GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Convegno Educazionale GITMO

LE TERAPIE CELLULARI IN EMATOLOGIA
TRA PASSATO, PRESENTE E FUTURO

Brescia, 28-29 novembre 2025

Centro Paolo VI

CAR-T: INDICAZIONI ED EFFICACIA:
Linfoma follicolare: possiamo eradicare la malattia?

REGIONE DEL VENETO
ULSS8 BERICA

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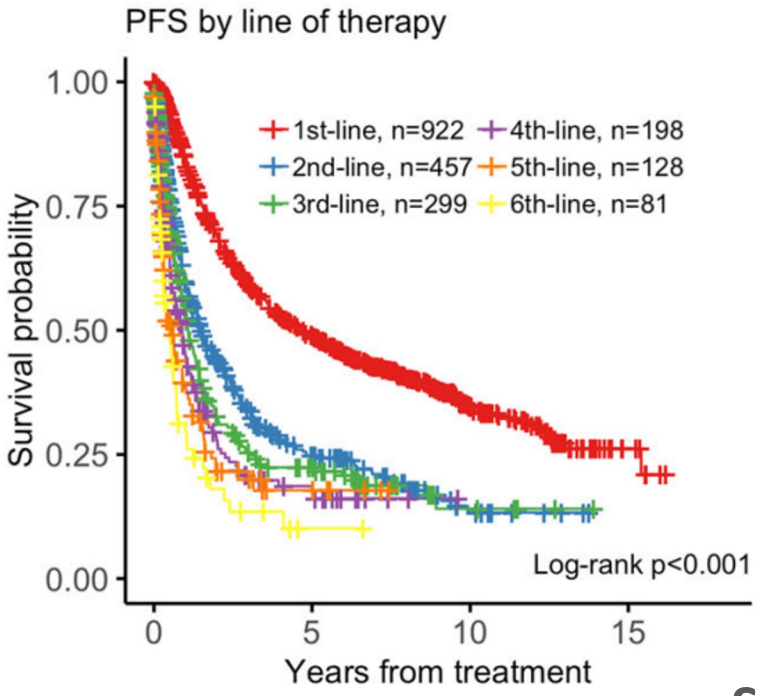
Disclosures of Tisi Maria Chiara

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Incyte					X	X	
BMS					X	X	
Gilead Science					X	X	
Novartis					X	X	
Beigene						X	
Roche					X	X	
Abbvie						X	
Lilly					X		
Sobi					X	X	

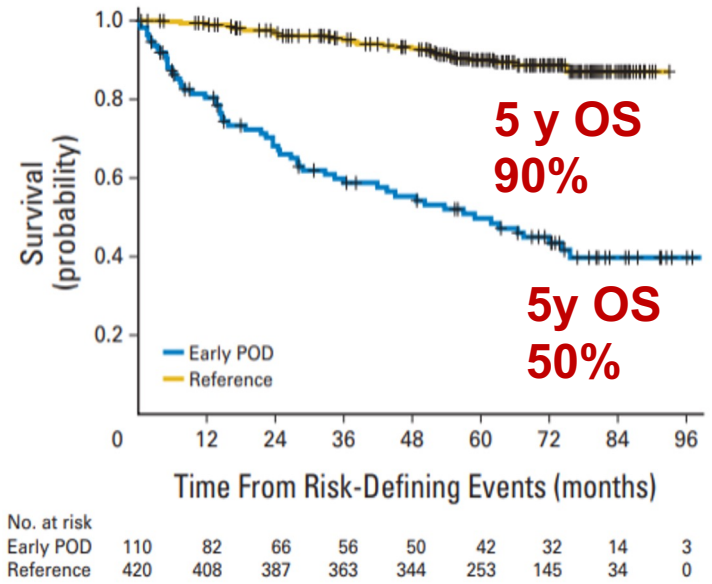
Outcomes of FL with each progressive line of therapy

FL is typically responsive to 1L therapy, but may later become refractory
Outcomes continue to worsen with each subsequent line of therapy



therapy line	PFS (median y)	OS (median y)
1° line	4.73	NR
2° line	1.51	11.67
3° line	1.07	8.75
4° line	0.9	5.34
5° line	0.55	3.13
6° line	0.48	1.93

(POD24) ~20% of patients with FL relapse within 24 months of chemoimmunotherapy



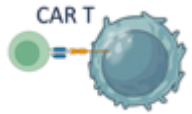
Shorter DOR to subsequent treatments

Batlevi CL, et al. Blood Cancer J. 2020; Rivas-Delgrado et al. BHJ, 2019

Casulo C, et al. JCO 2015; Casulo C, Barr PM. Blood. 2019; Batlevi CL, et al. Blood Cancer J. 2020

CAR T-cell for the Treatment of R/R Follicular Lymphoma

CAR-T											
Agent and trial	**Phase**	**Infused Pts, n**	**POD24, %**	**Prior tx median**	**BT, %**	**Median time for infusion, days**	**ORR (CR),%**	**Follow-up median mo**	**PFS median mo**	**OS, median mo**	**CRS-ICANS (any/ gr ≥3), %**
Tisa-cel (ELARA)[1,2,3]	II	97	62	4 (2-13)	45	53*	86 (68)	**53**	24mo: 58	24mo: 88	48/0 4/1
Axi-cel (ZUMA-5)[4,5]	II	124	55	3 (2-4)	4	41^	94 (79)	**62**	60mo: 50	NR	97/8 56/15
Liso-cel[6,7] **(TRANSCEND-FL)**	I/II	101	43	3 (2-10)	NA	NA	97 (94)	**24**	NR	NR	58/1 15/2



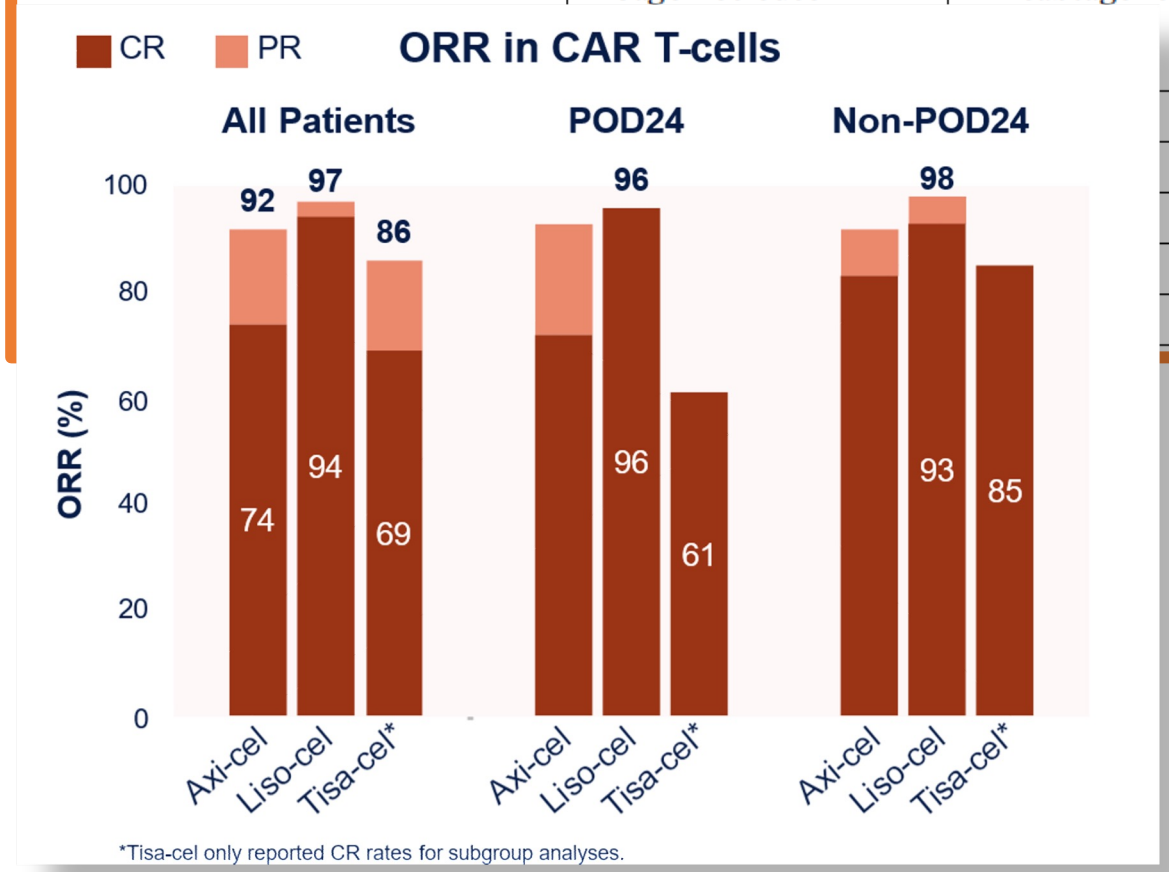
Cooming Soon ASH 2025:
- ELARA: 61 mo (5y) update
- TRANSCEND – FL: 3Y update

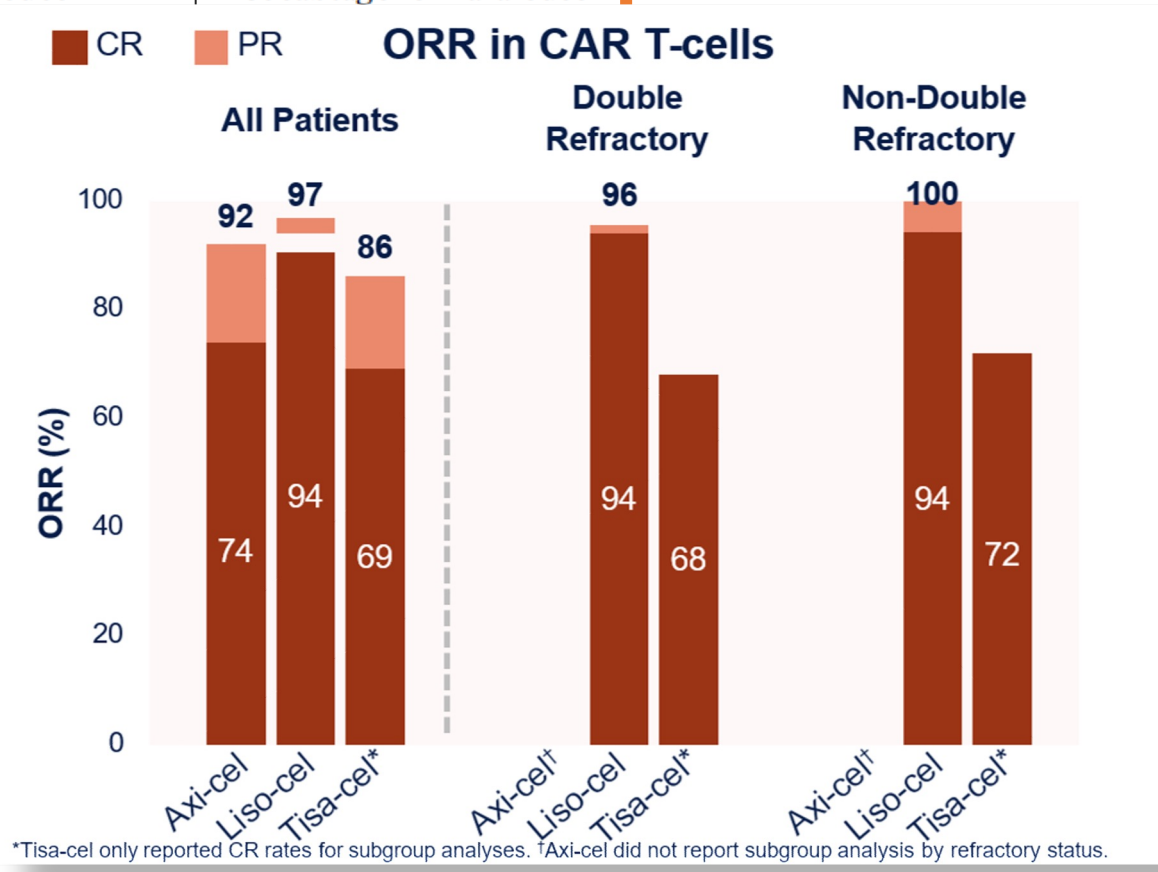
**median time from enrollment to infusion; ^ median time from leukapheresis to infusion*

1. Dreyling M. et al. Blood 2024. 2. Fowler N.H. et al, Nature Med 2022, 3. Thieblemont C. et al. ICML 2025; 4 Jacobson A.C. et al, Lancet Oncol 2022; 23: 91–103. 5 Neelapu S. et al. ASH 2024. 6. Morschauser F et al. Nature 2024 . 7. Nastoupil L. et al. ASH 2024

Pivotal studies: Patients and Disease Characteristics and Response rates

	Tisagenlecleucel	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel





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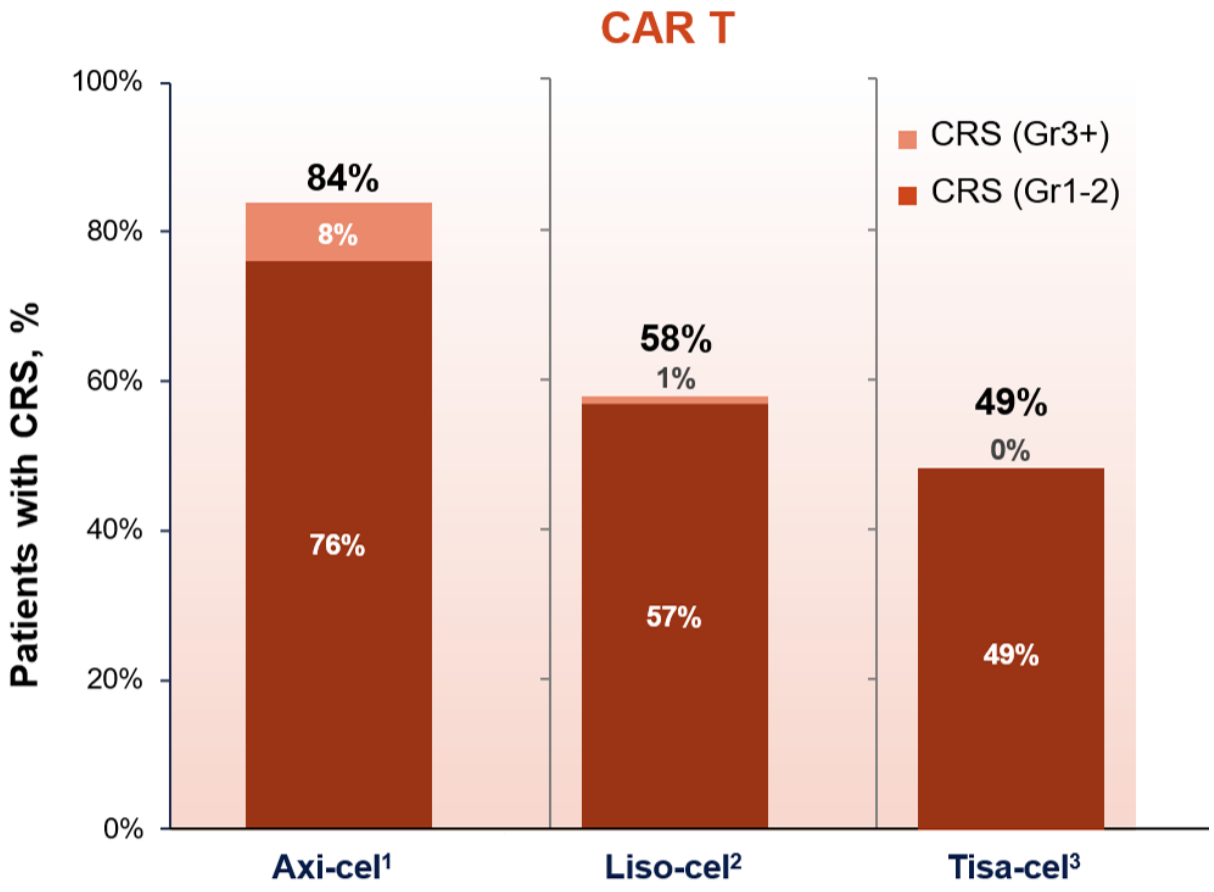
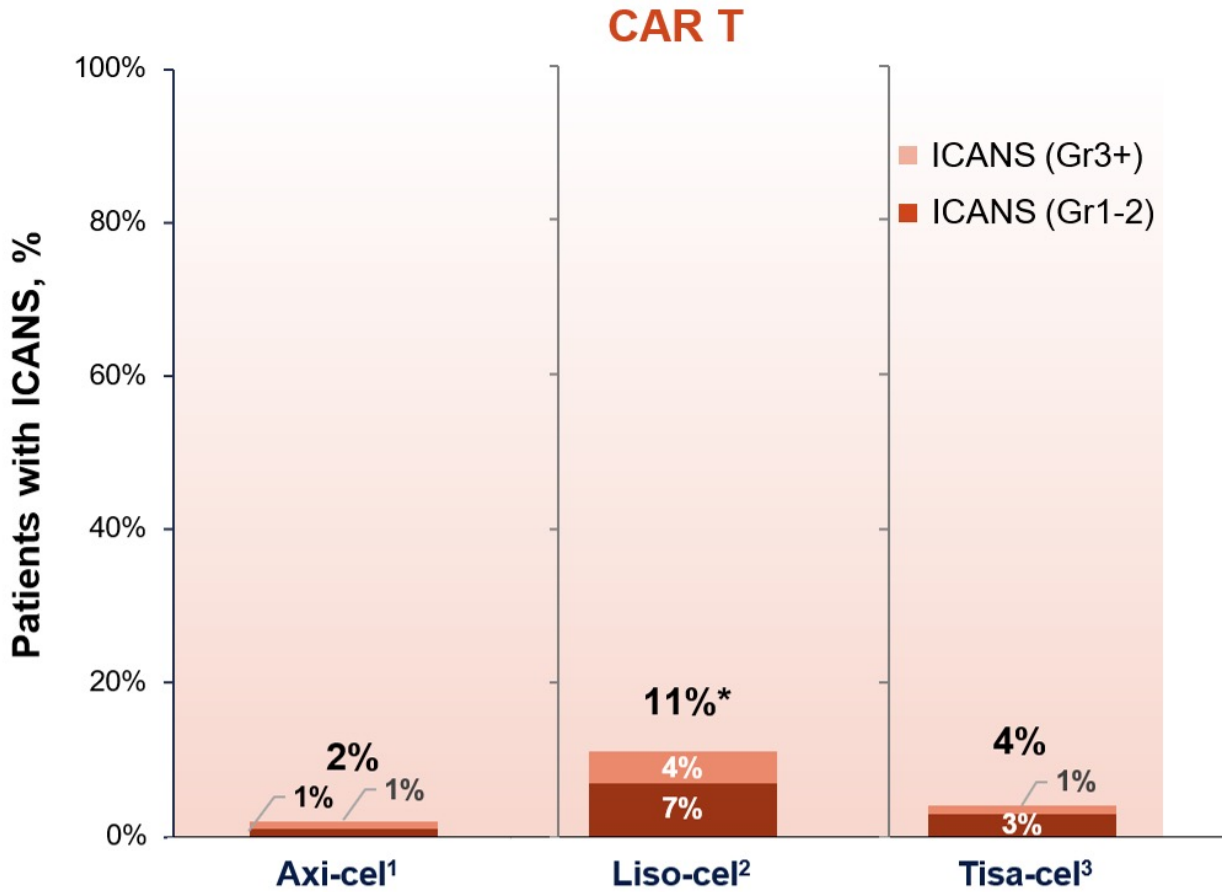
Pivotal studies: Specific Adverse Events





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ELARA: subgroups analysis for CR

Tisa-Cel in RR FL

- In subgroup analyses, most baseline high-risk disease characteristics (double-refractory disease, bulky disease, POD24, and high FLIPI) were not associated with inferior overall or complete response
- The one exception to this was patients with a high metabolic tumor volume.

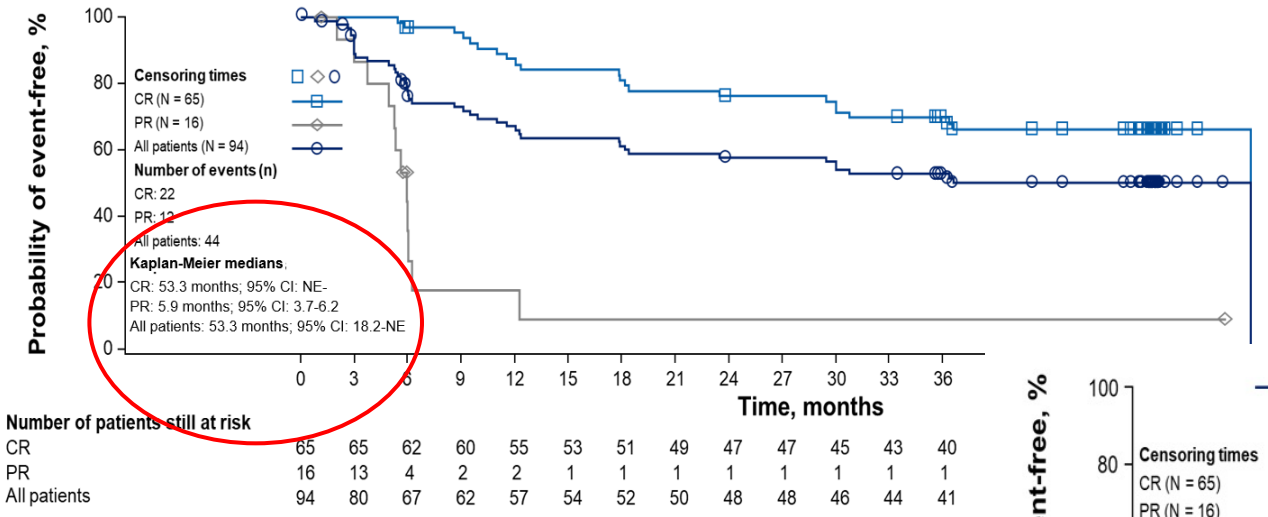
		CRR, n/N (%)	[95% CI]
All patients	All patients (N = 94)	65/94 (69.1)	[58.8-78.3]
Age	<65 years (N = 70)	46/70 (65.7)	[53.4-76.7]
	≥65 years (N = 24)	19/24 (79.2)	[57.8-92.9]
Sex	Female (N = 30)	22/30 (73.3)	[54.1-87.7]
	Male (N = 64)	43/64 (67.2)	[54.3-78.4]
Race	Asian (N = 11)	9/11 (81.8)	[8.2-97.7]
	White (N = 79)	54/79 (68.4)	[56.9-78.4]
Ethnicity	Not Hispanic or Latino (N = 87)	60/87 (69.0)	[58.1-78.5]
FLIPI at study entry	Low/Intermediate (N = 37)	29/37 (78.4)	[61.8-90.2]
	High (N = 57)	36/57 (63.2)	[49.3-75.6]
Histological grade	1-2 (N = 85)	59/85 (69.4)	[58.5-79.0]
	3A (N = 9)	6/9 (66.7)	[29.9-92.5]
Number of prior lines	≤2 lines (N = 24)	14/24 (58.3)	[36.6-77.9]
	3-4 lines (N = 43)	35/43 (81.4)	[66.6-91.6]
	>4 lines (N = 27)	16/27 (59.3)	[38.8-77.6]
PI3K inhibitor use	Pre-treated (N = 19)	15/19 (78.9)	[54.4-93.9]
	Naive (N = 75)	50/75 (66.7)	[54.8-77.1]
Prior HSCT therapy	Yes (N = 35)	22/35 (62.9)	[44.9-78.5]
	Relapsed ≤12 months (N = 14)	10/14 (71.4)	[41.9-91.6]
	Relapsed >12 months (N = 21)	12/21 (57.1)	[34.0-78.2]
	No (N = 59)	43/59 (72.9)	[59.7-83.6]
Disease status to last line	Refractory (N = 74)	52/74 (70.3)	[58.5-80.3]
	Relapsed (N = 17)	11/17 (64.7)	[38.3-85.8]
POD24	Yes (N = 61)	37/61 (60.7)	[47.3-72.9]
	No (N = 33)	28/33 (84.8)	[68.1-94.9]
Bulky disease at baseline	Yes (N = 62)	41/62 (66.1)	[53.0-77.7]
	No (N = 32)	24/32 (75.0)	[56.6-88.5]
Bridging therapy	Yes (N = 44)	29/44 (65.9)	[50.1-79.5]
	No (N = 50)	36/50 (72.0)	[57.5-83.8]
LDH at study entry	≤ULN (N = 53)	39/53 (73.6)	[59.7-84.7]
	>ULN (N = 41)	26/41 (63.4)	[46.9-77.9]
Prior R2 use	Pre-treated (N = 16)	12/16 (75.0)	[47.6-92.7]
	Naive (N = 78)	53/78 (67.9)	[56.4-78.1]
US sites	Yes (N = 26)	17/26 (65.4)	[44.3-82.8]
	No (N = 68)	48/68 (70.6)	[58.3-81.0]
Double refractory	Yes (N = 65)	44/65 (67.7)	[54.9-78.8]
	No (N = 29)	21/29 (72.4)	[52.8-87.3]
MTV at baseline	High tumor burden (N = 20)	8/20 (40.0)	[19.1-63.9]
	Low tumor burden (N = 72)	55/72 (76.4)	[64.9-85.6]

C. Thieblemont et al, Oral presented n.138 at the 18th International Conference on Malignant Lymphoma, June 17–21, 2025, Lugano, Switzerland

ELARA: survival

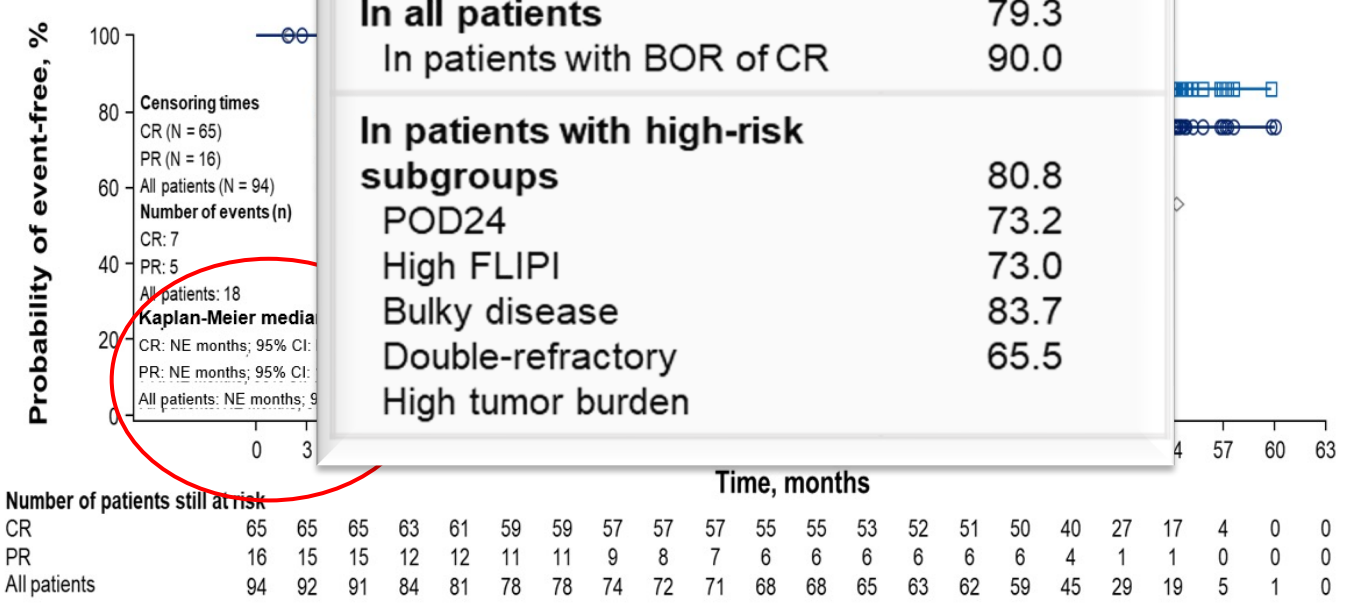
Durable and High Responses Reported

Median follow-up:
53 months (Range 46-62)



	48-mo PFS, %
In all patients	50.2
In patients with BOR of CR	66.1

- High response post-infusion (C



	48-mo OS, %
In all patients	79.3
In patients with BOR of CR	90.0
In patients with high-risk subgroups	80.8
POD24	73.2
High FLIPI	73.0
Bulky disease	83.7
Double-refractory	65.5
High tumor burden	

C. Thieblemont et al, Oral presented n.138 at the 18th International Conference on Malignant Lymphoma, June 17–21, 2025, Lugano, Switzerland

ELARA: Exploratory Biomarker Analyses Reported Higher MRD-negativity Rate

MRD[a]-Negative Rate by Timing After Tisagenlecleucel Infusion

	N = 31[b], % (n/N)
Day 28	82.0 (22/27)
Month 3	75.0 (12/16)
Month 6	69.0 (11/16)
Month 12	76.0 (13/17)
Any time	90.0 (28/31)

- MRD data were available for 31 of 94 patients (33.0%)
  - **90.3% of evaluable patients (28/31) achieved MRD negativity at any time point**
  - 63.6% of patients with MRD-negative status at month 6 (7/11) are ongoing without relapse
  - All 5 patients with MRD-positive status at month 6 relapsed
- CAR transgene persistence was observed for up to 1680 days; median T_{last} was 210 days (range: 13-1680)

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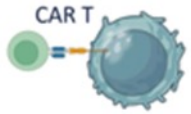
ZUMA-5: survival

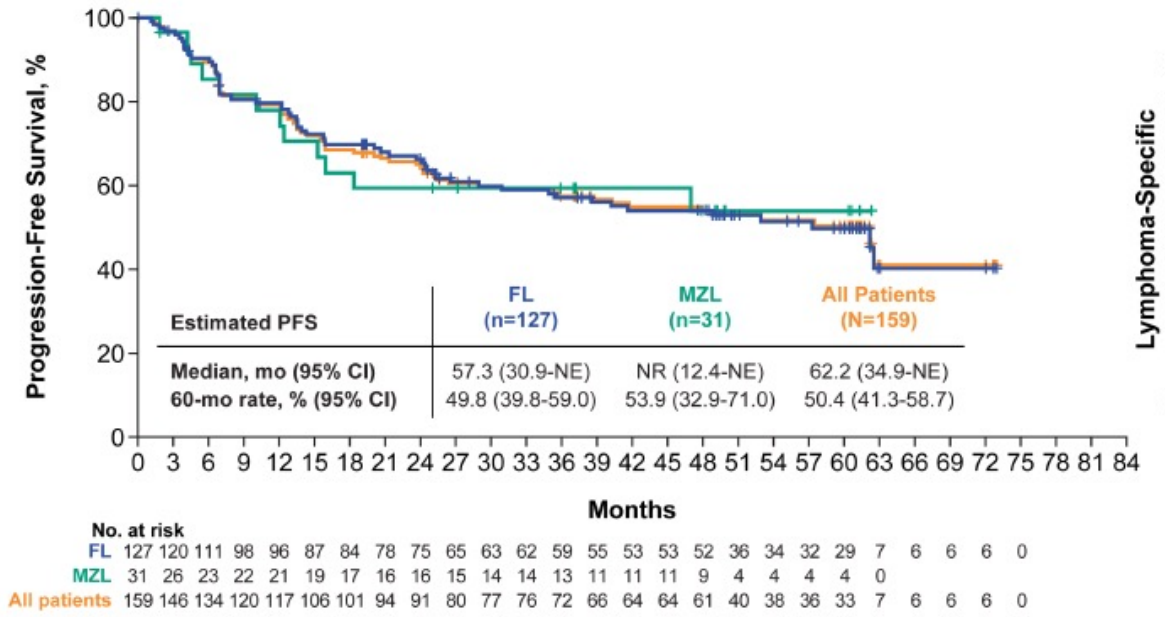
Axi-Cel in RR FL

Is there a curative potential of the novel agents?

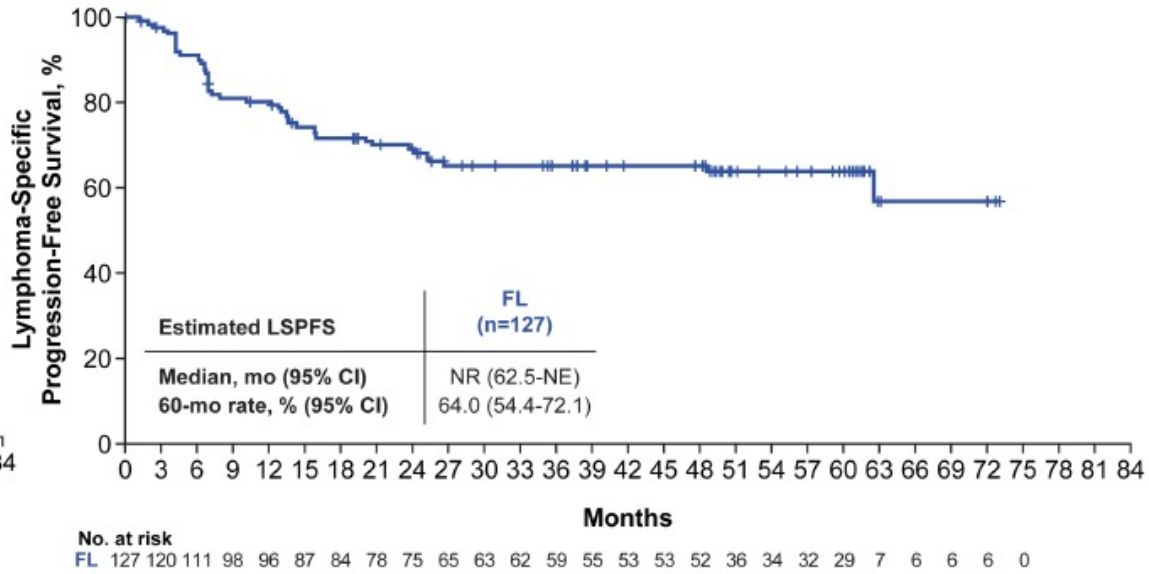


Median follow-up:
62 months

Progression-Free Survival[a]



Lymphoma-Specific Progression-Free Survival[a,b]



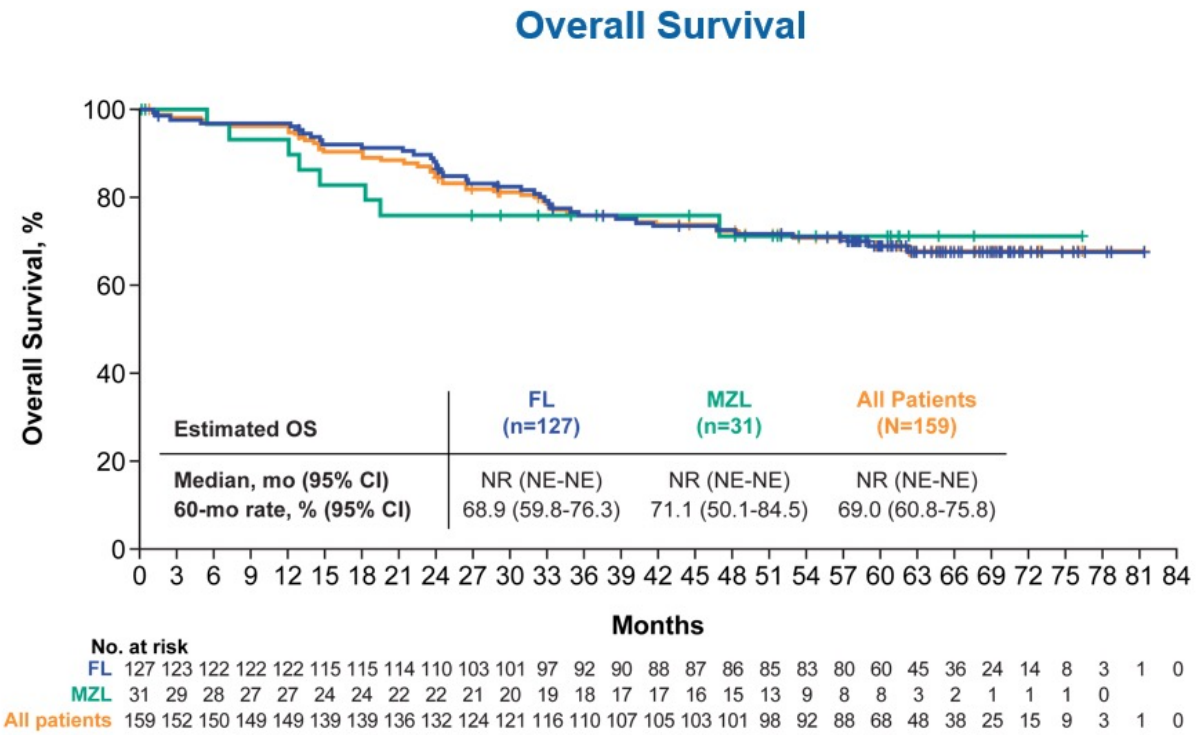
Only 4 pts progressed > 24 mo; 2 pts progressed > 30 mo

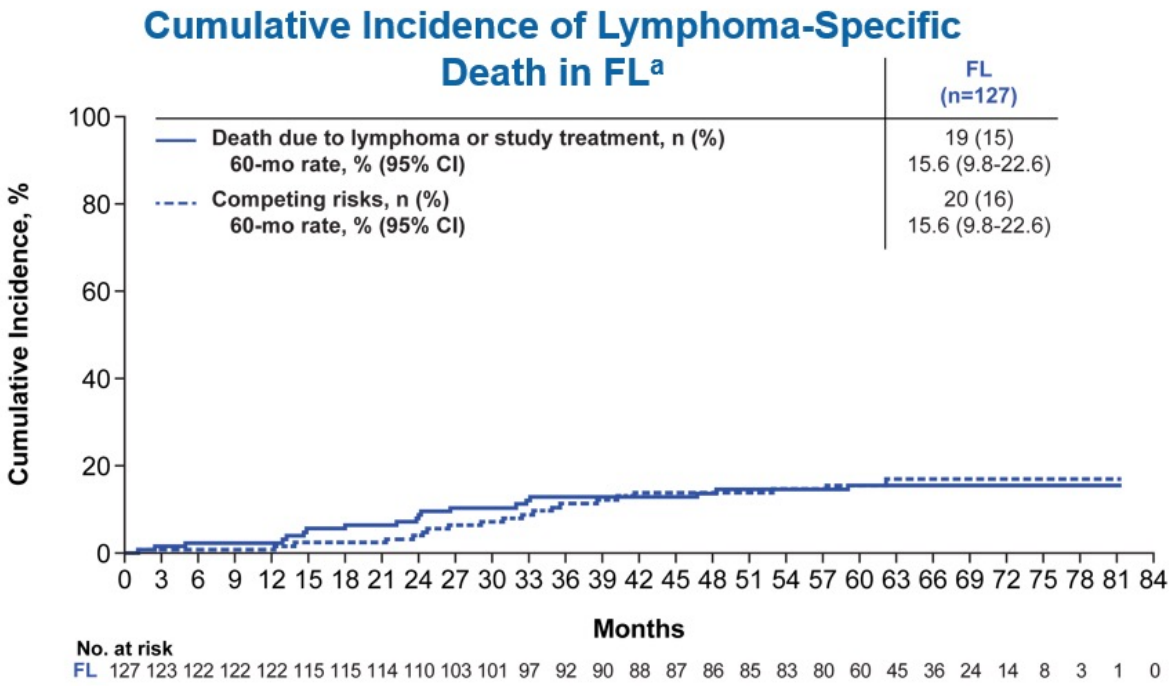
In FL, PFS events are likely to occur over a longer period, including PD- and non–PD-related events, with no obvious plateau within 2 years

Neelapu et al. ASH 2024

ZUMA-5: survival

Median follow-up:
62 months





- Median OS remained not reached[4]
- The rate of lymphoma-specific death at 60 months in FL was 15.6%
  - A total of 19 patients died due to lymphoma or study treatment (lymphoma, n=15; study treatment, n=4)

Neelapu et al. ASH 2024

ZUMA-5: long term safety and deaths by year

Following the 4-year analysis[1]:

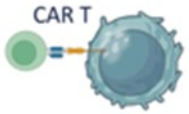
- 3 new events not related to axi-cel were reported, including Grade 3 prostate cancer, Grade 1 bladder cancer, and Grade 4 myelodysplastic syndrome
- 1 patient died due to pneumonia (not related to axi-cel)
  - No patients died of disease progression following the previous analysis

n, (%)	All Patients N=152	Years Post–Axi-Cel Infusion					
		0-1	1-2	2-3	3-4	4-5	>5
Patients who died	46 (30)	10 (7)	15 (10)	11 (7)	6 (4)	3 (2)	1 (1)
Relapse mortalities							
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)	0
Non-PD after PD	9 (6)	1 (1)	3 (2)	4 (3)	1 (1)	0	0
Non-relapse mortalities							
Secondary malignancy[a]	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0	0
Cardiac-related	3 (2)	0	1 (1)	0	1 (1)	0	1 (1)
Infection-related[b]	11 (7)	2 (1)	2 (1)	4 (3)	1 (1)	2 (1)	0
Other[c]	3 (2)	1 (1)	2 (1)	0	0	0	0

Neelapu et al. ASH 2024

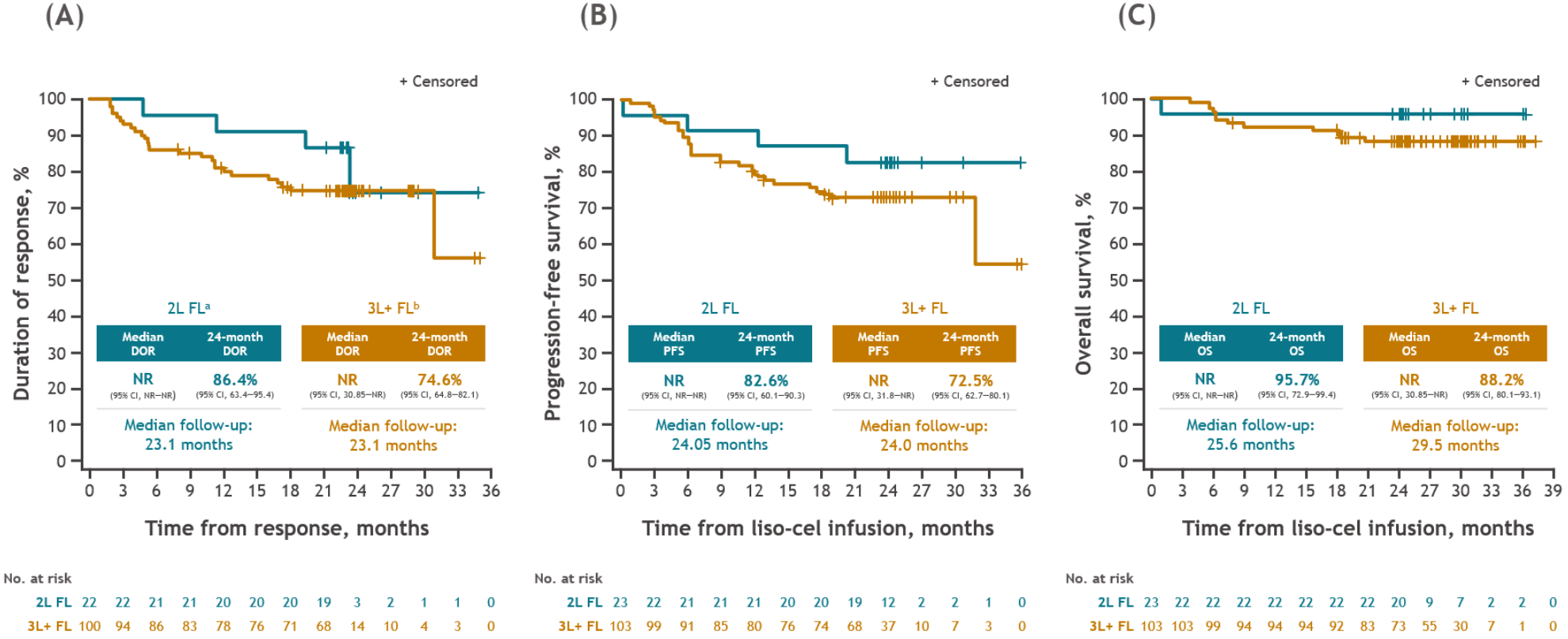
TRANSCEND FL: survival

Liso-Cel in RR FL



Median follow-up:
24 months

Efficacy outcomes after 2 years f-up (A) DOR, (B) PFS, (C) OS

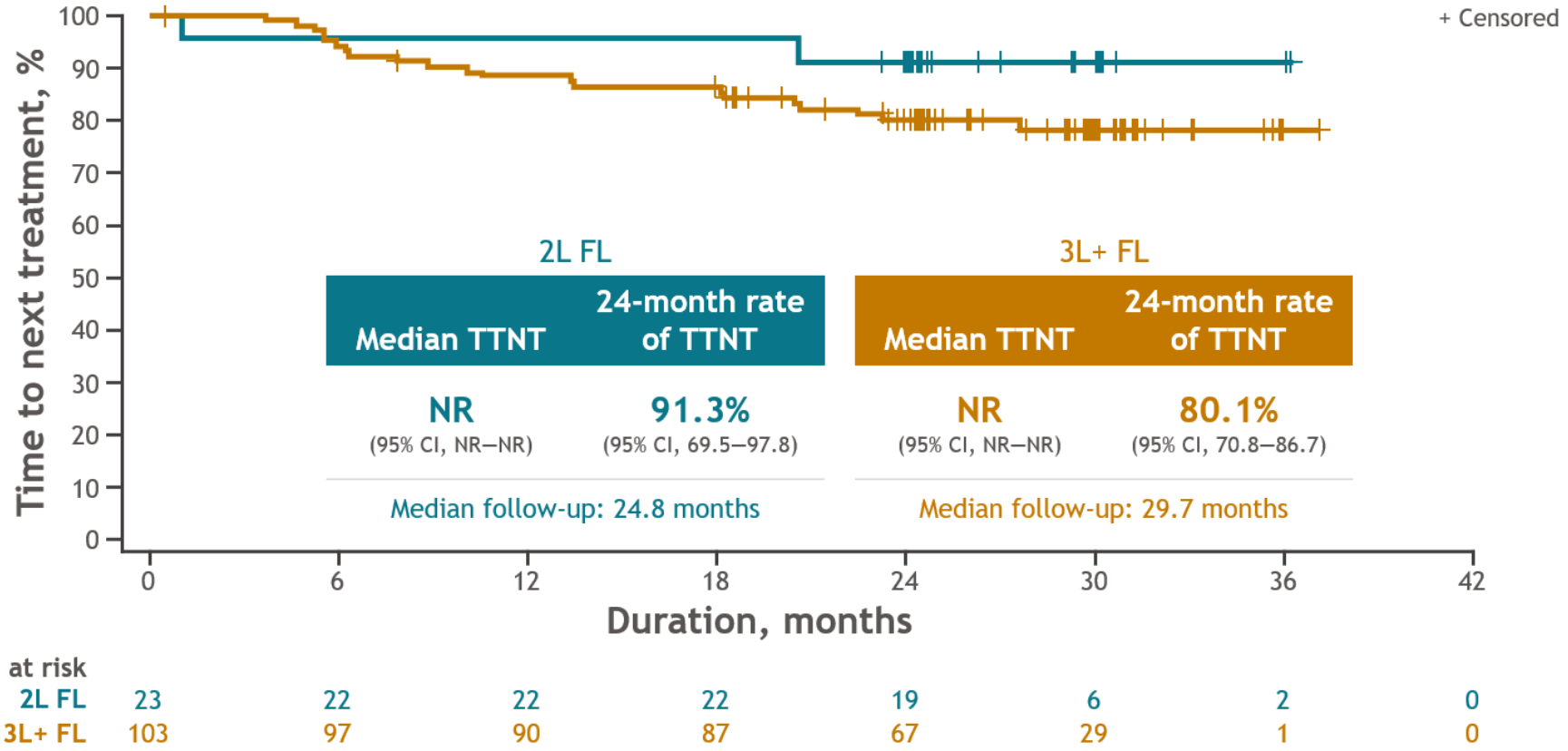


[a]Twenty-two of the 23 patients with 2L FL were responders; [b]One hundred of the 103 patients with 3L+ FL were responders.
NR, not reached.

Nastoupil L. et al. ASH 2024

TRANSCEND FL: Time to next treatment

Median follow-up:
24 months

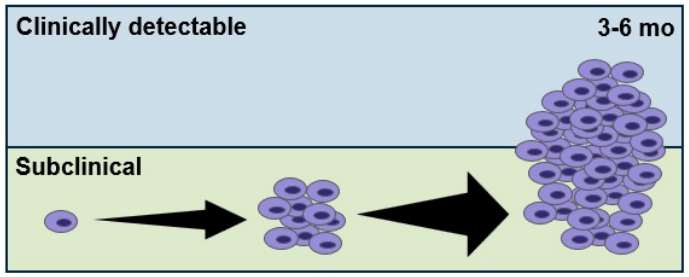


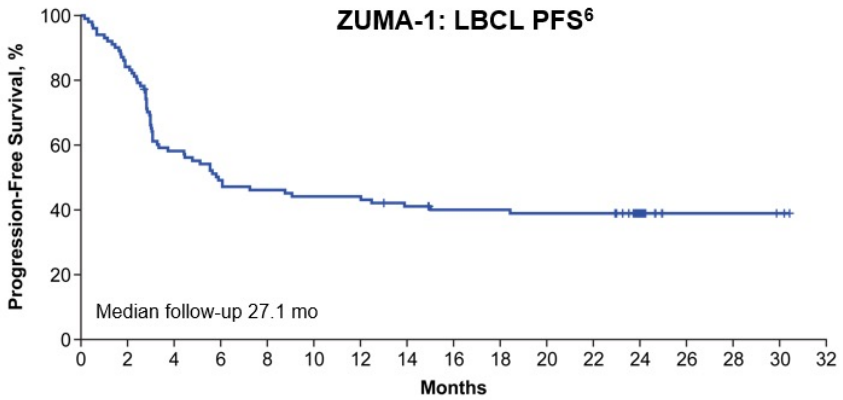
TTNT defined as time from index date to the start date of subsequent systemic treatment or death from any cause, whichever occurred first.

Nastoupil L. et al. ASH 2024

Conclusions - 1

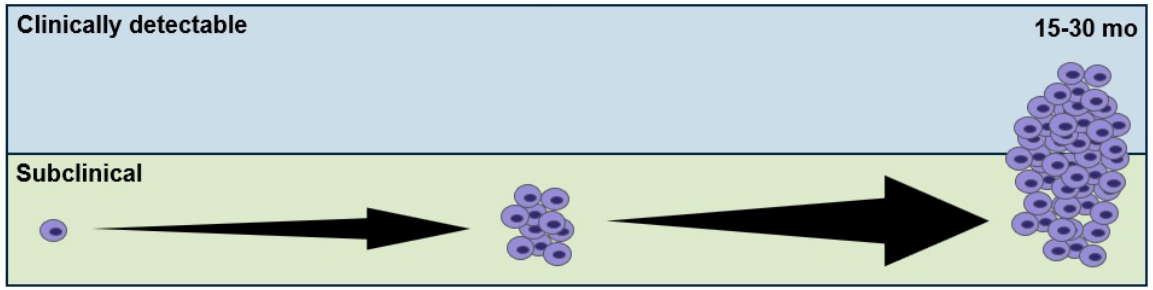
LBCL

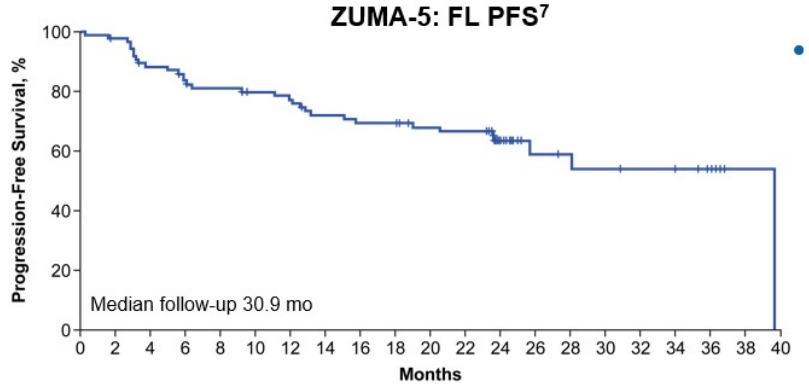




- With curative therapies in LBCL, most PFS events are PD-related, occurring early and resulting in a plateau within 2 years

FL





- In FL, PFS events are likely to occur over a longer period, including PD- and non–PD-related events, with no obvious plateau within 2 years

- Lymphoma-specific assessment of survival may be necessary to determine curative potential in FL

Adapted from Neelapu ,ASH 2024

Conclusions - 2

FUTURE PERSPECTIVES:

ZUMA 22: Axicabtagene Ciloleucel vs Standard of Care Therapy in Adult R/R Follicular Lymphoma

COMPLETED

LEDA TRIAL: A Phase III Trial Compating Tisagenlecleucel to Standard of Care (SoC) in Adult Participants With r/r Follicular Lymphoma

RECRUITING

TRANSFORM FL: A Global Randomized Multicenter Phase 3 Trial to Compare the Efficacy and Safety of Lisocabtagene Maraleucel (JCAR017/BMS-986387) to Standard of Care in Adults With Relapsed or Refractory Follicular Lymphoma

COMPLETED

Conclusions -3

- With a medium-term follow-up of pivotal studies for CART in FL, deep and durable responses are confirmed, but follow-up is still maturing
- Also patients with unfavorable disease chacteristcs have good response, with the expection of high metabolic tumor volume/bulky disease
- Patients with a rapid complete remission, MRD negative, stable remission > 3-5 years have more probability to be cured
- We have reason for cautious optimism but **true “conclusive” long-term statements** about cure, late toxicities, optimal sequencing, and survival comparisons versus existing standards still require longer randomized data and real-world validation

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