therapy for R/R LBCL

Meta-analysis for V2Vt and V2Vt subintervals

Figure 2

A

V2Vt and V2Vt subintervals and subgroups	Number of studies	Number of patients	Median days (95% CI)	Median days (95% CI)
Leukapheresis-to-infusion (V2Vt)				
Overall	**21**	**1,910**		**30.6 (28.3–33.0)**
Study design				
Clinical trials	2	124		25.5 (19.7–31.4)
Observational studies	19	1,786		31.1 (28.7–33.5)
Geography				
United States only	11	1,096		27.1 (26.6–27.7)
Europe only	7	663		37.9 (36.1–39.6)
Leukapheresis-to-infusion (V2Vt)				
Overall	**10**	**911**		**48.4 (42.9–52.9)**
Study design				
Clinical trials	1	155		52.0 (48.1–55.9)
Observational studies	9	756		48.0 (41.9–54.1)
Geography				
United States only	2	115		42.7 (37.8–47.6)
Europe only	4	429		50.5 (48.0–52.9)
Leukapheresis-to-infusion (V2Vt)				
Overall	**3**	**419**		**35.9 (34.8–37.0)**
Study design				
Clinical trials	3	419		35.9 (34.8–37.0)
Observational studies	–	–		–
Geography				
United States only	2	330		35.8 (34.0–37.7)
Europe only	–	–		–

axi-cel

tisa-cel

liso-cel

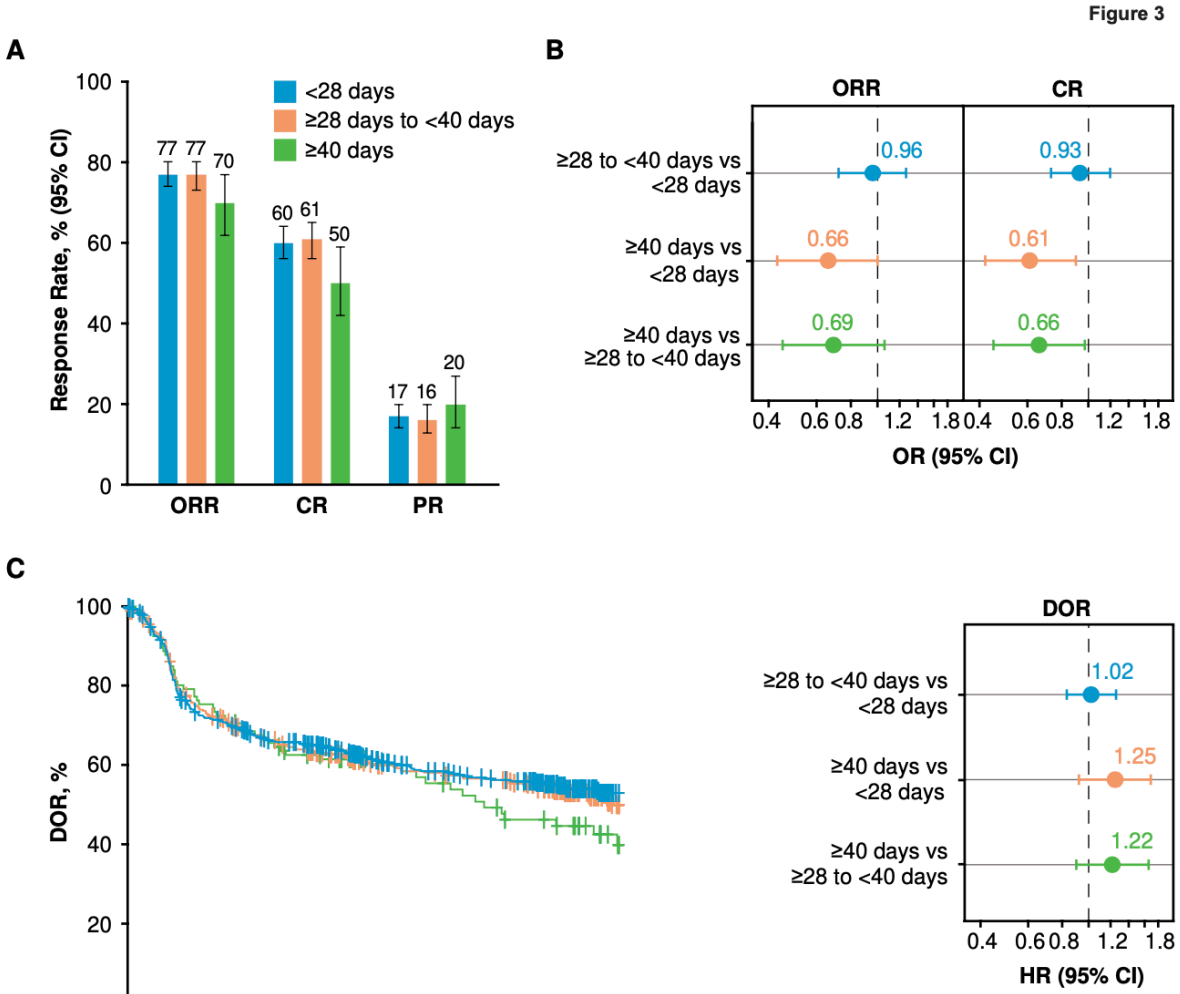
Patients treated with axi-cel had a significantly shorter median V2Vt (30.6 days, 95% CI: 28.3–33.0) when compared with tisa-cel (48.4 days, 95% CI: 42.9–52.9) or liso-cel (35.9 days, 95% CI: 34.8–37.0), irrespective of geography or study design

Locke FL, et al. Blood Advances 2024

Table 1. Baseline patient and disease characteristics of patients treated with axi-cel*

Characteristic	V2Vt			Overall N=1,383
	<28 days n=697	≥28 days to <40 days n=533	≥40 days n=153	
Median age at infusion, years (range)	61.5 (19.6–86.0)	62.5 (19.6–90.8)	63.1 (28.2–84.4)	62.1 (19.6–90.8)
≥65 years, n (%)	239 (34)	217 (41)	65 (42)	521 (38)
<65 years, n (%)	458 (66)	316 (59)	88 (58)	862 (62)
ECOG PS prior to infusion, n (%)				
0–1	613 (88)	460 (86)	132 (86)	1,205 (87)
≥2	35 (5)	20 (4)	9 (6)	64 (5)
Unknown	49 (7)	53 (10)	12 (8)	114 (8)
Histologic transformation, n (%)	202 (29)	159 (30)	41 (27)	402 (29)
Double/triple hit, n (%)†	106 (26)	87 (29)	18 (20)	211 (26)
Chemoresistant‡ prior to infusion, n (%)	469 (67)	355 (67)	101 (66)	925 (67)
Number of prior lines of systemic therapy, n (%)†,¶				
1–2	197 (29)	153 (30)	26 (18)	376 (28)
≥3	485 (71)	361 (70)	118 (82)	964 (72)
Use of bridging therapy, n (%)†	132 (20)	109 (22)	65 (46)	306 (23)
Elevated LDH at initial diagnosis, n (%)†	210 (67)	156 (74)	43 (75)	409 (70)

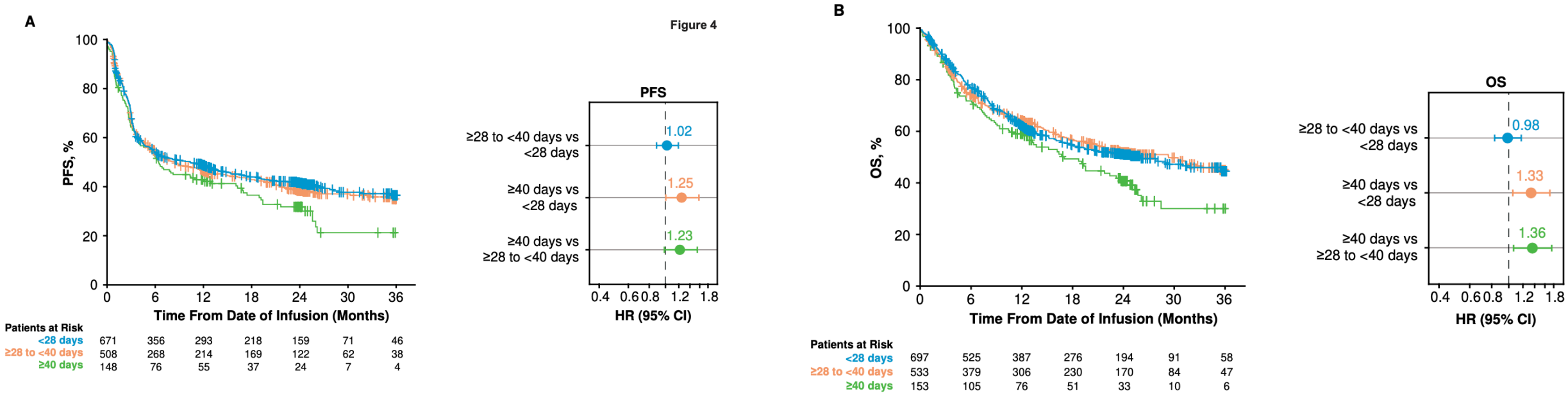
Axi-cel response rates by V2Vt



Panels show
(A) response rate by V2Vt,
(B) adjusted odds ratios of ORR and CR
(C) adjusted DOR by V2Vt in patients treated with axi-cel

Axi-cel adjusted PFS and OS by V2Vt.

Panels show (A) adjusted PFS and (B) adjusted OS by V2Vt in patients treated with axi-cel.



RESEARCH ARTICLE

A Multicenter Real-life Prospective Study of Axicabtagene Ciloleucel versus Tisagenlecleucel Toxicity and Outcomes in Large B-cell Lymphomas

Federico Stella[1], Annalisa Chiappella[2], Beatrice Casadei[3], Stefania Bramanti[4], Silva Ljevar[5], Patrizia Chiusolo[6], Alice Di Rocco[7], Maria C. Tisi[8], Matteo G. Carrabba[9], Ilaria Cutini[10], Massimo Martino[11], Anna Dodero[2], Francesca Bonifazi[3], Armando Santoro[4], Federica Sorà[6,12], Barbara Botto[13], Anna M. Barbui[14], Domenico Russo[15], Maurizio Musso[16], Giovanni Grillo[17], Mauro Krampera[18], Jacopo Olivieri[19], Marco Ladetto[20], Federica Cavallo[21,22], Massimo Massaia[23], Luca Arcaini[24,25], Martina Pennisi[2], Pier L. Zinzani[3,26], Rosalba Miceli[5], and Paolo Corradini[1,2]

real-world prospective observational study across 21 Italian centers (*CART-SIE*) compares axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) out- comes in 485 patients with relapsed/refractory large B-cell lymphoma with baseline characteristics matched by stabilized inverse propensity score weighting.

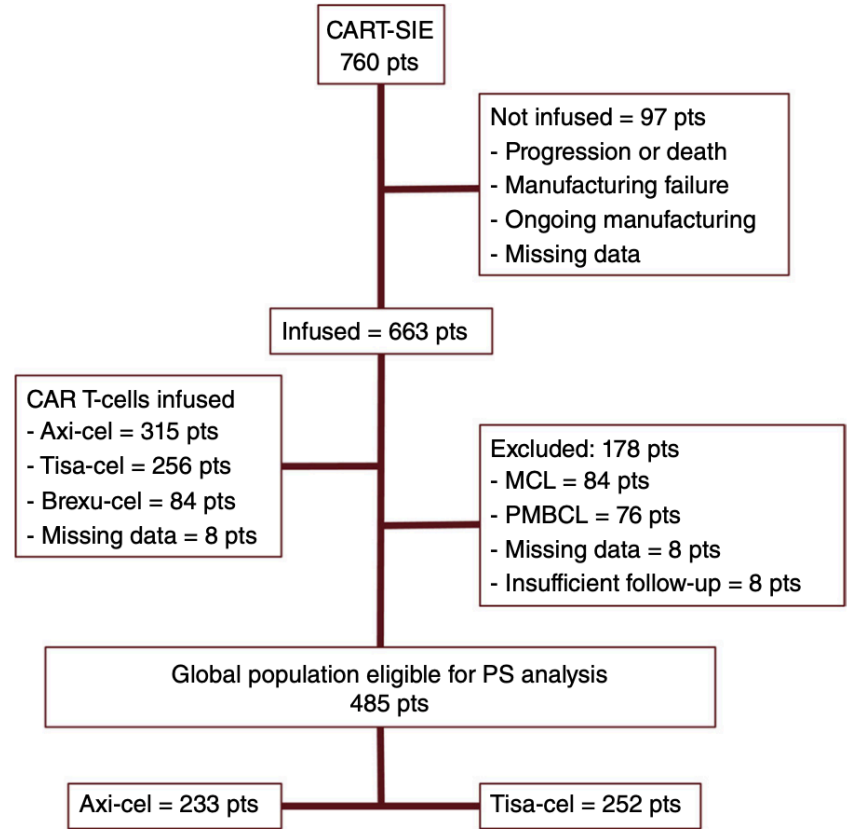


Figure 1. Patient flow diagram. MCL, mantle cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; pts, patients.

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Survival from infusion of tisa-cel vs. axi-cel before (continuous line) and after (dotted lines) PS weighting. **A,** OS. **B,** PFS.

PFS at 1 year AXI 46.5% vs.TISA 34.1%, *P* = 0.0009)

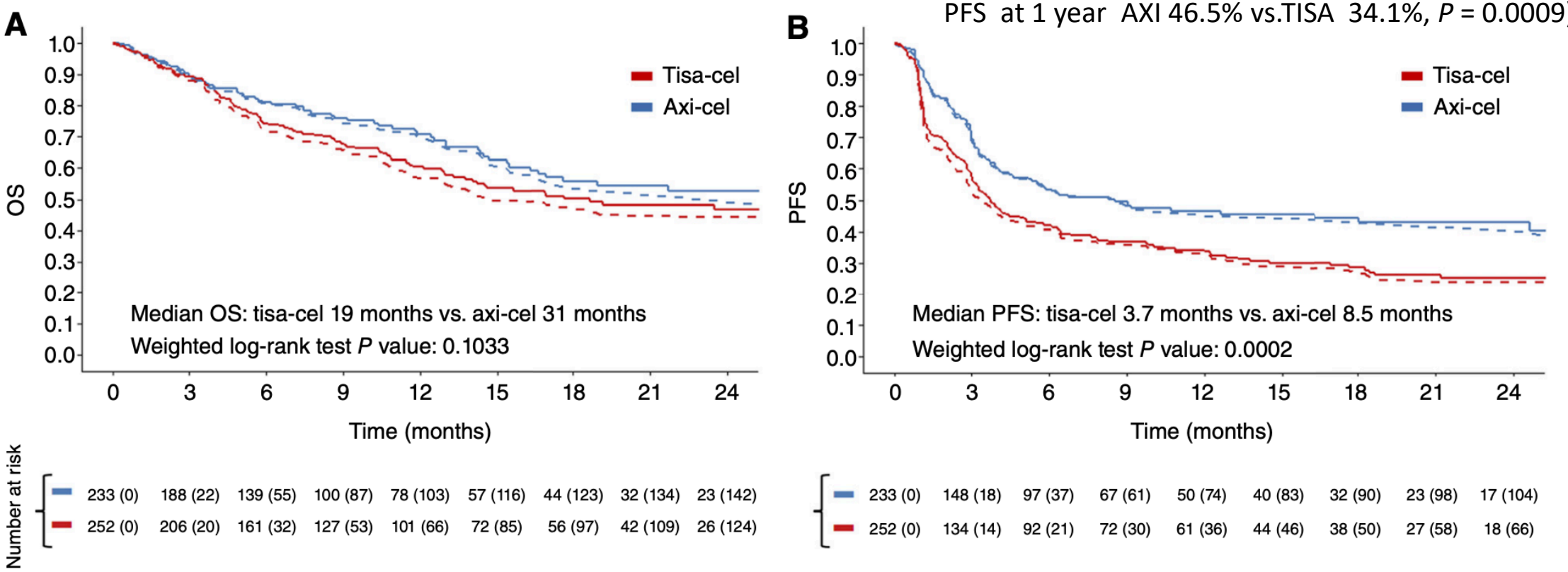

Figure 2. Survival from infusion of tisa-cel vs. axi-cel before (continuous line) and after (dotted lines) PS weighting. **A,** OS. **B,** PFS.

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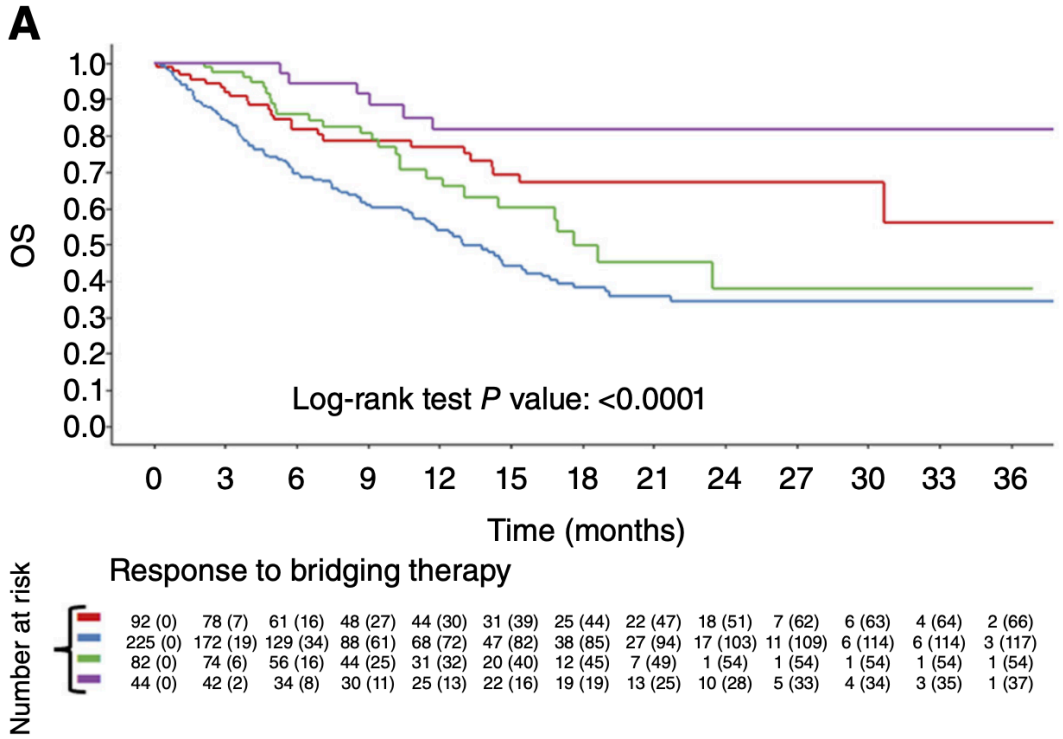
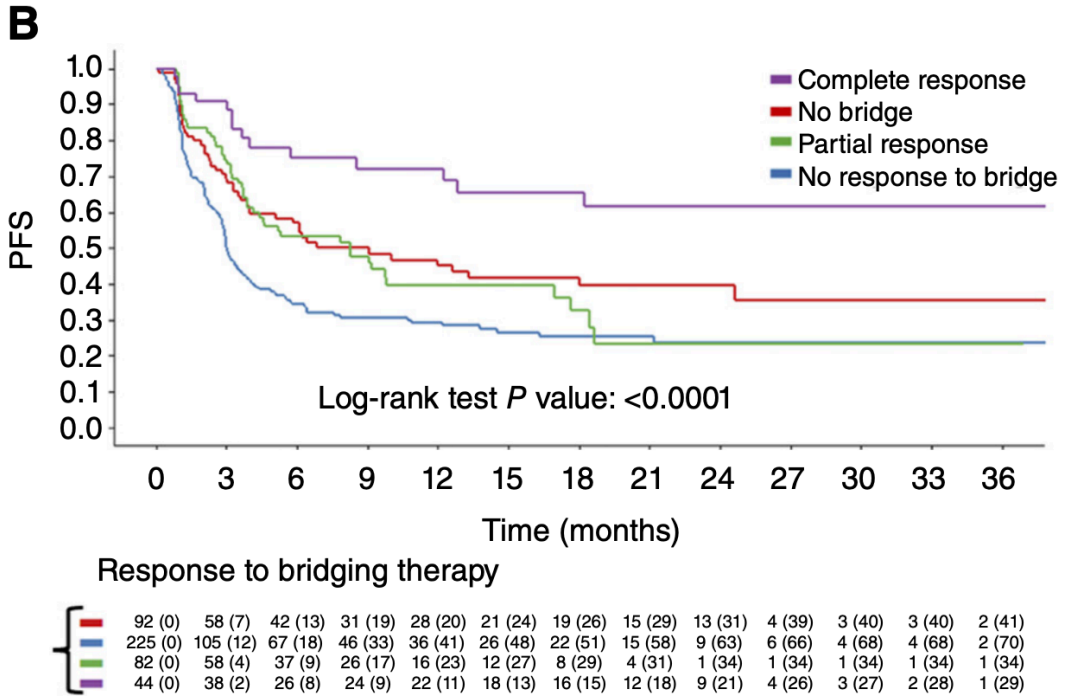
OS according to response to bridging therapy.



PFS according to response to bridging therapy.



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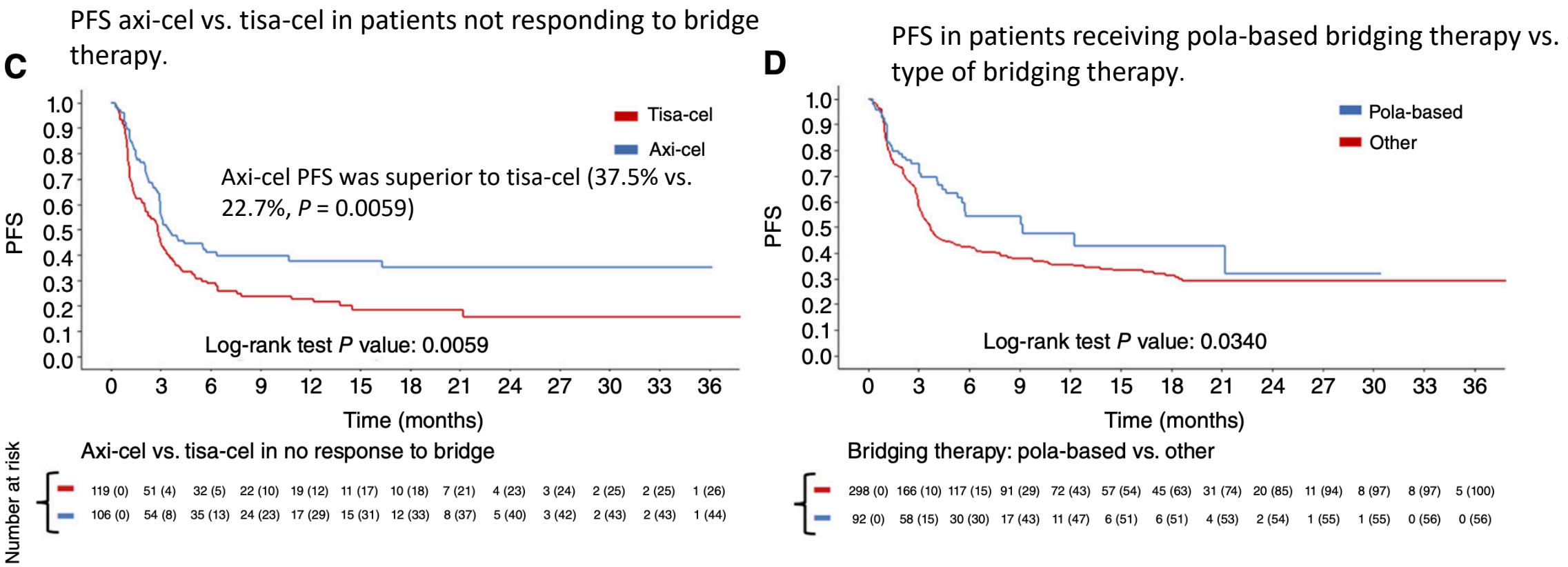

Figure 3. Survival according to response to bridging therapy. **A,** OS according to response to bridging therapy. **B,** PFS according to response to bridging therapy. **C,** PFS axi-cel vs. tisa-cel in patients not responding to bridge therapy. **D,** PFS in patients receiving pola-based bridging therapy vs. other type of bridging therapy.

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Autologous transplant or CAR-T therapy in patients with DLBCL treated while in complete remission?

360 patients with LBCL who received auto-HCT (n = 281) or CAR-T (n = 79) while in a CR

Characteristic	Auto-HCT (*n* = 281)	CAR-T (*n* = 79)	*P* Value
Age			0.14[a]
Median (min–max)	59.4 (18.2–75.6)	64.1 (20.1–76.0)	
>65 - no. (%)	92 (32.7)	35 (44.3)	
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements - no. (%)			0.03[a]
Yes	31 (27.0)	11 (13.9)	
No	84 (73.0)	68 (86.1)	
Refractory to first line therapy - no. (%)			0.22[a]
No	180 (64.1)	45 (57.0)	
Yes	56 (19.9)	23 (29.1)	
Not assessed/not reported	45 (16.0)	11 (13.9)	
Early therapy failure in 12 months - no. (%)	163 (58.0)	57 (72.2)	0.02[a]
Total lines of therapies - median (min-max)	2.0 (2.0–8.0)	3.0 (2.0–8.0)	<0.01[b]

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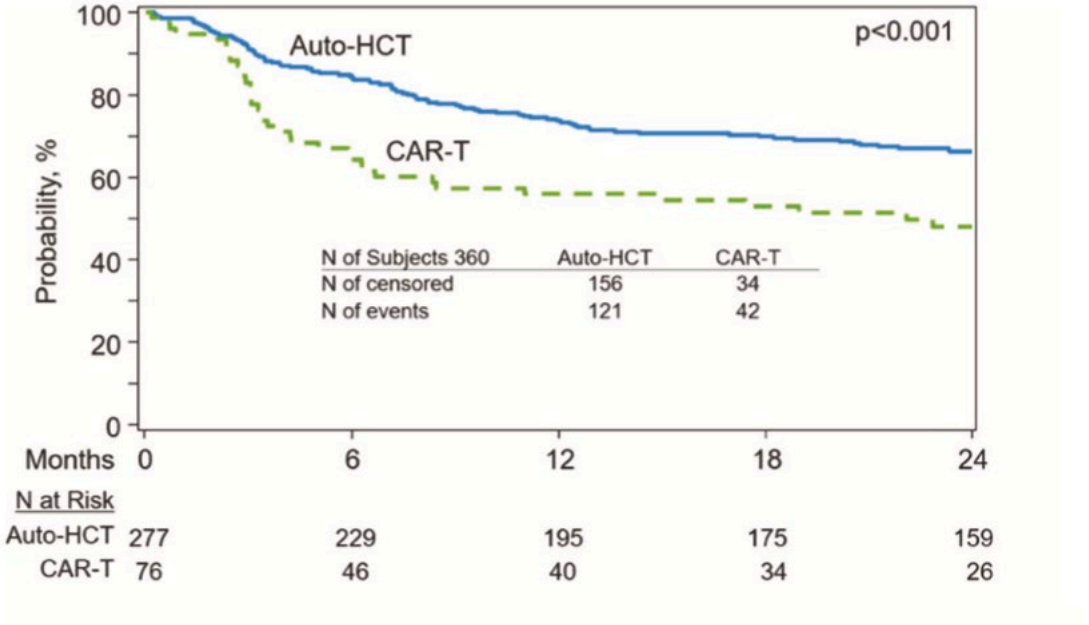
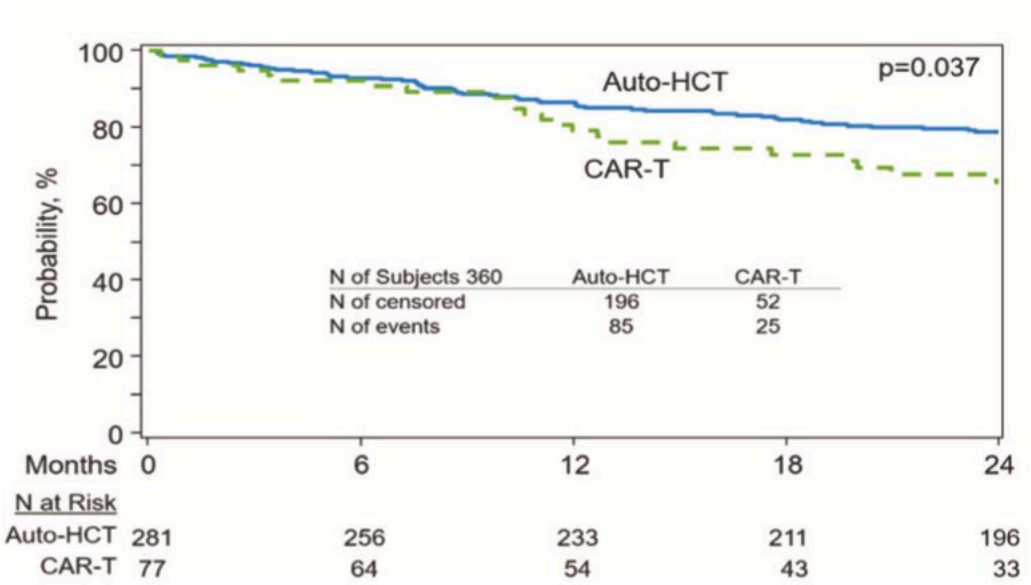
A

Progression-free Survival



C

Overall Survival



	Auto-HCT		CAR-T		*P*-value
	N	Prob (95%CI)	N	Prob (95%CI)	
Progression-free survival	277		76		<0.001
1-year		73.7% (68.3-78.8)		55.7% (44.4-66.8)	
2-year		66.2% (60.4-71.8)		47.8% (36.4-59.4)	
Overall survival	281		77		0.037
1-year		86.7% (82.4-90.4)		79.1% (69-87.7)	
2-year		78.9% (73.9-83.6)		65.6% (53.6-76.6)	

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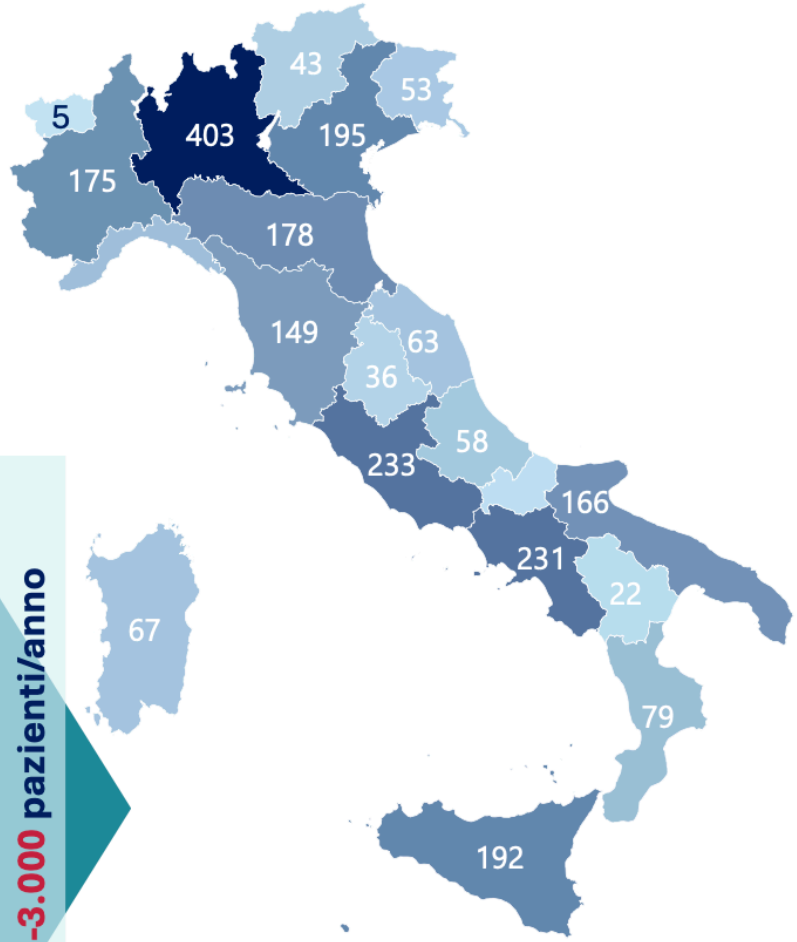
I pazienti eleggibili al trattamento CAR-T in Italia

Sulla base delle attuali indicazioni per le CAR-T e del contesto epidemiologico, il numero di pazienti, adulti e pediatrici, che potrebbe beneficiare di tale trattamento si aggira annualmente tra i 1.800 e 3.000, numero 4 volte superiore ai pazienti trattati, se si considerano le sole CAR-T commerciali.



Linfoma diffuso a grandi cellule B (DLBCL):
800 - 1.200 pazienti/anno
(Pazienti con malattia refrattaria o recidivante dopo almeno 1 linea di trattamento)

Linfoma follicolare:
200-300 pazienti/anno
(Malattia refrattaria o recidivante)

Leucemia linfoblastica acuta a cellule B:
120-180 pazienti/anno
(Malattia refrattaria o recidivante)

Linfoma mantellare (MCL):
100 - 200 pazienti/anno
(Malattia refrattaria o recidivante dopo trattamenti standard)

Mieloma multiplo:
600 - 900 pazienti/anno
(Pazienti con malattia recidivante o refrattaria dopo almeno 4 linee di trattamento)

Totale stimato nazionale: 1.800-3.000 pazienti/anno

Figura 13. Stima annuale dei pazienti eleggibili al trattamento CAR-T per indicazione terapeutica a livello nazionale e regionale (numero), 2024 – *Fonte: The European House – Ambrosetti su fonti varie, 2024*

Esempi di modelli organizzativi a livello regionale

LOMBARDIA, PIEMONTE E VENETO

Lombardia, Piemonte, Puglia e Veneto hanno da tempo istituito reti ematologiche strutturate, che hanno facilitato la presa in carico dei pazienti CAR-T, seppur con modelli differenti.

Il Veneto ha 3 Centri CAR-T, di cui uno pediatrico, che sono inseriti grazie alla Rete Ematologica Veneta, in un modello a rete Hub & Spoke.

Il Piemonte, dove la Rete CAR-T è parte della Rete Oncologica del Piemonte e della Valle d'Aosta, ha 4 Centri CAR-T di cui uno pediatrico, articolati in una Rete Hub & Spoke.

In Lombardia i Centri CAR-T per adulti sono organizzati secondo il modello del Comprehensive Cancer Care Center.

Esempi di modelli organizzativi a livello regionale

LAZIO

Nel Lazio ci sono 3 Centri autorizzati per le CAR-T, di cui 2 per adulti (Policlinico Umberto I e Policlinico Gemelli - IRCCS) e 1 pediatrico (Ospedale Bambino Gesù). A ottobre 2024, la Det. G12917 ha ratificato quanto stabilito dalla Nota Prot. 1474913 di dicembre 2023, istituzionalizzando la Commissione di esperti, di cui fanno parte i Centri clinici di riferimento, i referenti dell'Area Farmaci e dispositivi e dell'Area Ospedaliera della Regione e il Dipartimento di Epidemiologia del Servizio Sanitario Regionale del Lazio, oltre al Centro Regionale Trapianti (CRT). Inoltre è stato recepito il documento «La Rete per le terapie CAR-T nel Lazio», è stata istituita presso il CRT la lista unica di pazienti eleggibili al trattamento CAR-T, ed le attività della rete CAR-T sono state integrate nella nascente Rete Oncologica Regionale.

Esempi di modelli organizzativi a livello regionale

EMILIA ROMAGNA

La Regione Emilia Romagna nel 2019 ha istituito una rete sul modello Hub & Spoke con l'AOU di Bologna quale unico Centro operativo per la somministrazione delle CAR-T in collegamento e coordinamento con le altre Unità di Ematologia provinciale. Contestualmente, è stata istituita una Lista unica di pazienti eleggibili alle CAR-T. Il buon funzionamento della Rete CAR-T ha ispirato l'istituzione della Rete oncologica ed emato-oncologica regionale nel 2022, di cui la stessa Rete CAR-T è parte integrante. La Delibera N. 210 di febbraio 2024 ha individuato anche le Unità di Ematologia dell'AUSL di Reggio Emilia – IRCCS e dell'AOU di Modena come sedi per l'utilizzo delle CAR-T.

Il problema del «DRG»

REGIONE EMILIA ROMAGNA

Secondo uno studio realizzato in Emilia Romagna all'interno di un ampio CAR-T Hub, dopo aver escluso il costo del prodotto CAR-T, le principali voci di costo del percorso sono i ricoveri ospedalieri (43,9%), seguiti da esami/procedure (26,3%) e altri farmaci (25,4%). Per quanto riguarda i costi dei farmaci e dei trattamenti diversi dai prodotti CAR-T, le voci di spesa più elevate riguardano gli eventi avversi, sia infettivi che extra-infettivi, verificatisi entro 30 giorni dall'infusione, che rappresentano il 63% del totale. In totale, il costo medio per paziente (escluso il costo delle CAR-T) è stato pari a circa 74.000 euro.

Voce di costo	Costo (euro)
Costo personale	1.110
Esami	19.416
Trasfusioni	1.654
Ospedalizzazioni	32.441
Aferesi	533
Terapie (CAR-T escluse)	18.751
TOTALE	73.905

Figura 21. Esempio di valorizzazione del percorso delle CAR-T – *Fonte: The European House – Ambrosetti su dati Di Staso, R., Casadei, B., Gentilini, M., Guadagnuolo, S., Pellegrini, C., Broccoli, A., ... & Argnani, L. (2024), "Economic evaluation of anti-CD19 CAR T-cell pathway for large B-cell lymphomas in the real-life setting: the experience of an Italian hub center in the first three years of activity", 2024*

Take Home Messages

- CAR T-cell therapy has made a significant impact in the treatment of relapsed and refractory (R/R) DLBCL.
- There are significant barriers to timely administration of CAR T.
- Vein-to-vein time (time between leukapheresis and CAR T infusion) is an important barrier reported by clinical trials.
- In the real world, administration of CAR T may be further delayed due to financial «problems»
- The time between CAR T referral and infusion (brain-to-vein) in the real-world is unknown.
- Understanding the barriers to timely administration of CAR T is crucial to expanding the access to CAR T for patients with R/R DLBCL