CAR-T and LBCL:
Real World in 2^ line

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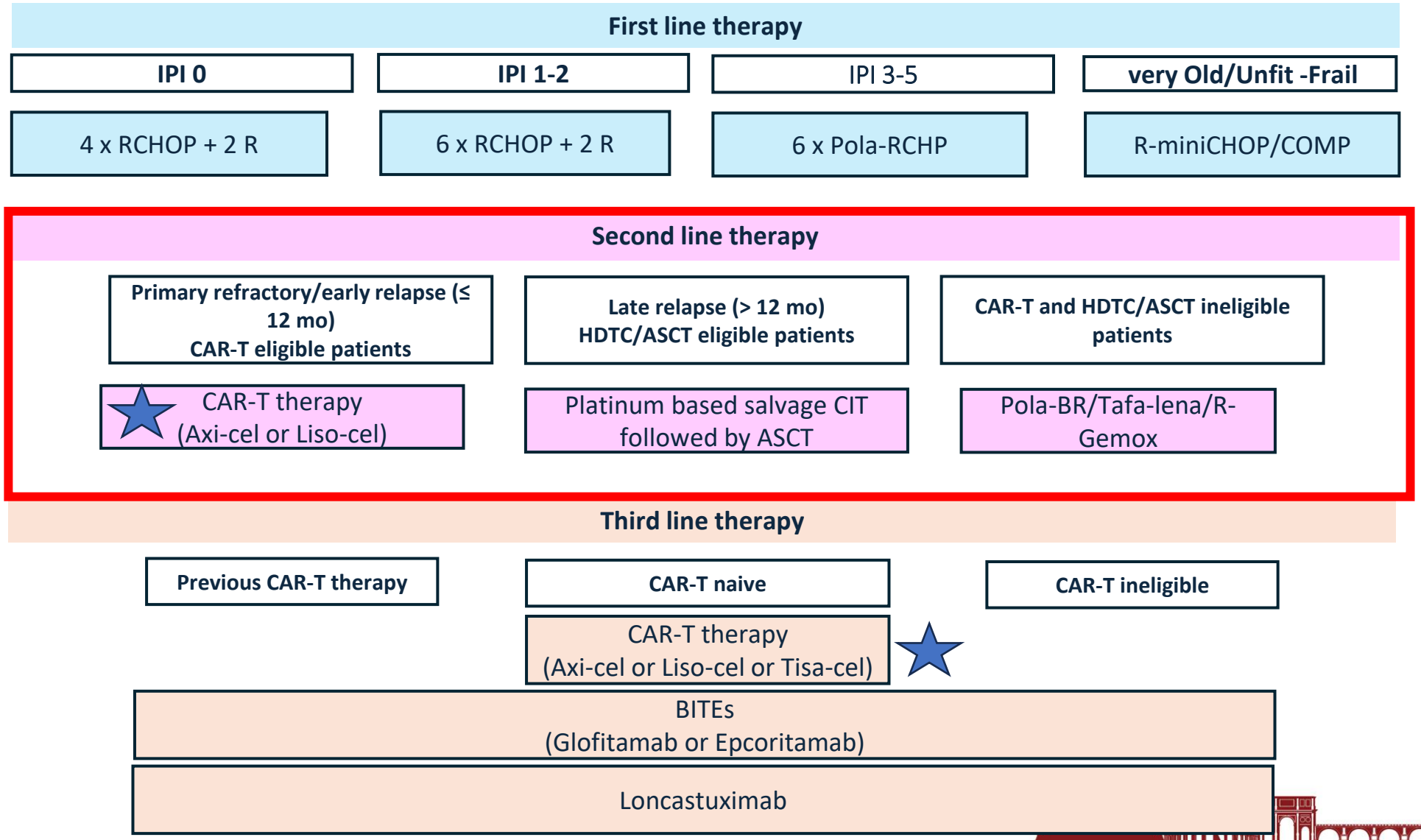
CAR-T:
e la storia continua...
migliorando

Roma, 9 Aprile 2025
Starhotels Metropole

Disclosures of Alice Di Rocco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie			x			X	
Jannsen					X		
Kite-Gilead			x		X	X	
Novartis					X		
Incyte			x		x		
Roche			X		X	X	
Eli-Lilly					X		
Takeda						X	
SOBI					x		
ASTRAZENECA						X	
RECORDATI RARE DISEASE					X		

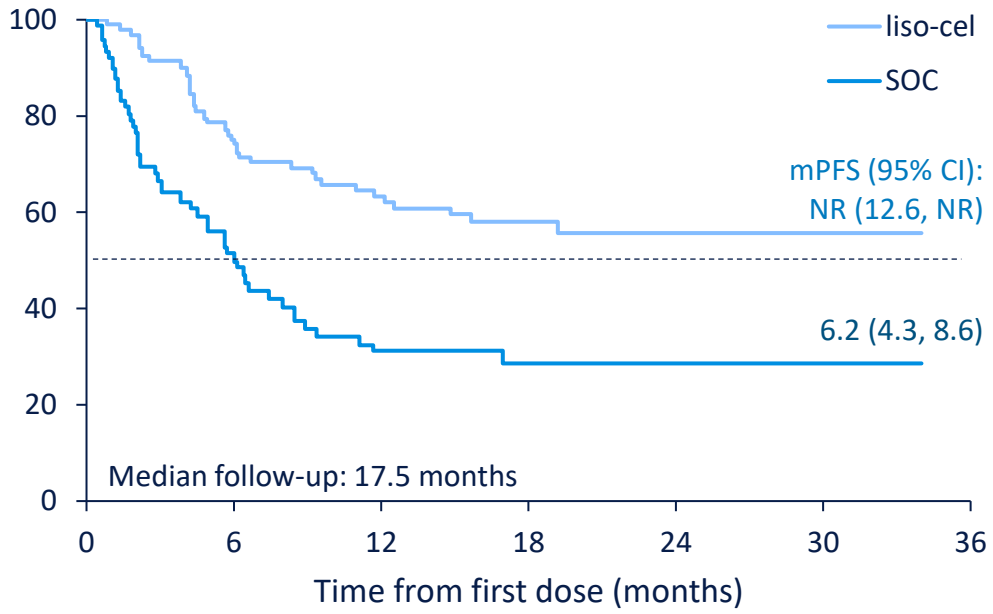
DLBCL: Sequencing therapy in the era of novel drug



Adapted from Karsten I et al. Br J Haematol. 2024;205:2163–2174.

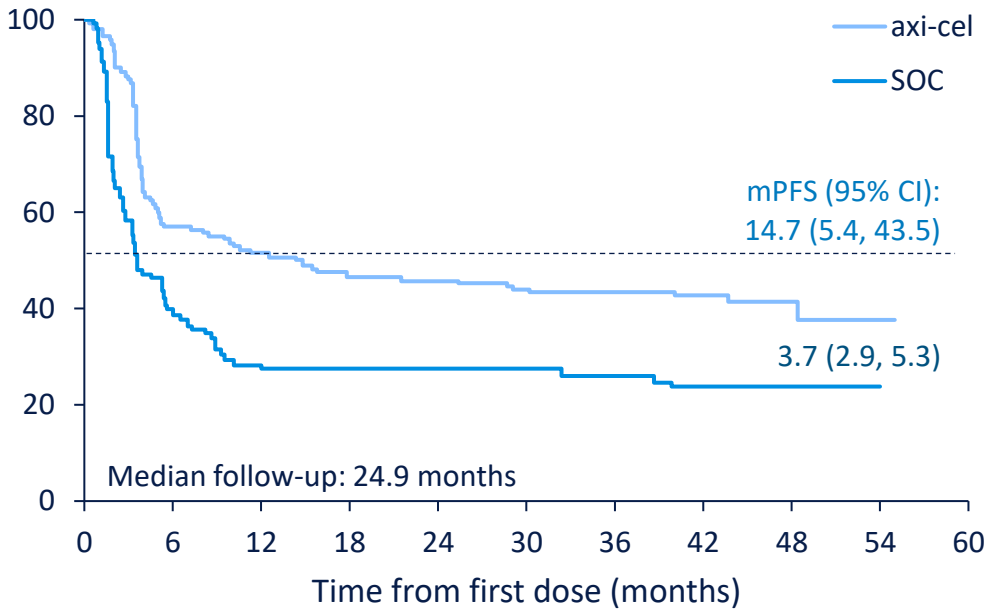
Evolving Unmet Needs in R/R DLBCL

PFS: Ph3 TRANSFORM (liso-cel 2L)[1]



Response	Liso-cel (n = 92)	SOC (n = 92)
ORR	**87%**	**49%**
CR	74%	43%

PFS: Ph3 ZUMA-7 (axi-cel 2L)[2]



Response	Axi-cel (N=180)	SOC (N=179)
ORR	**83%**	**45%**
CR	61%	34%

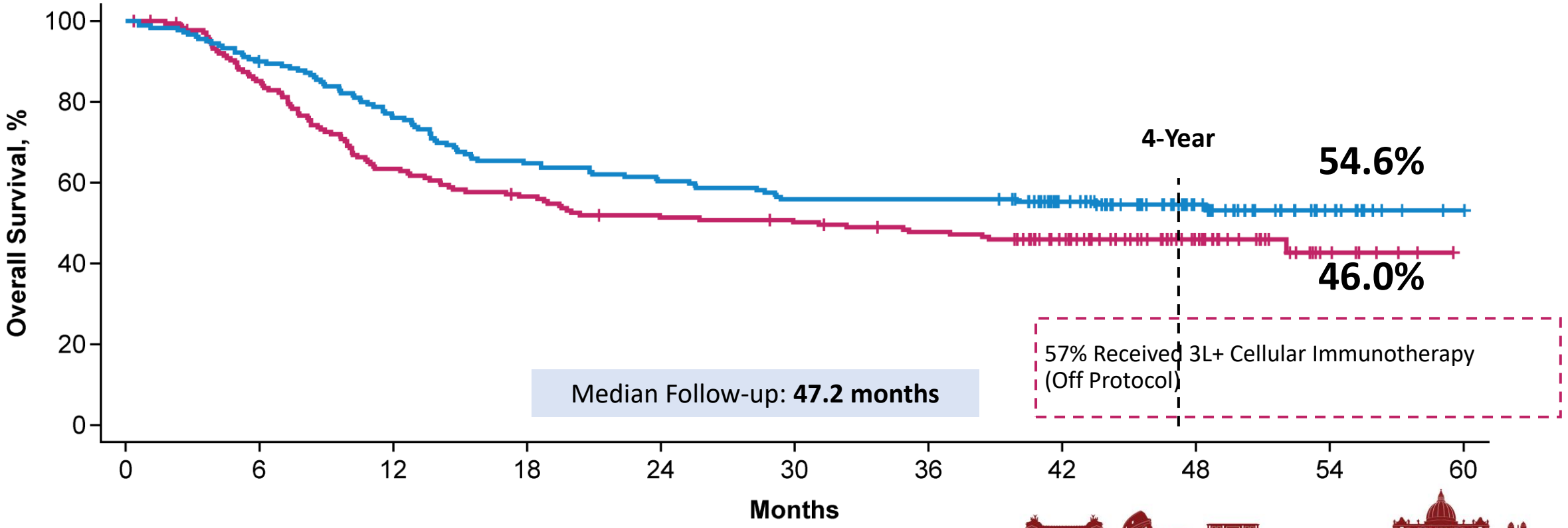
Abramson JS, et al. Blood (2023) 141 (14): 1675–1684.
Westin J, et al. N Engl J Med 2023; 389:148-157.

ORIGINAL ARTICLE

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

The NEW ENGLAND JOURNAL of MEDICINE

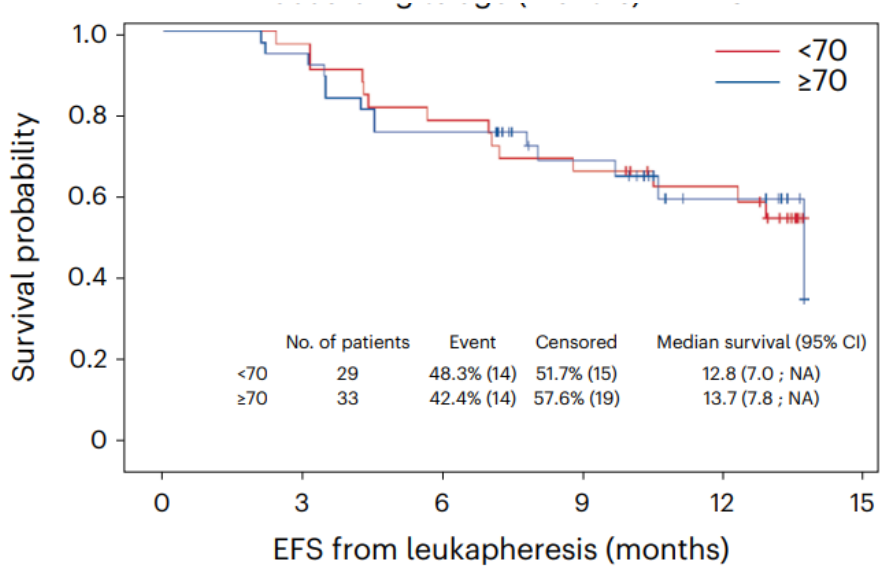
✓ *Axi-Cel Improved Overall Survival Versus Standard of Care*



Westin JR , et al. *N Engl J Med.* 2023;

Older Age is not a Contraindication for CAR-T Cell Therapy

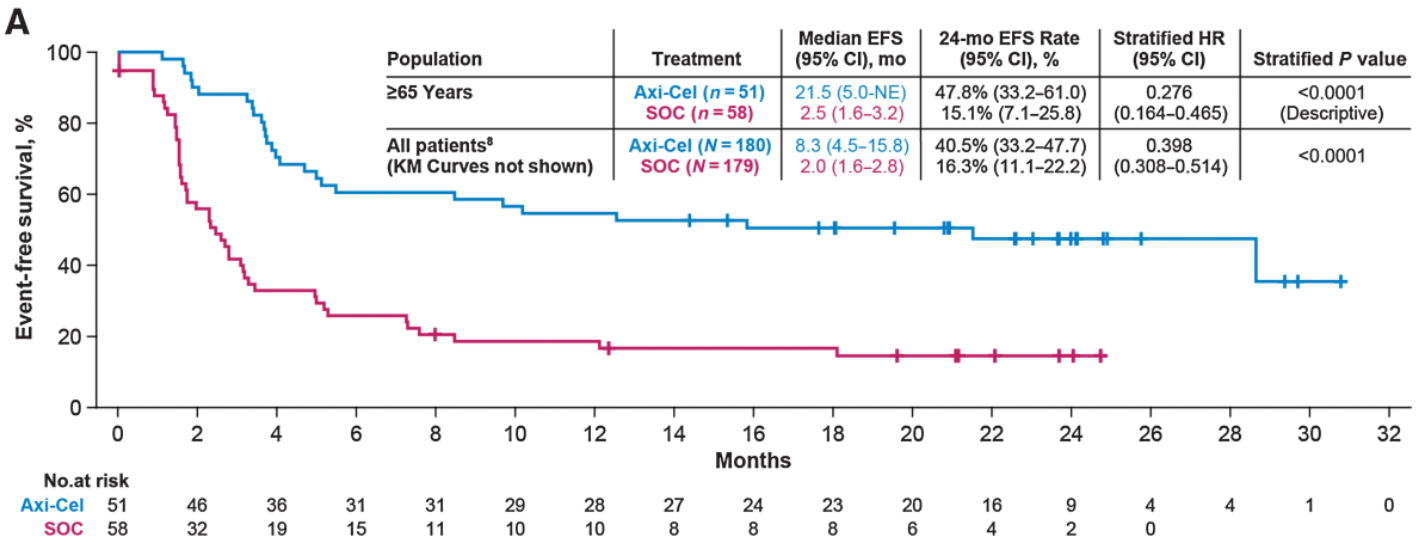
Alycante study
62 patients



At risk

All	<70	29	28	22	18	14	0
All	≥70	33	31	24	16	7	0

ZUMA-7 analysis
109 patients > 65 yrs

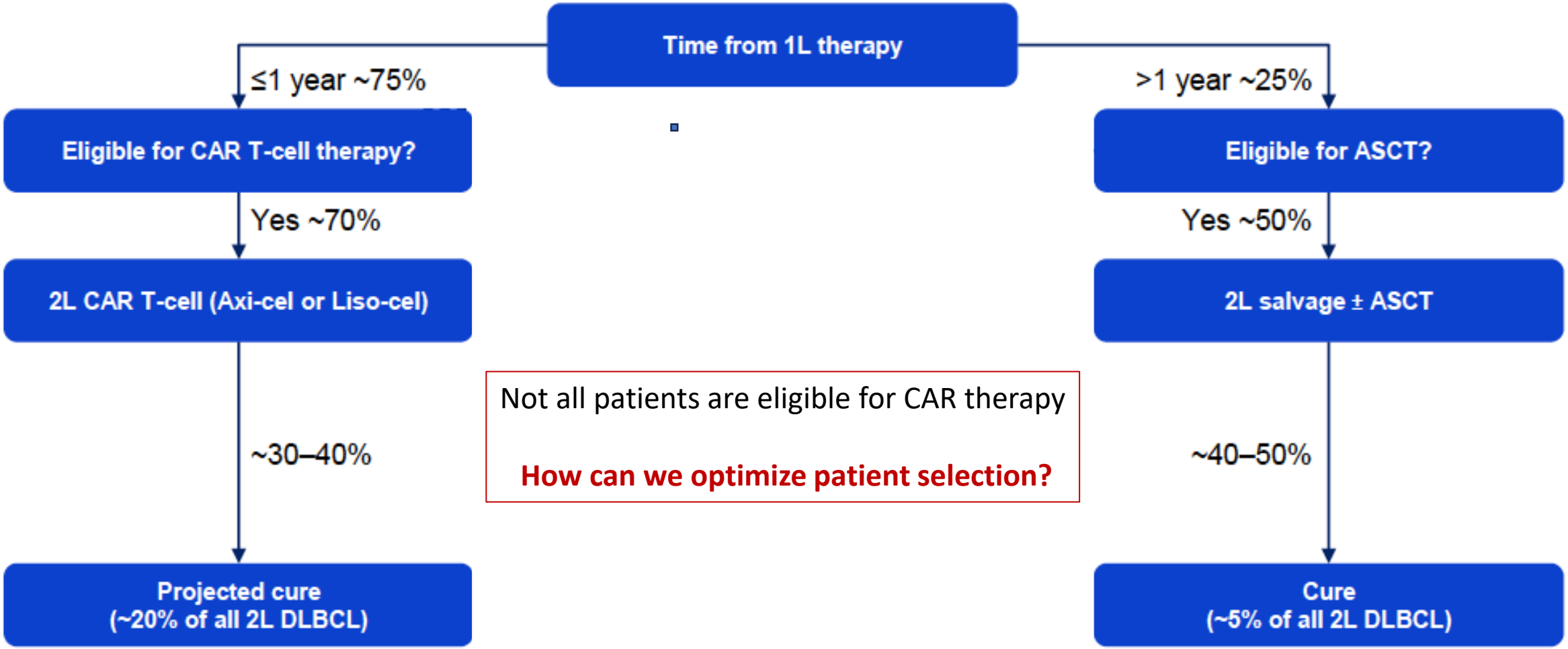


Population	Treatment	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %	Stratified HR (95% CI)	Stratified *P* value
≥65 Years	Axi-Cel (*n* = 51)	21.5 (5.0-NE)	47.8% (33.2–61.0)	0.276 (0.164–0.465)	<0.0001 (Descriptive)
	SOC (*n* = 58)	2.5 (1.6–3.2)	15.1% (7.1–25.8)		
All patients[8] (KM Curves not shown)	Axi-Cel (*N* = 180)	8.3 (4.5–15.8)	40.5% (33.2–47.7)	0.398 (0.308–0.514)	<0.0001
	SOC (*N* = 179)	2.0 (1.6–2.8)	16.3% (11.1–22.2)		

- neutropenia 66%
- thrombocytopenia 38%.
- CRS 95.5% (grade 3-4: 8%)
- ICANS 51.6% (grade 3-4: 14.5%)

Houot R. et al. Nat. Med 2023
Westin JR. et al. Clin Canc Res 2023

A new treatment algorithm for patients with R/R LBCL after 1L therapy



Not all patients are eligible for CAR therapy

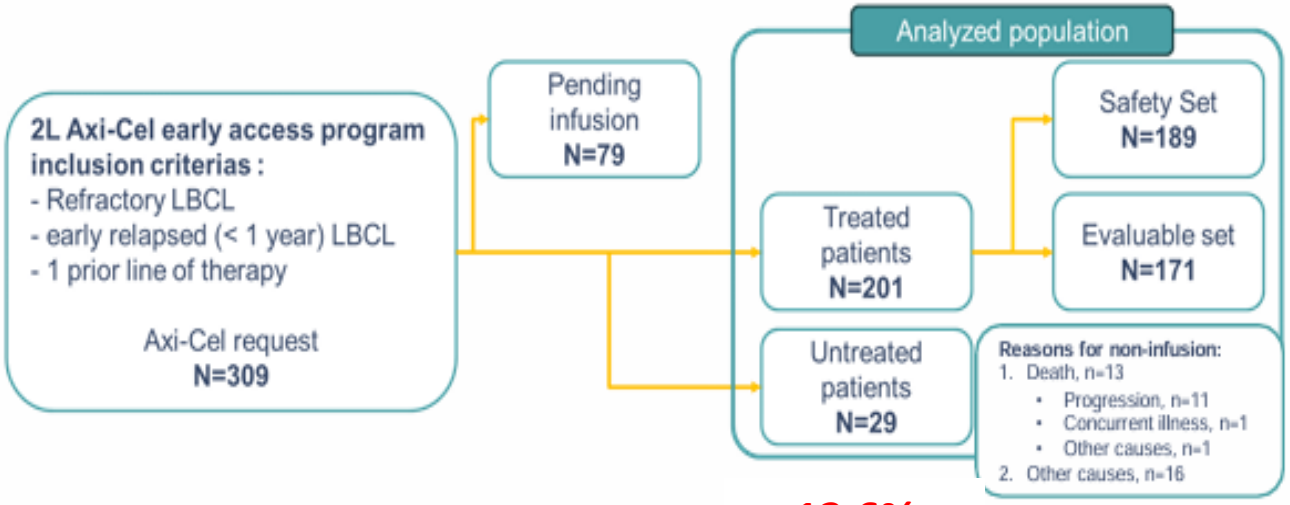
How can we optimize patient selection?

Adapted from Westin J and Sehn LH. Blood 2022.

Real World experience: Axi-cel in 2L, French DESCAR-T registry

	Treated patients N=201 (87.4%)		Untreated patients N=29 (12.6%)	
Sex Male	122	(60.7%)	16	(55.2%)
Age (years)				
Median (min; max)	61 (21; 82)		65 (34;80)	
Age >= 65 years	**77**	**(38.3%)**	**15**	**(51.7%)**
Bridging therapy	**177**	**(88.1%)**	**18**	**(62.1%)**
ECOG				
0-1	164	(81.6%)	14	(48.3%)
>=2	10	(5.0%)	3	(10.3%)
Missing	27	(13.4%)	12	(41.4%)
LDH > Normal				
No	75	(37.3%)	16	(55.2%)
Yes	122	(60.7%)	12	(41.4%)
Missing	4	(2.0%)	1	(3.4%)
Ann Arbor Stage				
I-II	30	(14.9%)	4	(13.8%)
III-IV	149	(74.1%)	20	(69.0%)
Unknown	22	(10.9%)	5	(17.2%)
Histology				
DLBCL	149	(74.1%)	22	(75.9%)
Transformed indolent	28	(13.9%)	6	(20.7%)
PMBL	6	(3.0%)	0	(0.0%)
HGBL	8	(4.0%)	1	(3.4%)
Other#	10	(5.0%)	0	(0.0%)
Primary refractory disease	**149**	**(74.1%)**	23	(79.3%)

Median Follow up from CAR-T infusion: 3 months!

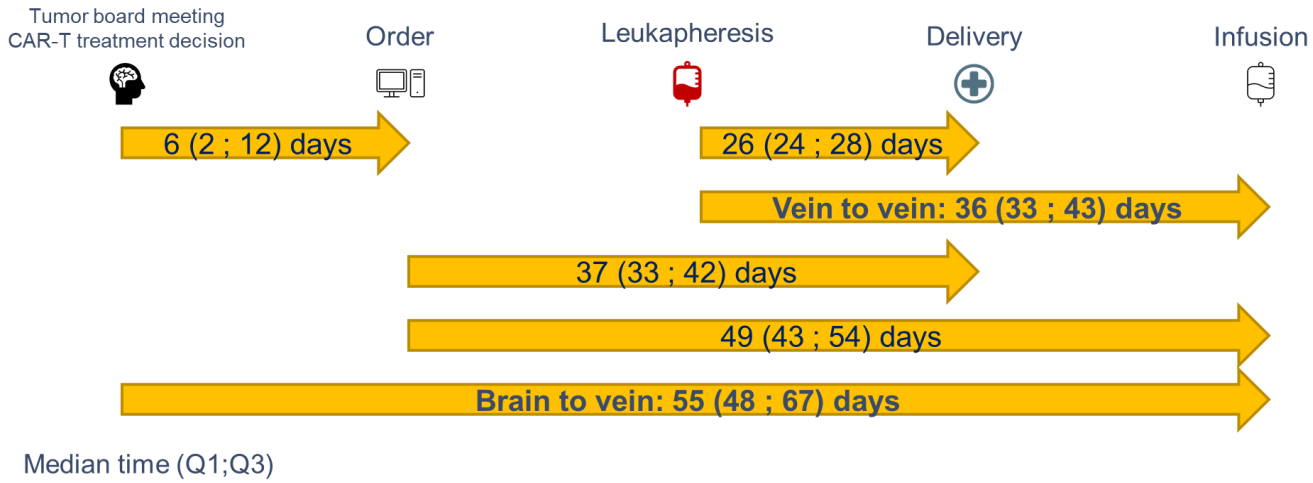


12,6% untreated

Brisou G, et al. ASH 2023.

Real World experience: Axi-cel in 2L, French DESCAR-T registry

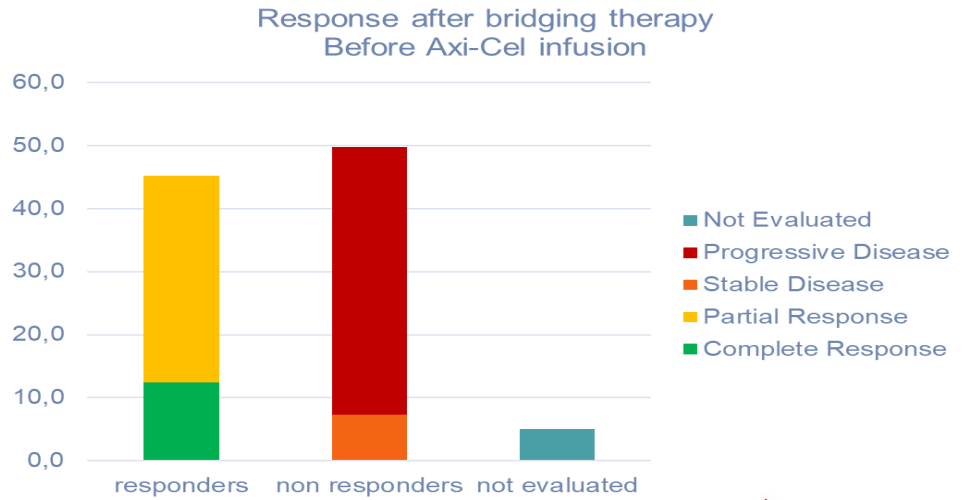
Time from decision to infusion



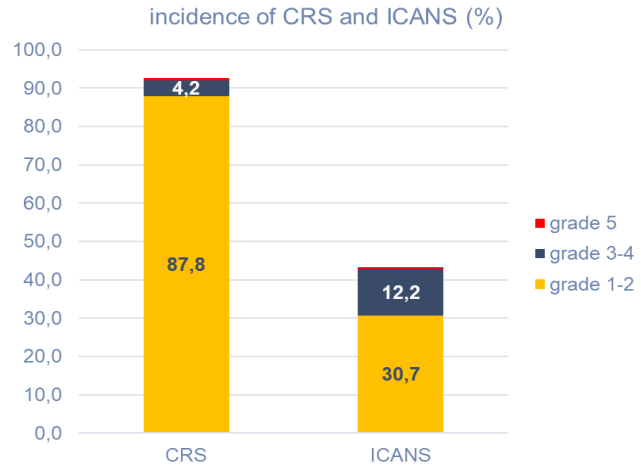
Bridging Therapies

Bridging therapy	**177**	**(88.1%)**
Number of bridging lines		
1	**153**	**(86.4%)**
2	19	(10.7%)
3	4	(2.3%)
4	1	(0.6%)
Type of treatment*		
Monoclonal antibody	**155**	**(87.6%)**
Anti-CD20	**153**	**(86.4%)**
Chemotherapy	**162**	**(91.5%)**
Platine-based regimen	**124**	**(70.1%)**
Radiotherapy	14	(7.9%)
IMiD	11	(6.2%)
Kinase inhibitor	14	(7.9%)
Corticosteroids	13	(7.3%)

* Several treatment possible



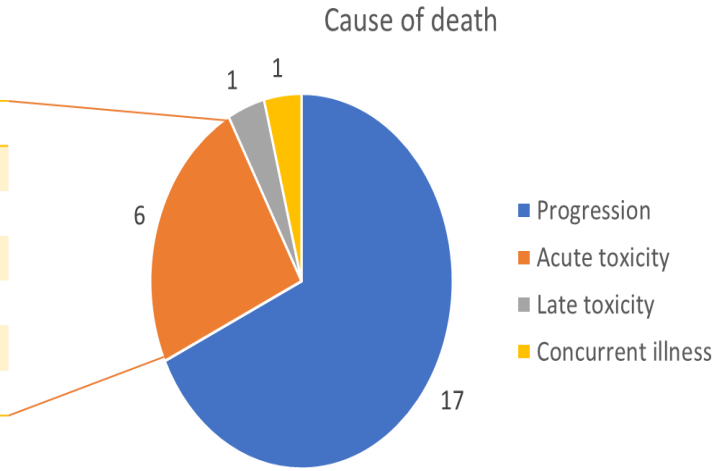
Axi-cel in 2L - French DESCAR-T registry: Toxicity



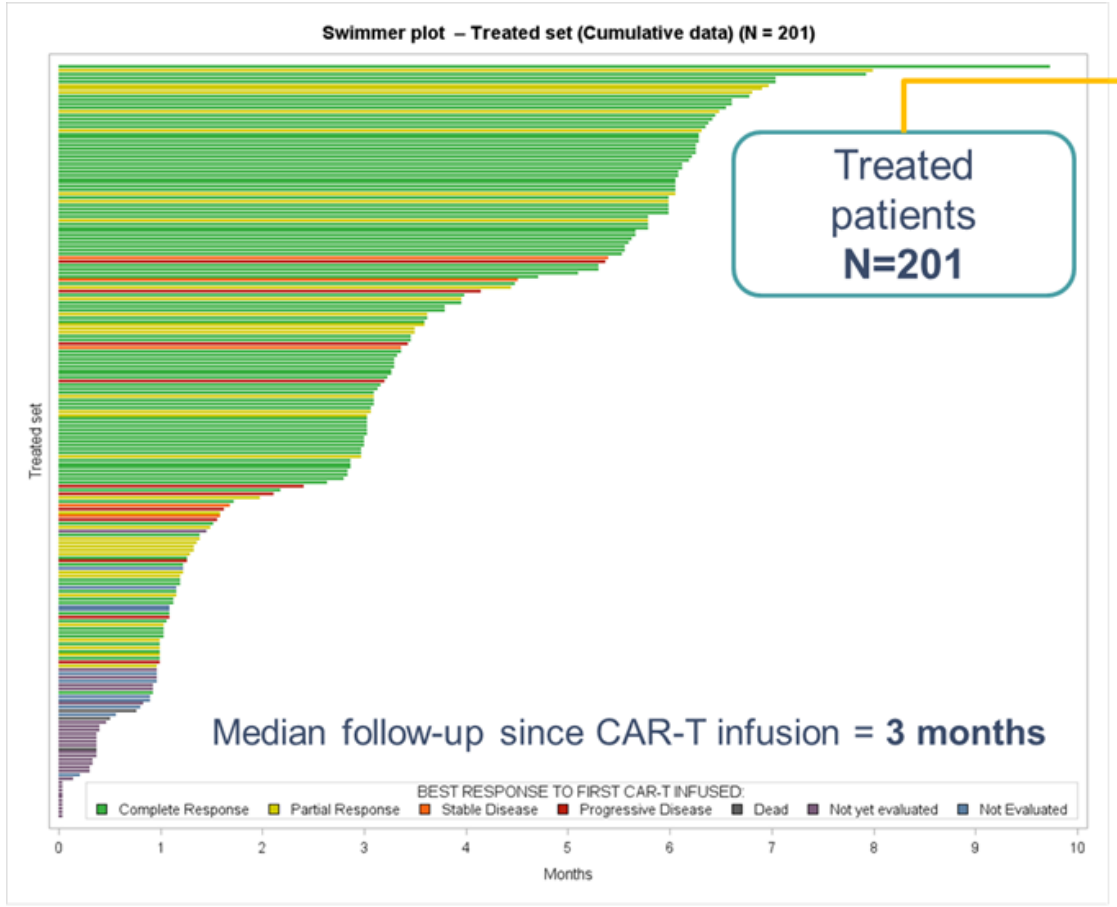
Treatment received for toxicities		
Yes	140	(80.0%)
More than one	94	(67.1%)
Intensive care unit	44	**(25.1%)**
Median number of days (min;max)	5.0 (1 ; 25)	
Pressor amines use	8	(4.6%)
Mechanical ventilation	7	(4.0%)
Tocilizumab use	**126**	**(72.0%)**
Median days of treatment (min;max)	2.0 (1 ; 7)	
Corticosteroid use	**99**	**(56.6%)**
Siltuximab use	4	(2.3%)
Anti-IL1: Anakinra	22	(12.6%)
Anticonvulsant use	30	(17.1%)

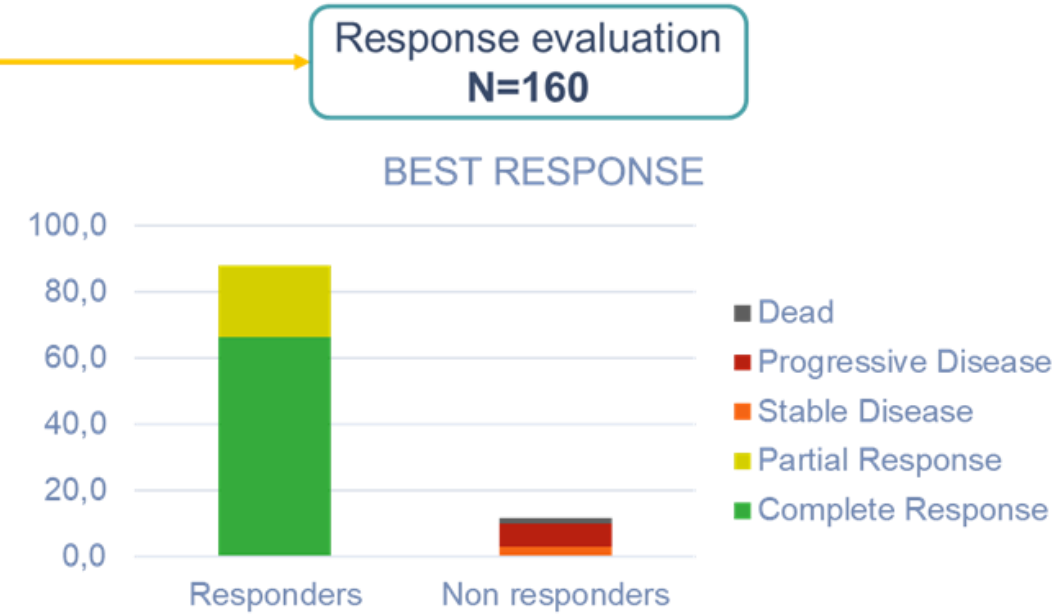
- ✓ Medically significant infection observed: n 49; **26%**
- ✓ **6 months NRM: 4%**

Cause of death	n
UNKNOWN	1
NEUROLOGICAL TOXICITY	1
ACUTE HEMATOTOXICITY (DEEP PANCYTOPENIA)	1
CRS	1
MULTIVISCERAL FAILURE	1
SEPTIC SHOCK	1



Axi-cel in 2L - French DESCAR-T registry: Response

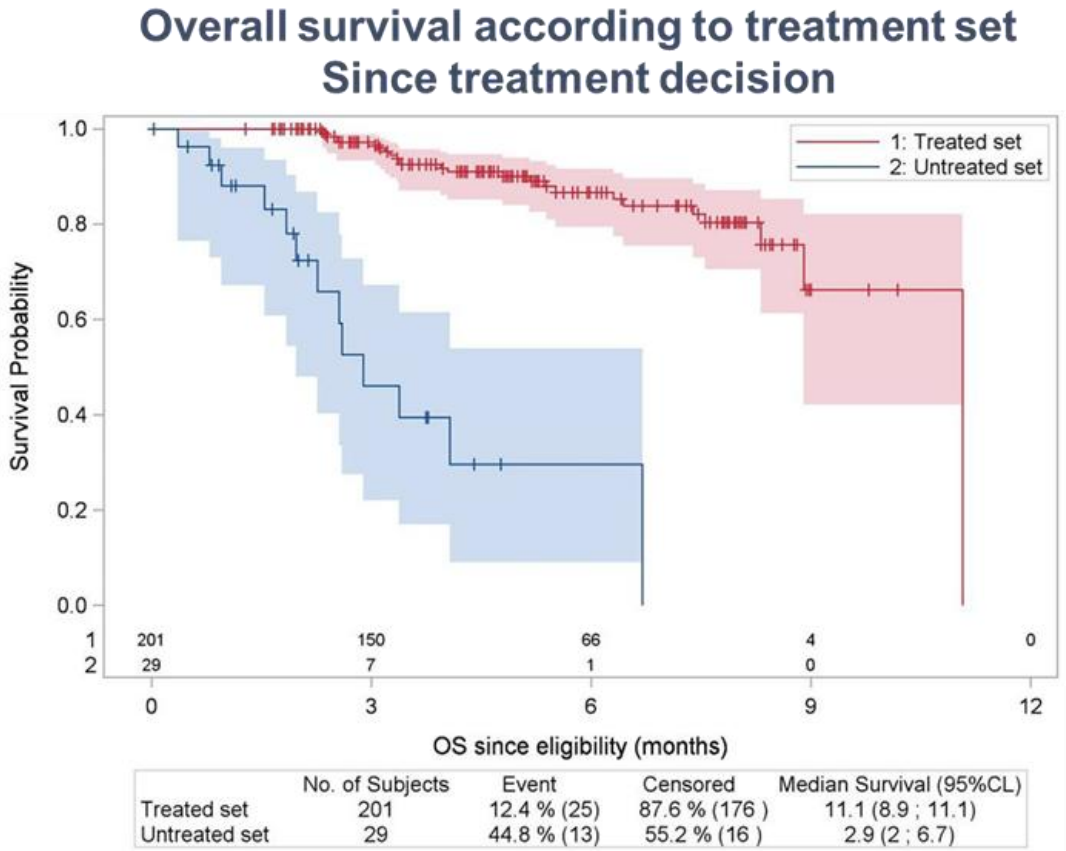


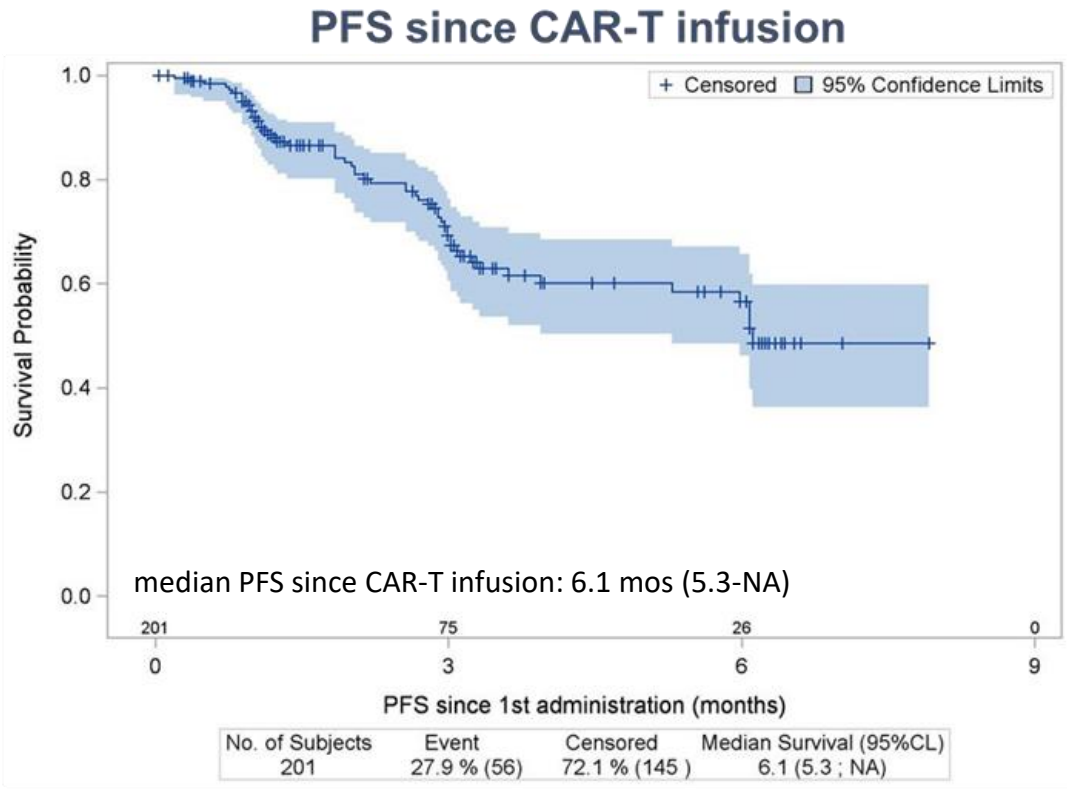


	n	%
Complete Response	106	66.3
Partial Response	35	21.9
Stable Disease	5	3.1
Progressive Disease	11	6.9
Dead	3	1.9

Brisou G. et al. ASH 2023 [Abstract 905]

Real World experience: Axi-cel in 2L, French DESCAR-T registry





median OS since eligibility

- treated set: 11.1 (8.9-11.1) months
- untreated set: 2.9 (2-6.7) months

Real-World Early Outcomes of Second-Line Axi-Cel Therapy in Patients With R/R LBCL

- N=**446 patients**
- axi-cel in 2L between **April 2022 and July 2023**
- **Median follow-up for all patients was 12.0 months** (95% CI, 11.5-12.1)
  - ZUMA-7 ineligible: 11.8 months (95% CI, 7.2-12.1)
  - ZUMA-7 eligible/unknown: 12.1 months (95% CI, 11.8-12.3)

Baseline patient and disease characteristics

Characteristic	All Patients N=446
Median age, years (range)	63.9 (19.5-86.0)
≥65 to <70, n (%)	74 (17)
≥70, n (%)	137 (31)
Male sex, n (%)	285 (64)
ECOG performance status 0-1,[a] n (%)	401 (97)
Disease type, n (%)	
DLBCL	349 (78)
PMBCL	13 (3)
HGBCL	79 (18)
FL Grade 3B	5 (1)
Elevated LDH levels pre-infusion, n (%)	199 (48)
Response to last line of therapy pre-leukapheresis, n (%)	228 (51)
Median vein-to-vein time, days, (IQR)	29.0 (27.0-35.0)
Bridging therapy,[a,d] n (%)	286 (66)

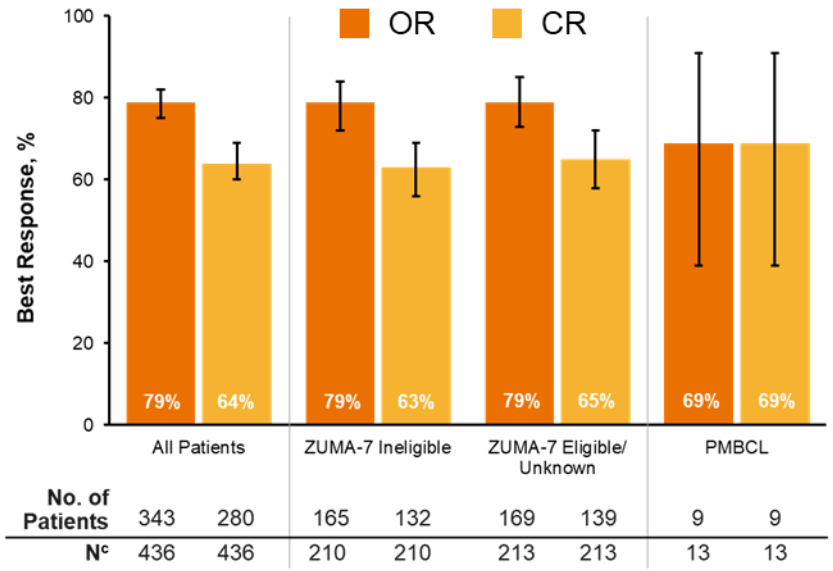
Eligibility and transplant ineligibility

Characteristic	All Patients N=446
ZUMA-7 eligibility,[a] n (%)	
Eligible	214 (48)
Not eligible	219 (49)
Organ impairment	150 (34)
Pulmonary (moderate/severe)	81 (18)
Cardiac	49 (11)
Bone marrow (platelets, ANC, and/or ALC)	37 (8)
Arrhythmia	26 (6)
Cerebrovascular disease	14 (3)
Renal (moderate/severe)	5 (1)
Heart valve disease	4 (<1)
Hepatic (moderate/severe)	1 (<1)
Prior malignancy	70 (16)
Other causes for ineligibility	48 (11)
PMBCL	13 (3)
Transplant ineligible, n (%)	226 (52)

Lee *et al.* ASH 2024 (Abstract 526; oral presentation)

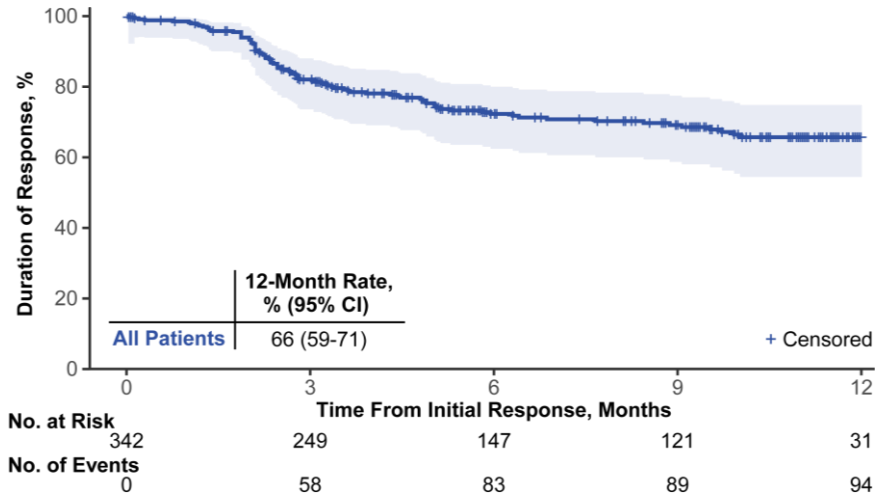
Real-World Early Outcomes of Second-Line Axi-Cel Therapy in Patients With R/R LBCL

ORs and CRs were similar across all patient groups



- Median time to OR in all patients was 2.1 months (IQR, 1.0-3.6)
- Median time to CR in all patients was 3.1 months(IQR, 1.1-NE)

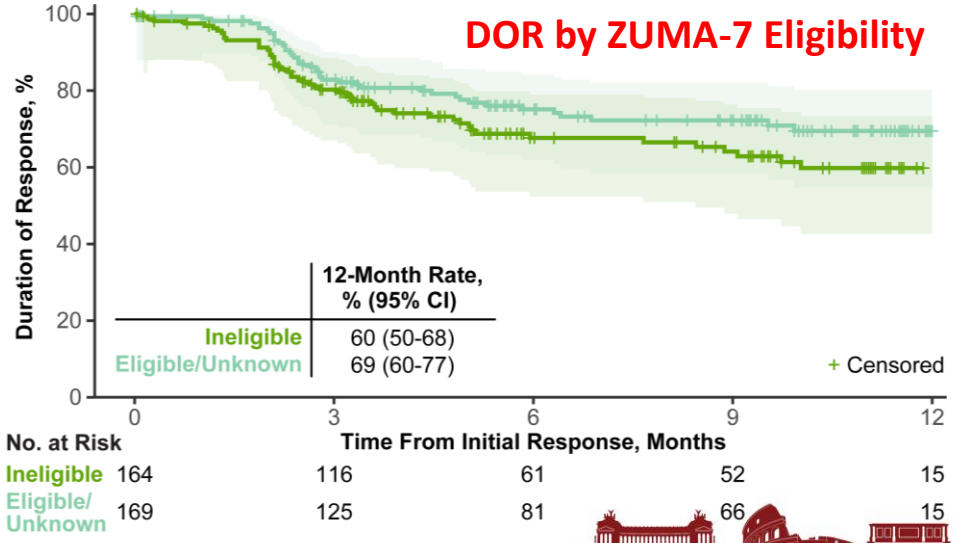
DOR in All Patients



All patients:
12-month DOR: 66%

median fup: 12 months

DOR by ZUMA-7 Eligibility

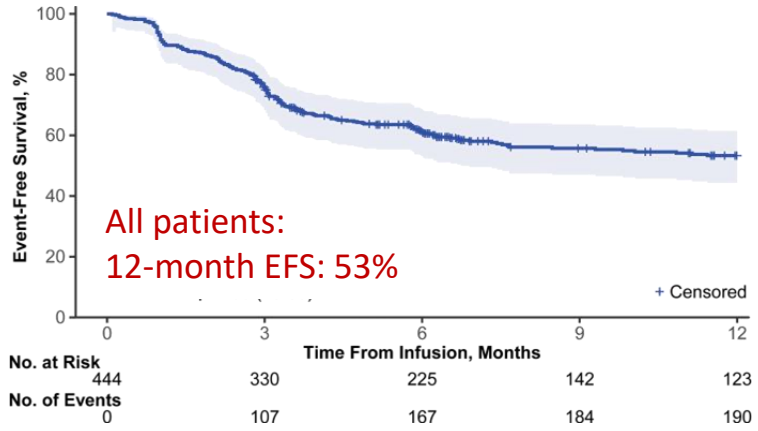


Patients ZUMA eligible:
12-month DOR: 69%

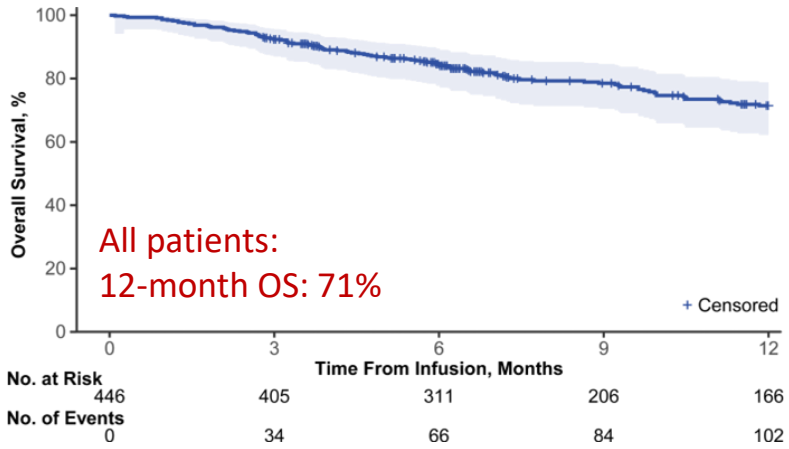
Patients ZUMA ineligible:
12-month DOR: 60%

RWE Axi-cel in second line in US : EFS and OS

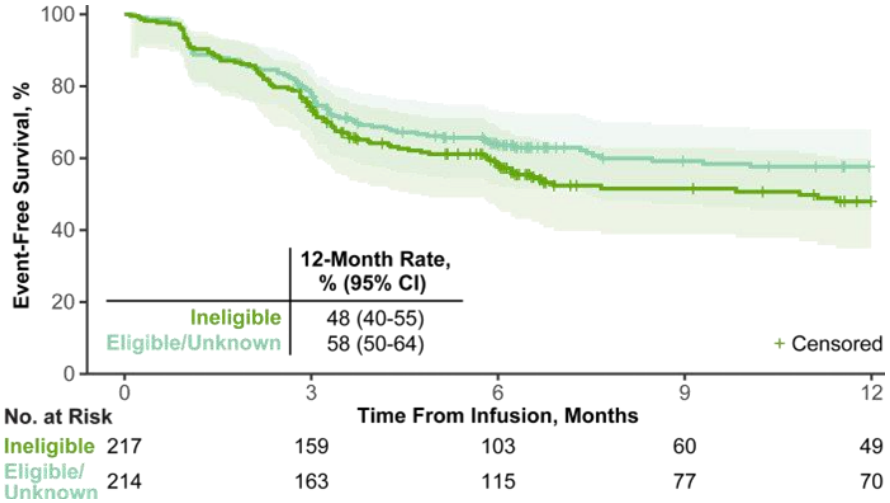
Event-free survival



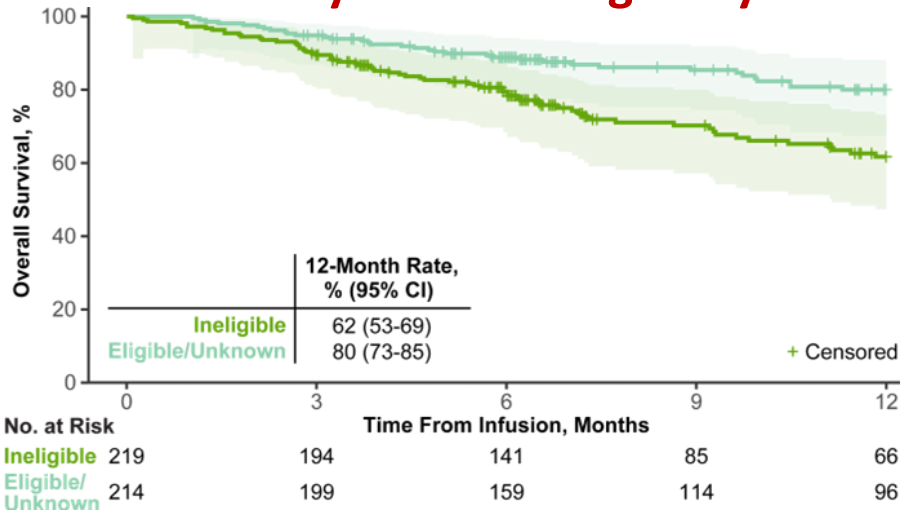
Overall survival



EFS by ZUMA-7 Eligibility



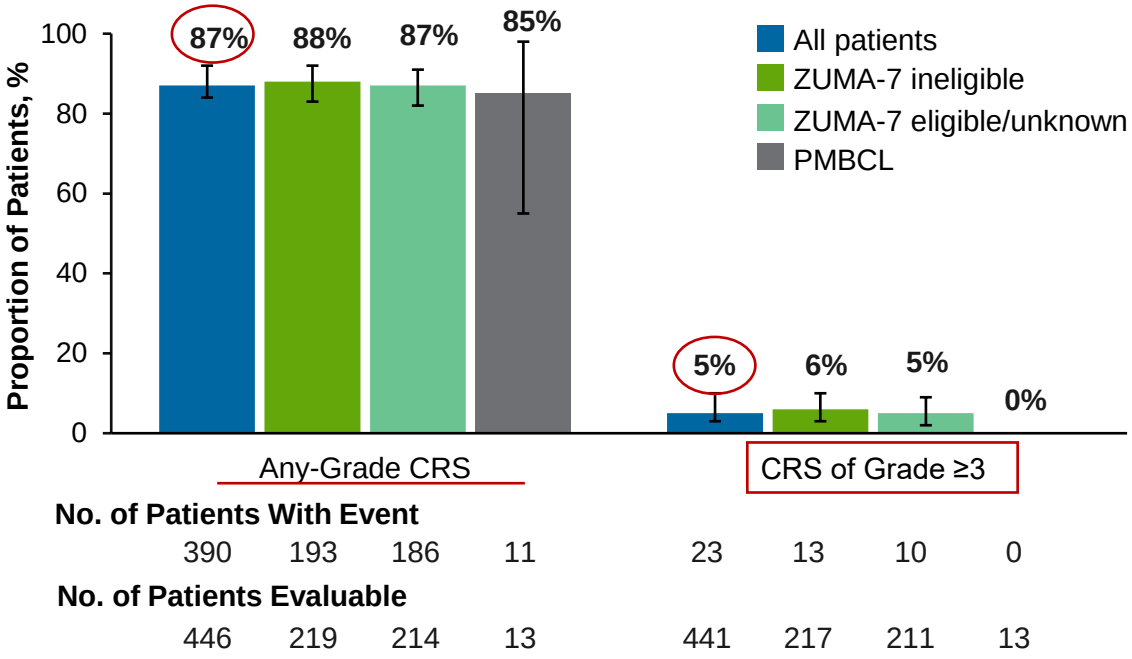
OS by ZUMA-7 Eligibility



Lee *et al.* ASH 2024 (Abstract 526)

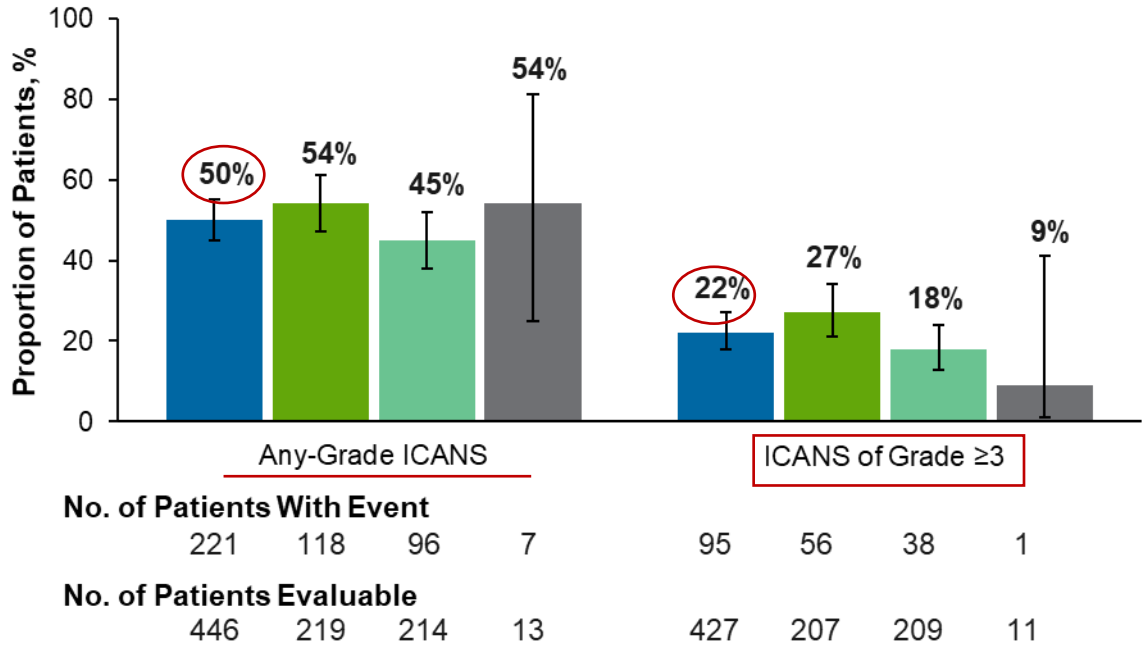
RWE Axi-cel in second line in US : Toxicity

Incidence of CRS



Incidence of any-grade CRS and Grade ≥3 CRS were similar across patient groups

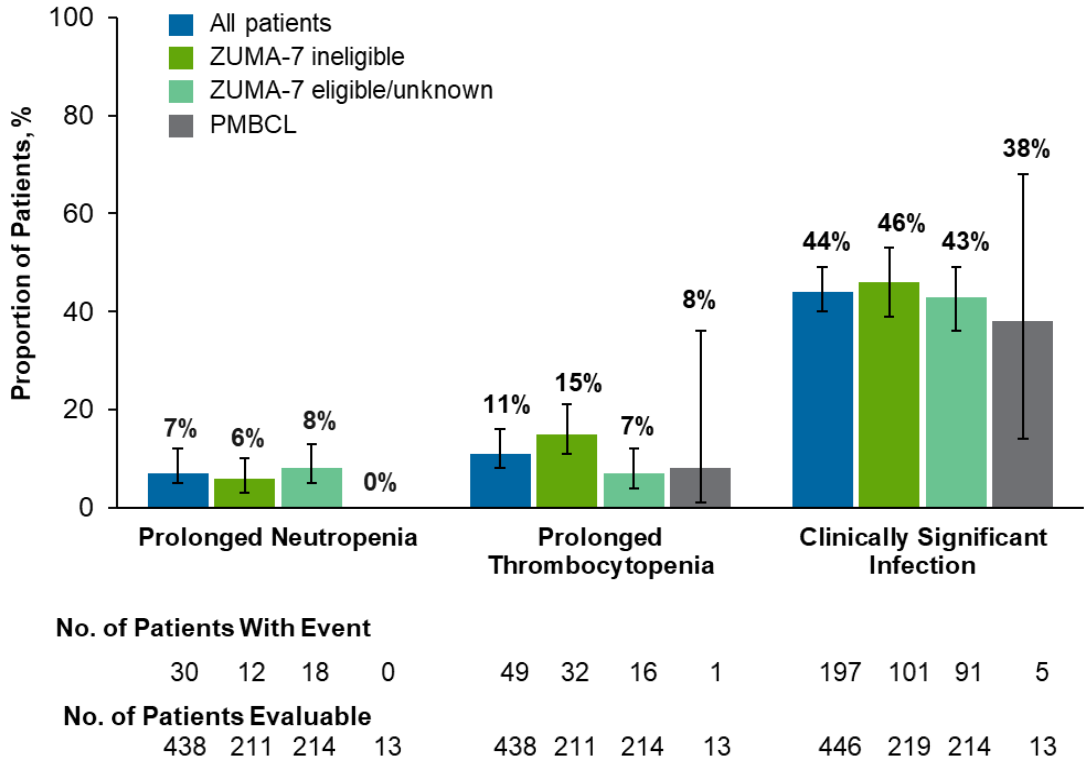
Incidence of ICANS



Incidence of any-grade ICANS and Grade ≥3 ICANS were similar across patient groups

The most common treatments given for CRS and/or ICANS were tocilizumab (80%), corticosteroids (65%), antiepileptics (19%), and anakinra (18%)

RWE Axi-cel in second line in US : Prolonged cytopenias and infections



- Incidence of prolonged cytopenia and infections were similar across patient groups[a,b]
- Prolonged neutropenia and thrombocytopenia occurred in 7% and 11% of all patients, respectively
- Almost half the patients (44%) had clinically significant infections

Cumulative incidence of non-relapse mortality at 6 months: 4 %

- Across all patient populations (median follow-up, 12 months), the primary cause of death was primary disease

Real-World Outcomes of Lisocabtagene Maraleucel as Second-Line Therapy in Patients with R/R LBCL: First Results from the Center for International Blood and Marrow Transplant Research Registry (CIBMTR)

N=157 patients

N=105 (67%) patients were ineligible for TRANSFORM (primarily due to age and/or severity of comorbidities)

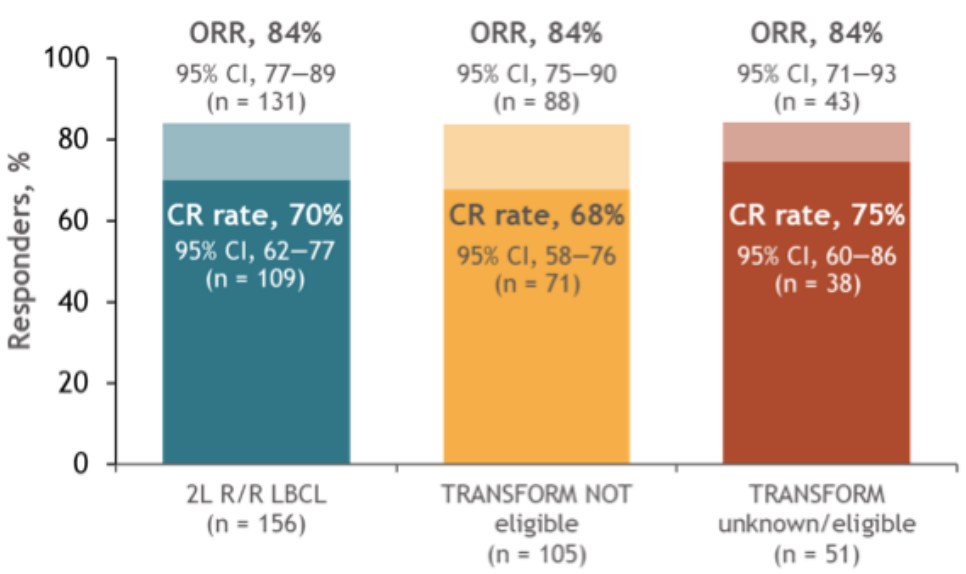
	2L R/R LBCL (n = 157)
Median (range) age,[a] y	72 (27—85)
Male, n (%)	90 (57)
Histology, n (%)	
DLBCL[b]	132 (84)
Activated B-cell type	57 (36)
Germinal center B-cell type	61 (39)
NOS	13 (8)
THRBCL	1 (1)
High-grade B-cell lymphoma	18 (11)
Other, including PMBCL	7 (4)
Disease status at time of infusion, n (%)	
Active disease	137/156 (88)
Primary refractory	79 (50)
Early relapse[c]	76 (48)
CNS involvement, n (%)	5 (3)

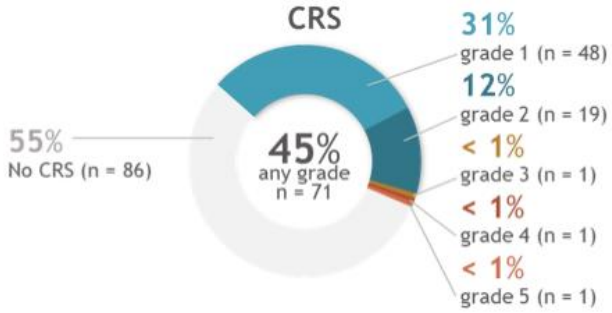
	2L R/R LBCL (n = 157)
ECOG PS, n/N (%)	
0—1	128/135 (95)
2 / 3—4	7/135 (5) / 0
Patients with ≥ 1 comorbidity, n/N (%)	76/126 (60)
Cardiac[d]	34/126 (27)
Pulmonary[d]	22/126 (17)
Obesity[d]	15/126 (12)
Elevated LDH at infusion, n/N (%)	62/151 (41)
Prior therapeutic exposure, n (%)	
Received R-CHOP	137 (87)
Single regimen	89 (65)
Intrathecal therapy	23 (15)
Radiation therapy	35 (22)
Bridging therapy, n (%)	113 (72)

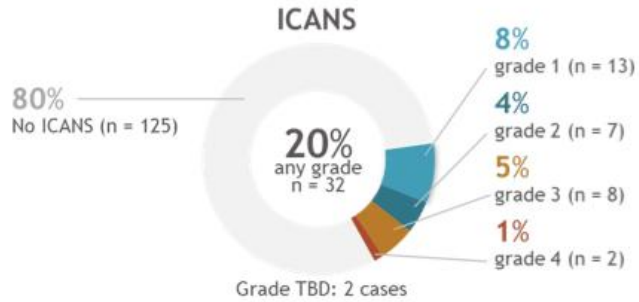
Bobillo MS, et al. ASH 2024 [Abstract 470]

Real-World Outcomes of Lisocabtagene Maraleucel as Second-Line Therapy in Patients with R/R LBCL: First Results from the Center for International Blood and Marrow Transplant Research Registry (CIBMTR)

median FU 6.4 (0.3-13.8) months







	2L R/R LBCL (n = 157)
6-mo cumulative incidence of NRM (95% CI)	1.3 (0.3—4.3)
6-mo cumulative incidence of relapse/progression or death due to primary disease (95% CI)	37.9 (29.6—46.0)

Results support Liso-cel as 2^SOC for pts, young and old alike with R/R LBLC for ASCT

Bobillo MS, et al. ASH 2024 [Abstract 470]

ARTICLE OPEN www.nature.com/bcj Blood Cancer Journal

Double hit & double expressor lymphomas: a multicenter analysis of survival outcomes with CD19-directed CAR T-cell therapy

	DHL *n* (%)	DEL *n* (%)	Other *n* (%)	*P* value
Number[a]	80	74	179	--
Age at CAR-T, median	58	60	59	0.6
Female sex	31 (40.8)	28 (39.4)	59 (34.7)	0.6
De novo DLBCL	61 (76.3)	56 (75.7)	146 (81.6)	0.5
GCB COO	41 (87.2)	36 (58.1)	82 (54.7)	<0.001
IPI ≥4 at diagnosis	12 (21.1)	13 (21.0)	27 (18.6)	0.9
Elevated LDH at diagnosis	41 (80.4)	44 (74.6)	80 (58.4)	0.006
LDH elevated at apheresis	44 (61.1)	32 (45.1)	90 (53.9)	0.2
Stage ≥3 at diagnosis	68 (89.5)	61 (87.1)	135 (80.4)	0.1
Bulky disease at diagnosis	24 (31.2)	27 (39.7)	36 (21.2)	0.01
CAR-T given second line	16 (20.0)	9 (12.2)	19 (10.6)	0.1
AutoHCT prior to CART	15 (19.7)	22 (31.0)	48 (28.2)	0.3
Bridging therapy	29 (38.2)	43 (60.6)	76 (44.7)	0.02
R/R within 12 mon of initial CIT	59 (74.7)	46 (62.2)	116 (66.3)	0.2
Time apheresis to CAR-T, mon, median	1.1	0.9	1.1	0.9
CAR-T on clinical trial	25 (31.3)	11 (15.1)	46 (25.7)	0.06
CAR-T product				0.3
Axi-cel	54 (67.5)	51 (69.9)	112 (62.9)	--
Tisa-cel	21 (26.3)	16 (21.9)	40 (22.5)	--
Liso-cel	5 (6.3)	6 (8.2)	26 (14.6)	--
Grade ≥3 CRS	14 (23.0)	10 (17.9)	19 (14.1)	0.3
Grade ≥3 ICANS	15 (30.6)	17 (38.6)	34 (34.0)	0.7

From 2015–2021 across 13 academic institutions in the United States (n=536)

- 80 patients with DHL **(20%)**
- CART response rates were similar for DHL vs DEL vs other (ORR 69 vs 64 vs 66%, p = 0.8; CR rate 49 vs 42 vs 48%, p = 0.6)
- Predictive Factor of inferior PFS (MVA):
  - 2 lines of therapy pre-apheresis
  - Use of BT
  - Elevated LDH

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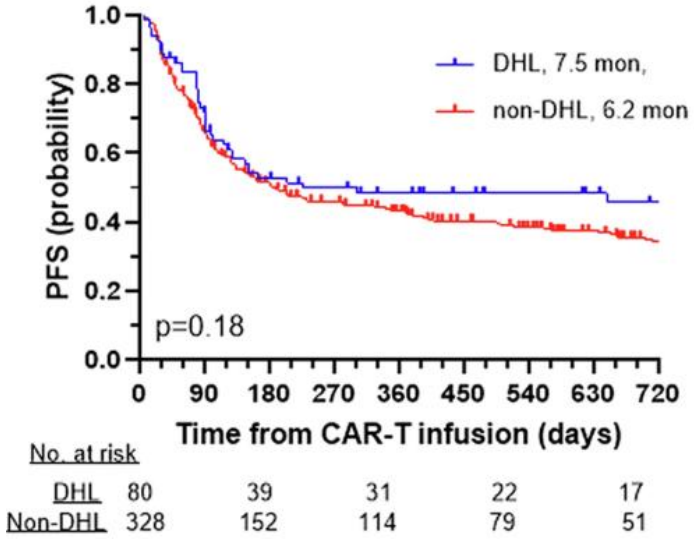
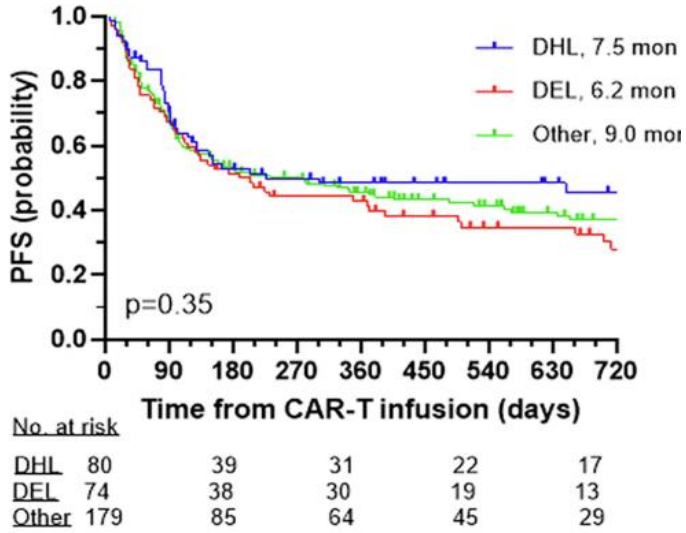
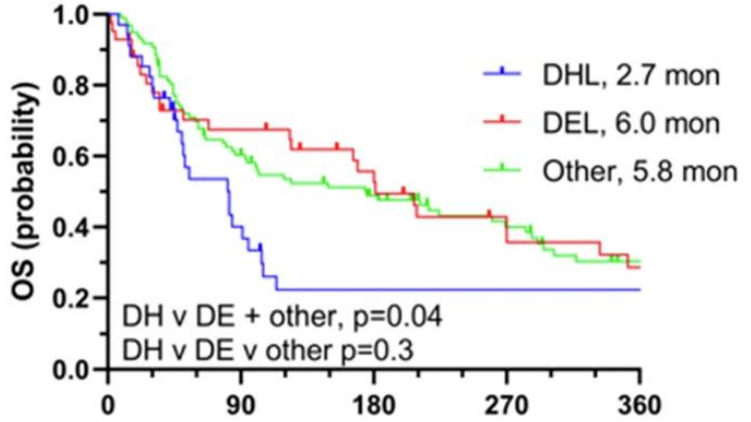
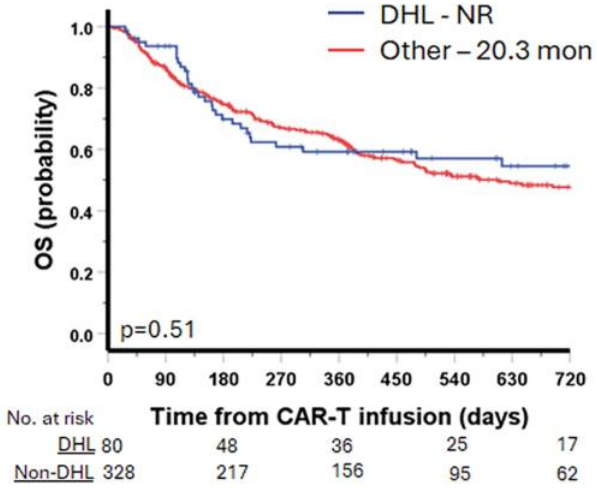
Progression-free and overall survival: DHL vs non DHL

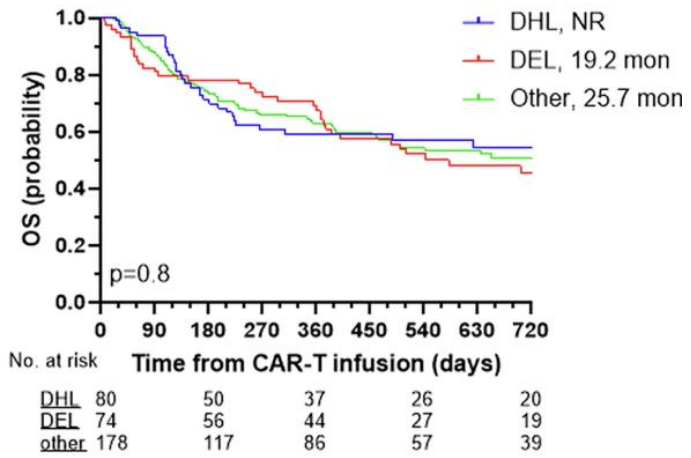




Overall survival after CART progression







Patients with DHL have dismal outcomes with a mOS of less than 3 months following CART progression

✓ **median follow-up was 17.7 months**

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Early identification & referral of candidates to 2L axi-cel

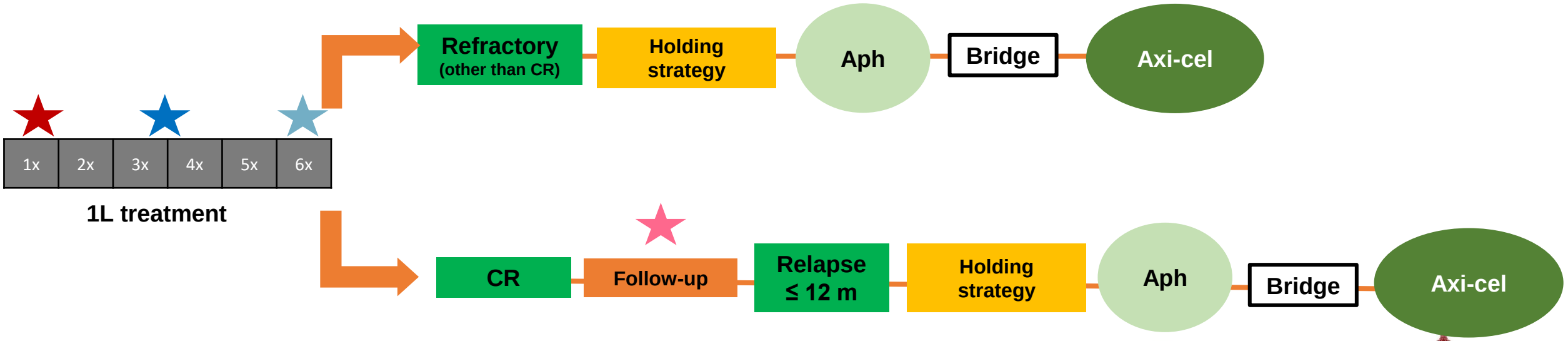
Diagnosis of high-risk disease (high IPI score, DH Lymphomas, HGBL NOS, Bulky?, other)

Interim Evaluation

- PD or SD→ Patient Referral
- PR → Discuss with CAR-T Expert

End of Treatment evaluation (active disease → Patient Referral)

Ensure identification of early relapse, active follow-up



Take Home Messages

- Real-world study results confirm the findings of registration trials, demonstrating superior efficacy of CAR-T therapy compared to standard treatment even in second-line DLBCL patients

- In real-world studies, both lisocabtagene maraleucel (liso-cel) and axicabtagene ciloleucel (axi-cel) have demonstrated comparable efficacy in terms of survival and response outcomes; however, liso-cel appears to exhibit a more favorable safety profile.

- CART cell therapy can overcome the poor prognostic impact of DHL and DEL DLBCL in the relapsed/refractory setting

- A strong relationship between referral and CART centers is needed to offer CART therapy to a larger number of patients

Grazie per l’attenzione