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UNIVERSITÀ DI BOLOGNA
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SCIENZE MEDICHE E CHIRURGICHE

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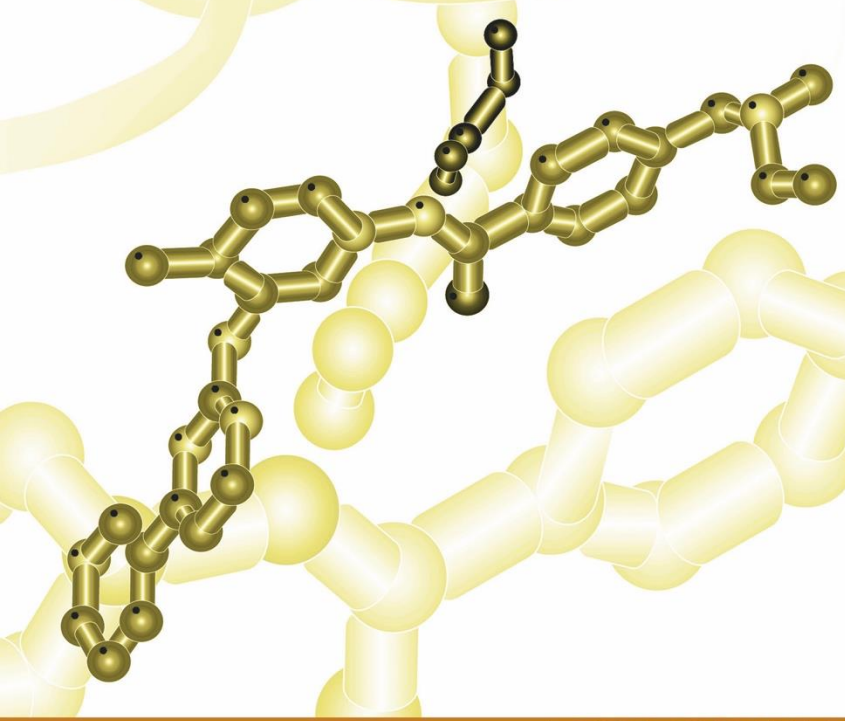

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

CAR T-cell Therapy Updates from Clinical Trials and Real-World Data: Follicular Lymphoma

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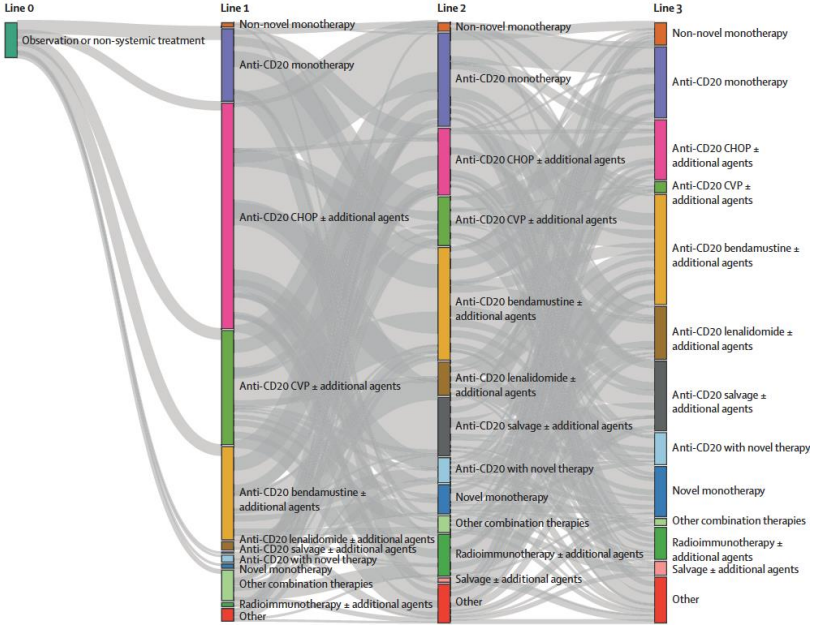
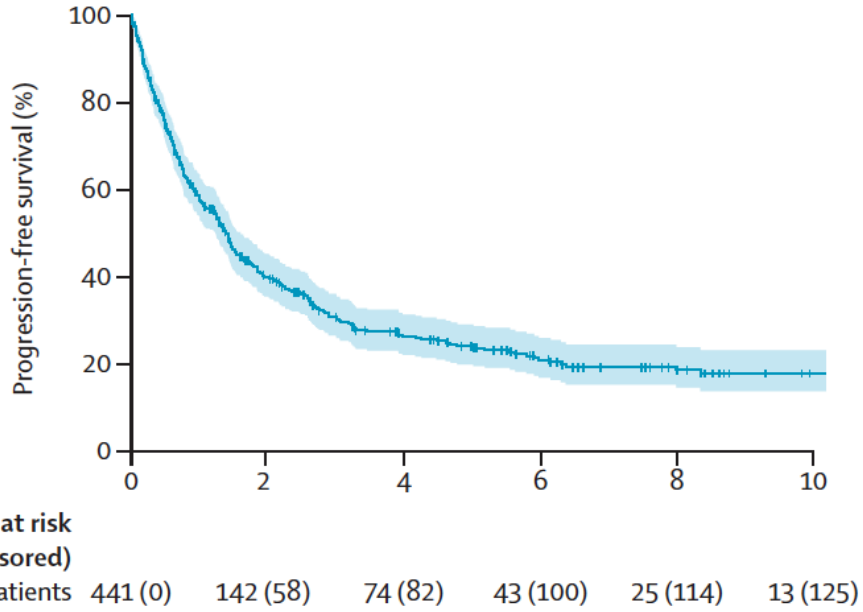
Disclosures of Caron Jacobson

- Consulting: Kite/Gilead, Novartis, BMS/Celgene, Ipsen, Miltenyi, Abintus Bio, Caribou Bio, ImmPACT Bio, Daiichi-Sankyo, Morphosys, ADC Therapeutics, Abbvie, AstraZeneca, Sana, Synthekine, Appia Bio, Janssen

- Research funding: Pfizer, Kite/Gilead

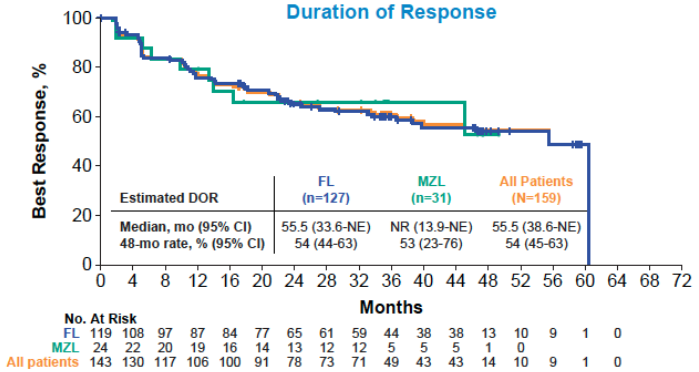
Outcomes in FL: Third Line and Beyond

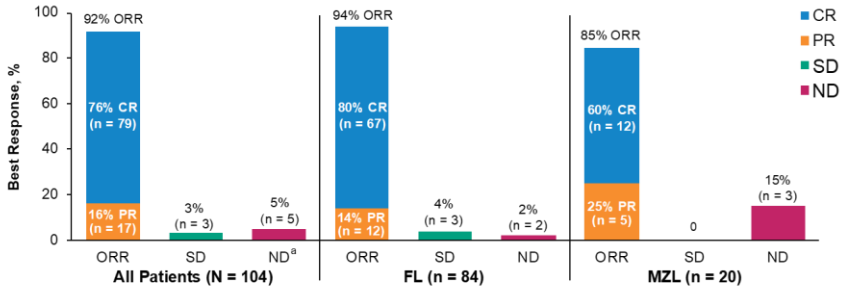


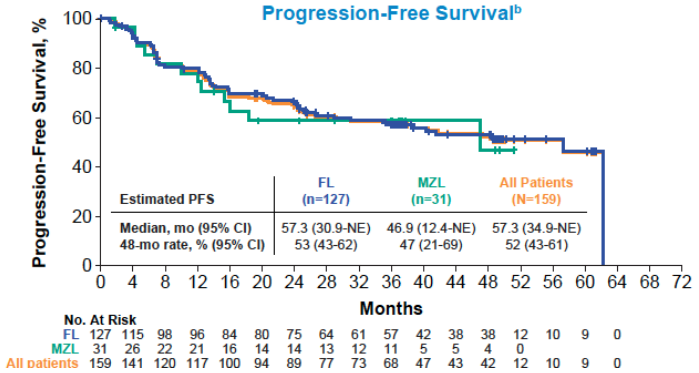


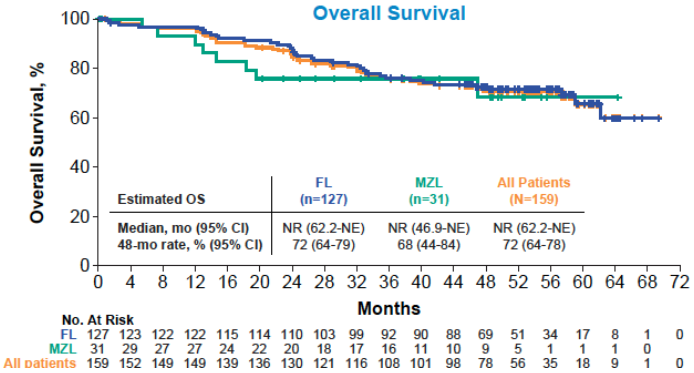
Casulo et al Lancet Haematol 2022;9:e289;

Axi-cel for iNHL: ZUMA-5



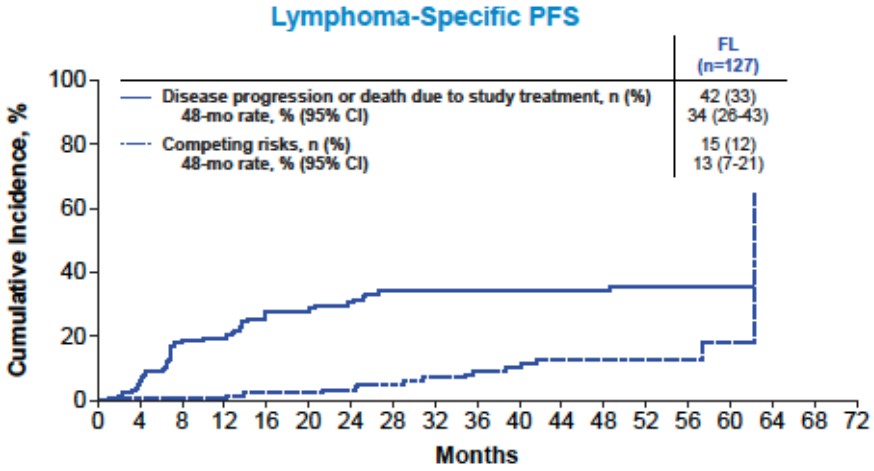


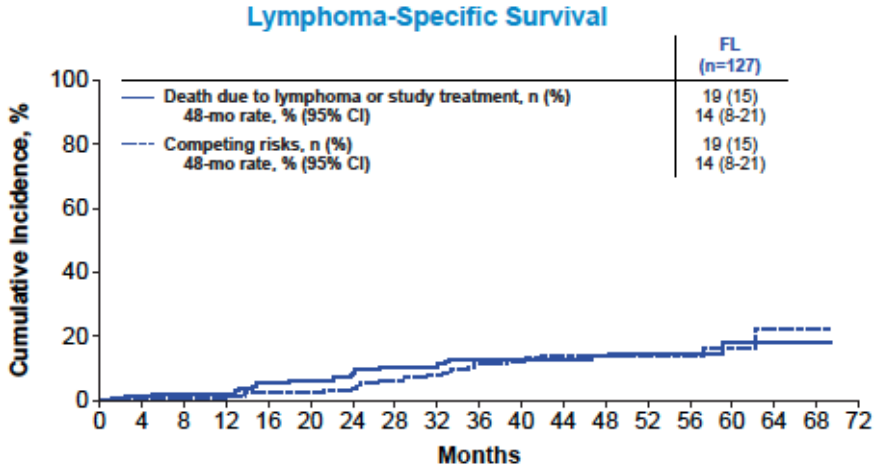




Jacobson ASH 2020; Neelapu ASH 2023

4-year ZUMA-5 Follow-Up: 1 Relapse after Month 28





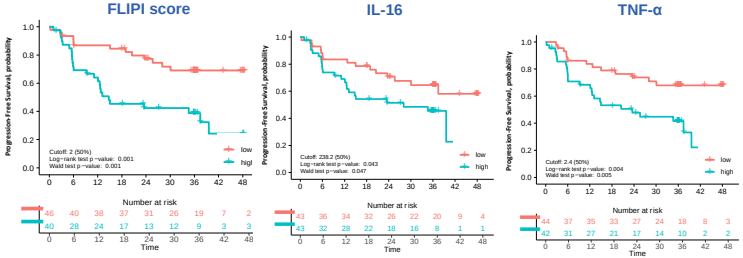
Neelapu ASH 2023

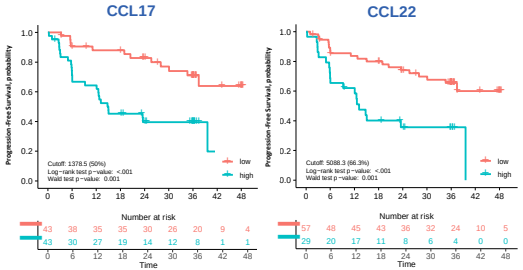
ZUMA-5 Outcomes by POD24 Status

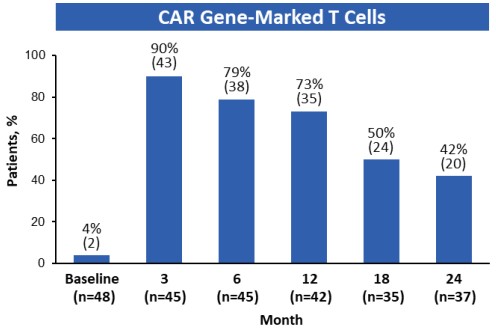
Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

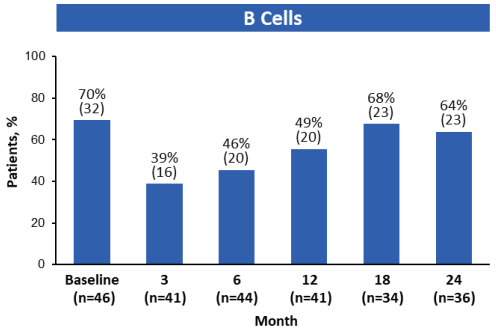
Neelapu ASH 2021

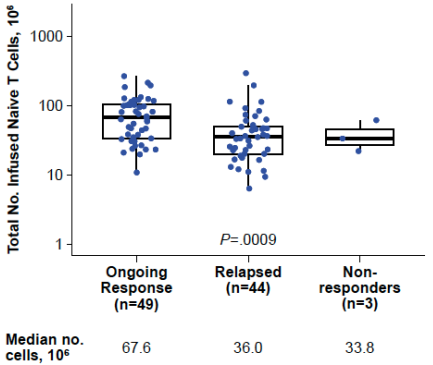
ZUMA-5 Predictors of Outcome and PK

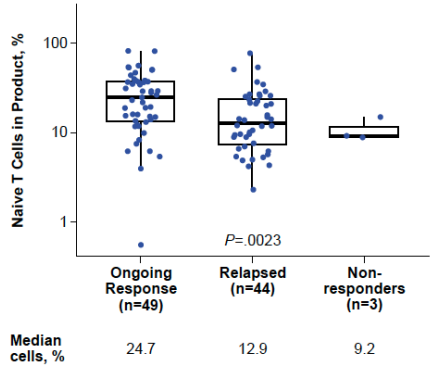












Neelapu ASH 2021, 2022, and 2023

ZUMA-5 CRS and ICANS

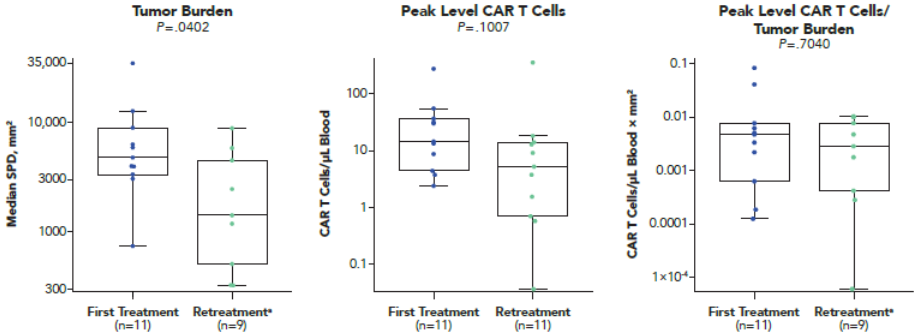
Parameter	CRS[a] FL (n=124)	CRS[a] MZL (n=22)	CRS[a] All Patients (N=146)	Neurologic Events[a] FL (n=124)	Neurologic Events[a] MZL (n=22)	Neurologic Events[a] All Patients (N=146)
Any grade	97 (78)	22 (100)	119 (82)	70 (56)	17 (77)	87 (60)
Grade ≥3	8 (6)	2 (9)	10 (7)	19 (15)	9 (41)	28 (19)
Most common CRS symptoms of any grade, n/n (%)						
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)	–	–	–
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)	–	–	–
Most common neurologic events of any grade, n/n (%)						
Tremor	–	–	–	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	–	–	–	28/70 (40)	7/17 (41)	35/87 (40)
Tocilizumab use, n (%)	56 (45)	15 (68)	71 (49)	7 (6)	2 (9)	9 (6)
Corticosteroid use, n (%)	19 (15)	6 (27)	25 (17)	38 (31)	14 (64)	52 (36)
Median time to onset (range), days	4 (1–15)	4 (1–9)	4 (1–15)	7 (1–177)	7 (3–19)	7 (1–177)
Median duration of events (range), days	6 (1–27)	6 (2–14)	6 (1–27)	14 (1–452)	10 (2–81)	14 (1–452)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]	67/70 (96)	14/17 (82)	81/87 (93)

Jacobson ASH 2020

ZUMA-5 Retreatment

Patient No.	Tumor Type	First Treatment		Retreatment Source	Retreatment	
		Best Response	DOR, months		Best Response	DOR, months
1	FL	PR	8.3	2nd bag	CR	12.0+
2	FL	CR	11.9	Re-Aph	CR	0.03+
3	FL	CR	5.3	PBMCs	PR	5.2
4	FL	CR	11.5	Re-Aph	CR	11.4+
5	FL	CR	5.0	Re-Aph	CR	2.1[a]
6	FL	CR	1.9	2nd bag	CR	4.9[a]
7	FL	CR	10.9	2nd bag	CR	13.9+
8	FL	CR	5.4	PBMCs	CR	5.0
9	FL	CR	5.0	Re-Aph	CR	7.7+
10	MZL	CR	10.6	2nd bag	CR	14.5+
11	MZL	CR	8.2	2nd bag	CR	0.03[b]
12	FL	CR	18.0	Re-Aph	PR	1.0
13	FL	SD[c]	–	PBMCs	PR	2.3

Retreatment
ORR 100%
12m estPFS 58%
Similar safety profile
Similar peak cytokines

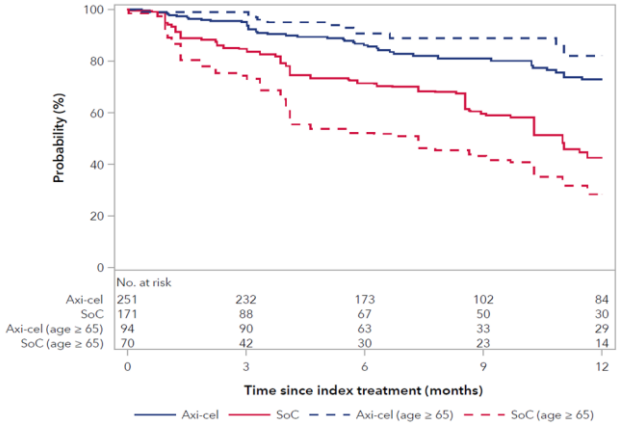


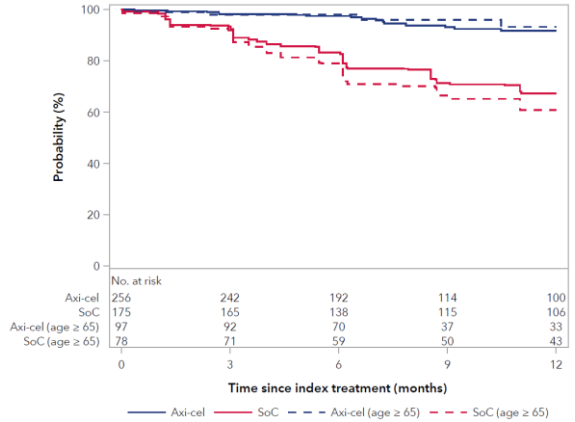
Chavez EHA 2021

ZUMA-5 vs SCHOLAR-5

Among patients who failed ≥2 prior lines of therapy (LoT)		SCHOLAR-5	ZUMA-5	Odds Ratio (95% CI)	p-value
Overall response rate	Yes	42 (49.9%)	81 (94.2%)	16.24 (5.63, 46.85)	<0.0001
	No	43 (50.1%)	5 (5.8%)		
Complete response	Yes	25 (29.9%)*	68 (79.1%) **	8.86 (4.3, 18.25)	<0.0001
	No	60 (70.1%)	18 (20.9%)		

PFS



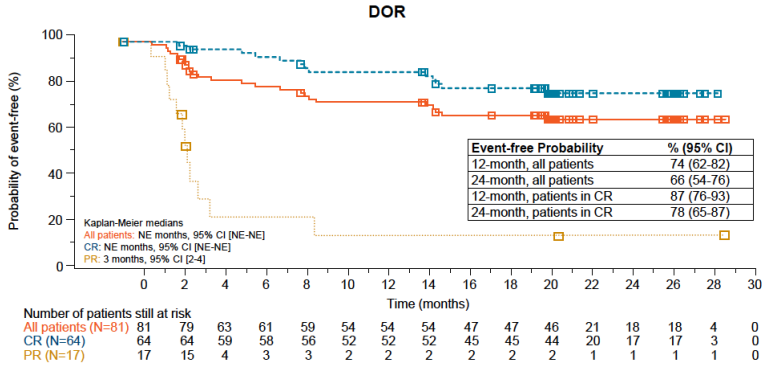


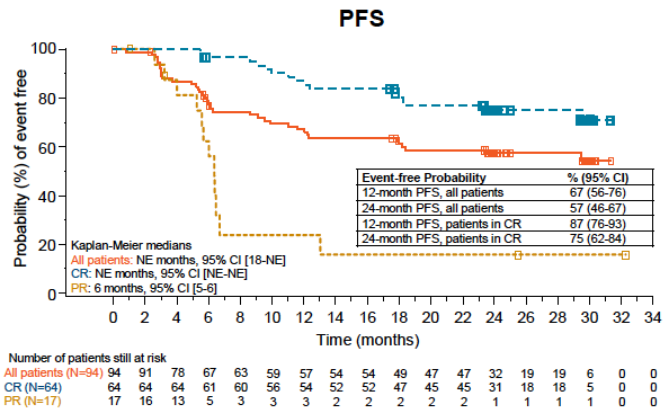
OS

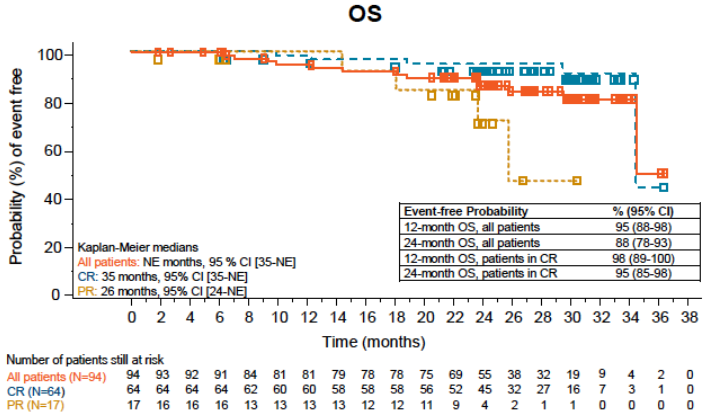
Ghione EHA 2021; Kambhampti ASH 2023

ELARA: Tisa-cel in r/r FL, Outcomes

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

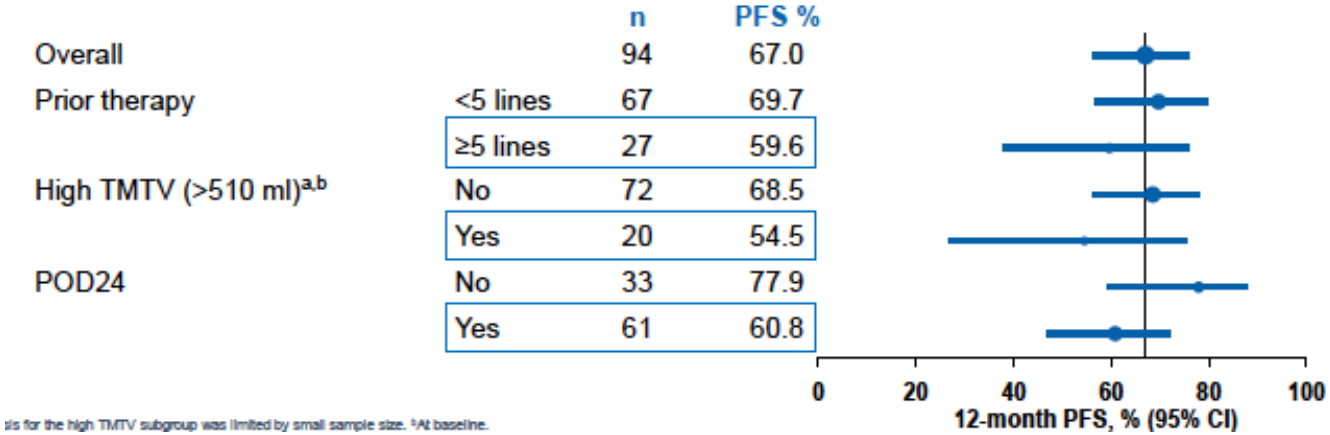






Dreyling ASH 2022

ELARA: Predictors of Outcome



sis for the high TMTV subgroup was limited by small sample size. [b]At baseline.

Disease Characteristic	Descriptive Analysis		Multivariate Analysis
	High-Risk 12-Month PFS (%)	Low-Risk 12-Month PFS (%)	Hazard Ratio (95% CI)
POD24	60.8	77.9	2.3 (1.0-5.3)
TMTV[a]	54.5	68.5	2.5 (1.3-5.6)

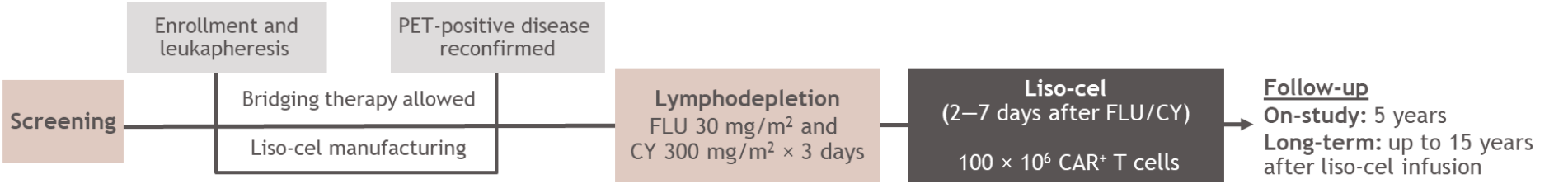
Thieblemont ASH 2021

ELARA: Toxicity

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	**All grades, %**	**Grade ≥3, %**
Cytokine release syndrome[a]	48.5	0
Serious neurological adverse reactions	9.3	1.0
Infections	18.6	4.1
Tumor lysis syndrome	1.0	0
Prolonged depletion of B cells/ agammaglobulinemia	9.3	0
Hematologic disorders including cytopenias		
Neutropenia[b,c]	28.9	24.7
Anemia[b]	22.7	12.4
Thrombocytopenia[b]	15.5	8.2

Fowler ASH 2020

TRANSCEND-FL: Liso-cel in r/r FL Study Design



Key patient eligibility criteria

- Age ≥ 18 years
- R/R FL
  - 4L+ cohort
  - 3L cohort
  - 2L cohort (POD24 and/or GELF)
- FL histologically confirmed ≤ 6 months before screening with PET-positive and measurable disease
- Received combination of anti-CD20 antibody and alkylator
- ECOG PS ≤ 1
- Adequate bone marrow, kidney, liver, and cardiac function

Primary endpoint

- ORR (BOR of CR or PR) per IRC by PET/CT using Lugano 2014 criteria[1] in the efficacy set

Secondary endpoints

- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by PET/CT using Lugano 2014 criteria[1] in the efficacy set
- OS
- Safety, cellular kinetics, HRQOL

Exploratory endpoint

- B-cell aplasia

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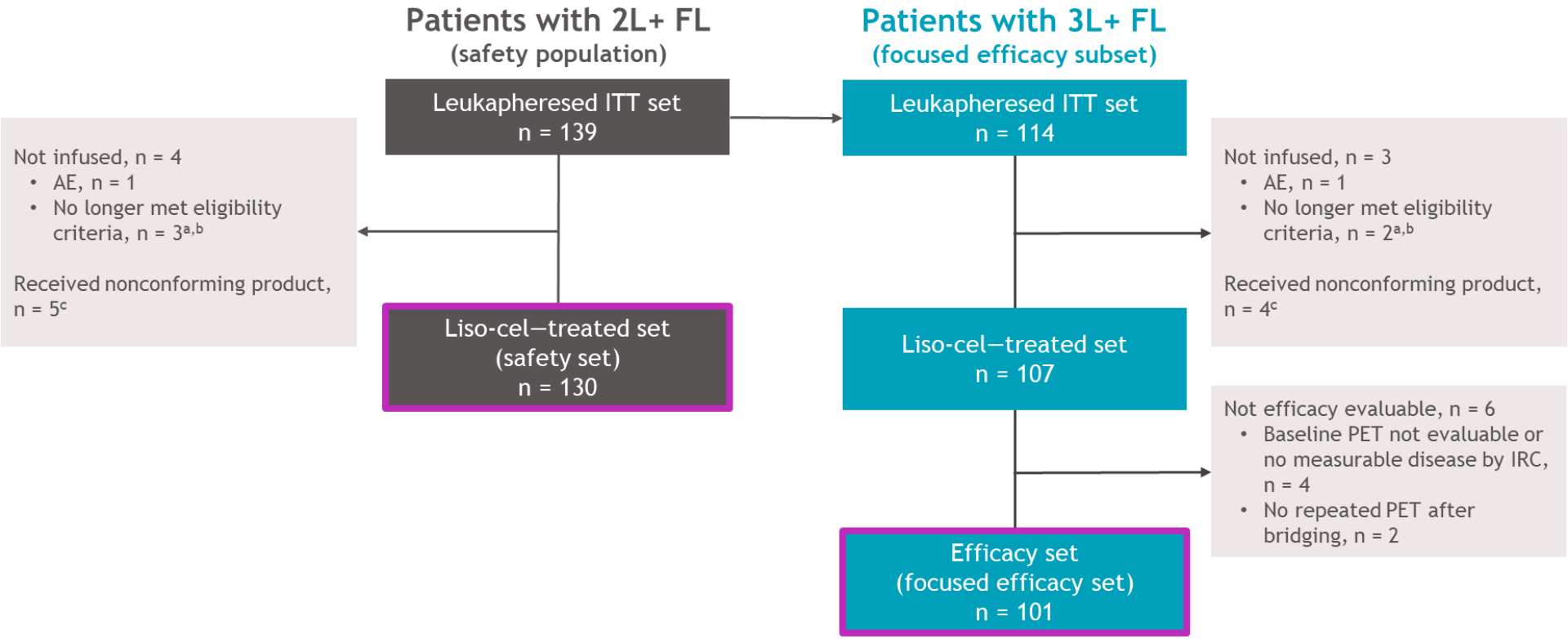
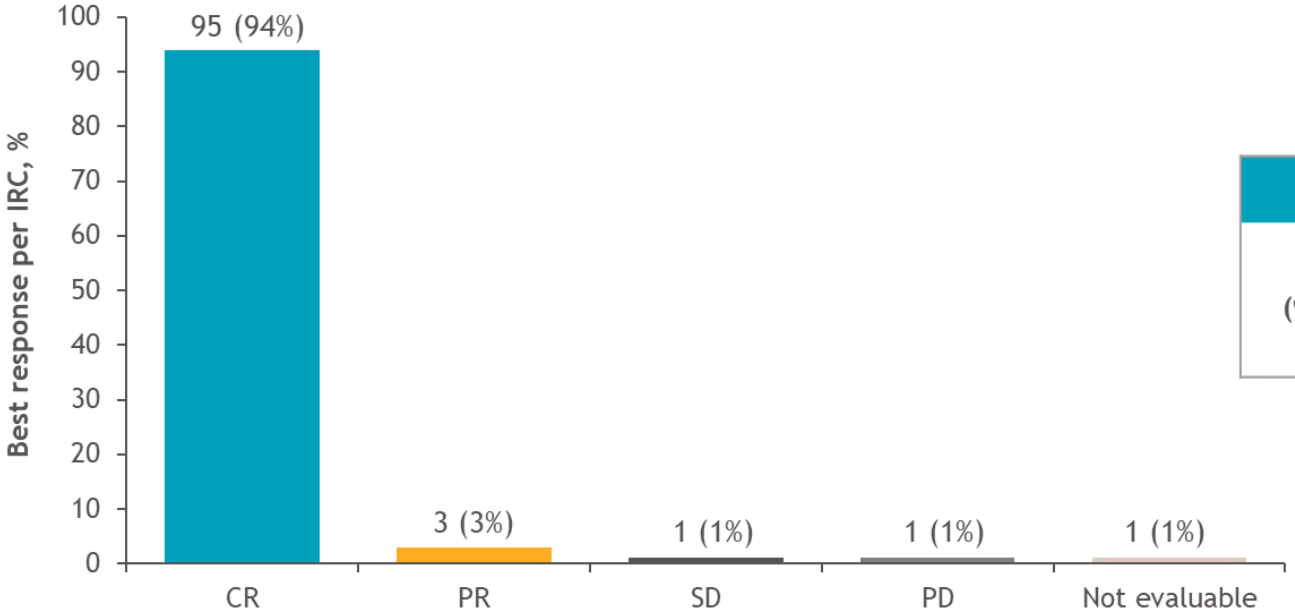
TRANSCEND-FL: Patient Disposition



Morschhauser et al ICML 2023

TRANSCEND-FL: Outcomes

3L+ FL efficacy set (n = 101)



ORR	CR rate
97% (95% CI, 91.6–99.4) *P* < 0.0001[a]	**94%** (95% CI, 87.5–97.8) *P* < 0.0001[a]

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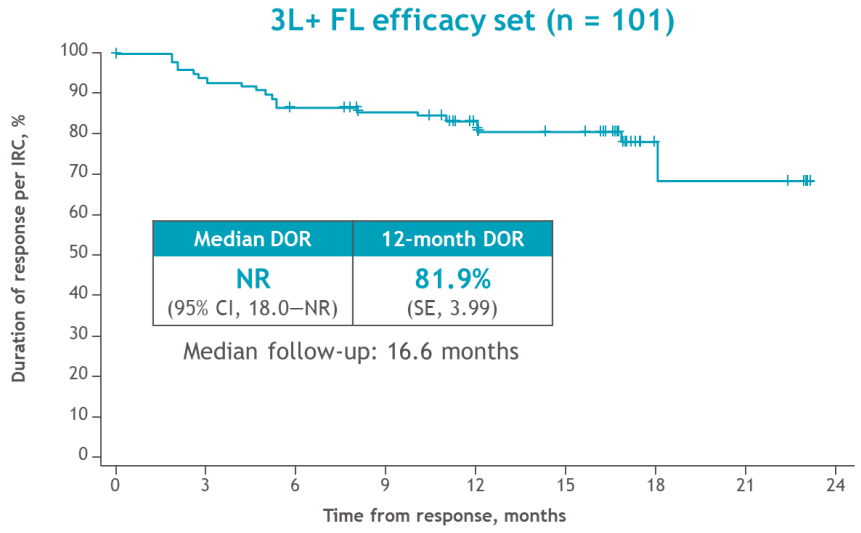
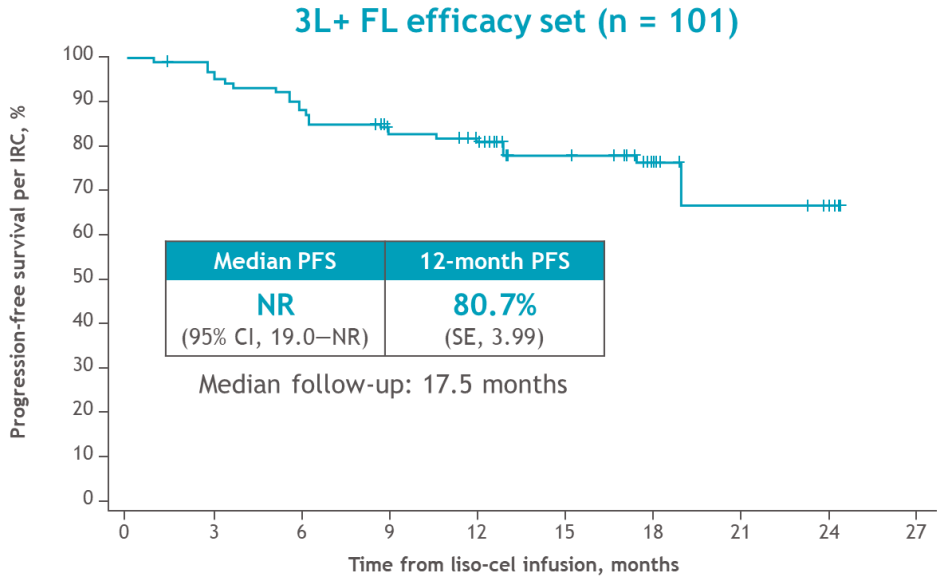
TRANSCEND-FL: DOR and PFS



No. at risk (censored)

3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)



No. at risk (censored)

3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)

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TRANSCEND-FL: Toxicities

Patients with CRS and NEs	2L+ FL liso-cel–treated set (n = 130)
CRS,[a] n (%)	
Any grade	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3	**1 (1)**
Grade 4/5	**0**
Median (range) time to onset, days	6 (1–17)
Median (range) time to resolution, days	3 (1–10)
NE,[b] n (%)	
Any grade	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3	**3 (2)**
Grade 4/5	**0**
Median (range) time to onset, days	8.5 (4–16)
Median (range) time to resolution, days	3.5 (1–17)

Other AESIs, n (%)	2L+ FL liso-cel–treated set (n = 130)
Prolonged cytopenia (grade ≥3 at Day 29)[c]	29 (22)
Recovery to grade ≤ 2 neutropenia at Day 90[d], n/N (%)	18/20 (90)
Recovery to grade ≤ 2 anemia at Day 90[d], n/N (%)	5/6 (83)
Recovery to grade ≤ 2 thrombocytopenia at Day 90[d], n/N (%)	11/19 (58)
Grade ≥ 3 infection[e]	7 (5)
MAS	1 (1)
Tumor lysis syndrome	0
Hypogammaglobulinemia[f]	6 (5)
SPM (2 AML, 1 rectal cancer, 1 colon adenocarcinoma)[f]	4 (3)

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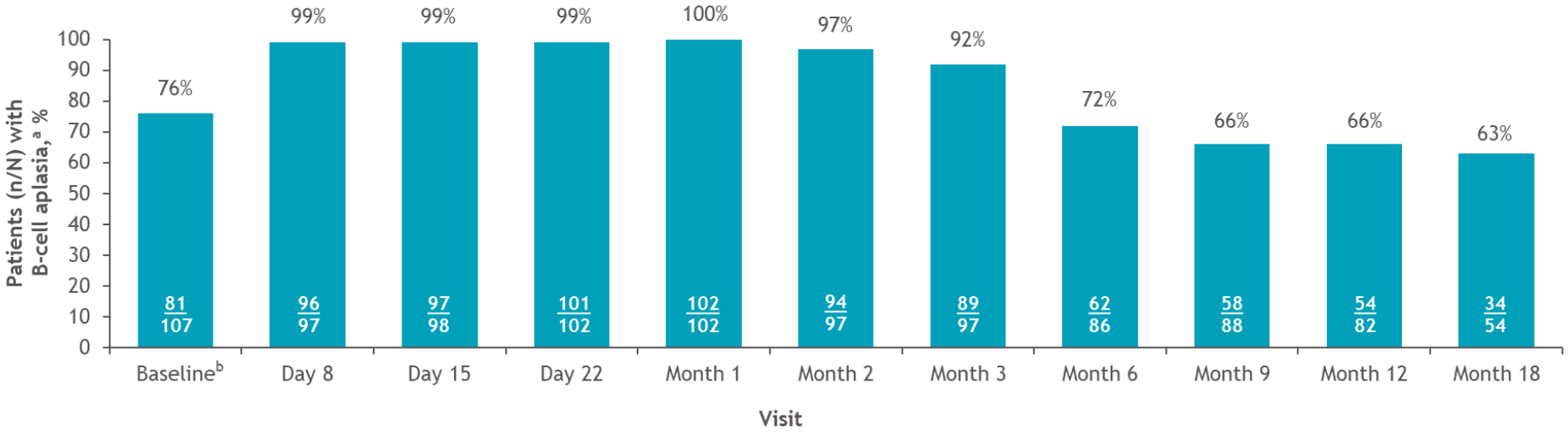
TRANSCEND-FL: B-cell Aplasia Over Time

3L+ FL liso-cel—treated set (n = 107)



- Majority of patients (76%) had B-cell aplasia at baseline
- Proportion of patients with B-cell aplasia increased after liso-cel infusion, was maintained above 90% through Month 3, then decreased at Month 6, but remained relatively constant through Month 18

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Axi-cel in FL in the Real-World: CIBMTR Analysis

Patients with R/R FL receiving commercial axi-cel at 72 US centers[a]

N=242

Patients excluded (n=91)

- **FL, grades 3A/3B unspecified (n=8)**
- **Patients with prior nontransplant cellular therapy (n=4)**
- **Follow-up not reported (n=79)**

Patients included in the analysis set

N=151

- Data cutoff date: September 23, 2022
- Median follow-up: 6.2 months (95% CI, 6.0-6.3)
- Median time from leukapheresis to infusion was 28 days (IQR, 26-33)

Jacobson et al EHA 2023

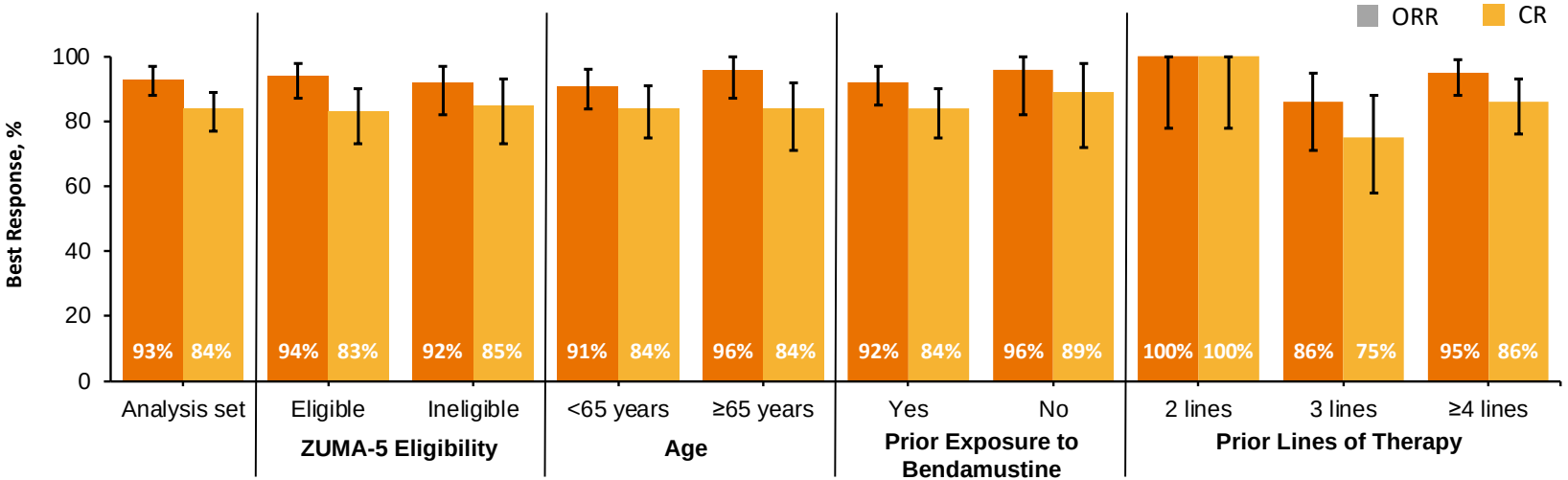
CIBMTR Axi-cel FL: Patient Disposition

Key Variable of Interest	Enrolled Patients in Analysis Set N=151	ZUMA-5 Eligibility[a]		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Median age (IQR), years	61 (55-68)	60 (54-68)	62 (55-69)	57 (51-61)*	70 (68-74)*
Male sex, n (%)	94 (62)	50 (56)*	44 (72)*	66 (69)*	28 (50)*
White race, n (%)	132 (87)	80 (89)	52 (85)	82 (86)	50 (89)
Hispanic ethnicity, n (%)	12 (8)	8 (9)	4 (7)	8 (9)	4 (7)
ECOG PS 0-1 at infusion,[b] n (%)	143 (98)	87 (100)	56 (95)	88 (97)	55 (100)
Clinically significant comorbidities,[c] n (%)	113 (75)	56 (62)*	57 (93)*	69 (73)	44 (79)
Disease stage at diagnosis[d]: III-IV, n (%)	79 (76)	46 (78)	33 (73)	57 (78)	22 (71)
Median no. of lines of prior therapies (IQR)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Prior bendamustine,[e] n (%)	107 (79)	62 (78)	45 (80)	69 (79)	38 (79)
Prior ASCT, n (%)	20 (13)	12 (13)	8 (13)	16 (17)	4 (7)
Elevated LDH prior to infusion,[f,g] n (%)	26 (28)	15 (26)	11 (32)	15 (26)	11 (32)
Chemoresistant prior to infusion,[h] n (%)	101 (80)	61 (82)	40 (77)	65 (78)	36 (84)
Median time from last line of therapy to infusion (IQR), months	7.1 (3.0-19.3)	7.9 (3.1-20.0)	5.8 (3.0-18.8)	5.6 (2.7-11.1)*	13.7 (4.6-25.7)*
Bridging therapy[i]: any type / systemic / radiation, n (%)	12 (9) / 10 (8) / 2 (2)	6 (8) / 5 (6) / 1 (1)	6 (11) / 5 (9) / 1 (2)	7 (8) / 7 (8) / 0	5 (10) / 3 (6) / 2 (4)
Outpatient,[j] n (%)	22 (15)	16 (18)	6 (10)	13 (14)	9 (16)

- Of 151 patients enrolled in the analysis set, 61 (40%) would have been considered ineligible for ZUMA-5
  - Reasons for ineligibility included comorbidities (70%), history of prior malignancy (18%), platelet count <75,000/μL (15%), pleura extranodal involvement (15%), cerebrovascular disease (11%), and ECOG PS ≥2 (5%)

Jacobson et al EHA 2023

CIBMTR Axi-cel FL: Outcomes by Variable



No. of patients	138	124	83	73	55	51	85	78	53	46	96	87	27	25	15	15	31	27	75	68
N	148	148	88	88	60	60	93	93	55	55	104	104	28	28	15	15	36	36	79	79

- Among 148 patients evaluable for response, for whom the median follow-up was 6.2 months, **138 patients (93%; 95% CI, 88-97) had an overall response, with 124 patients (84%; 95% CI, 77-89) achieving a CR**
- Overall response was comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine, and prior lines of therapy

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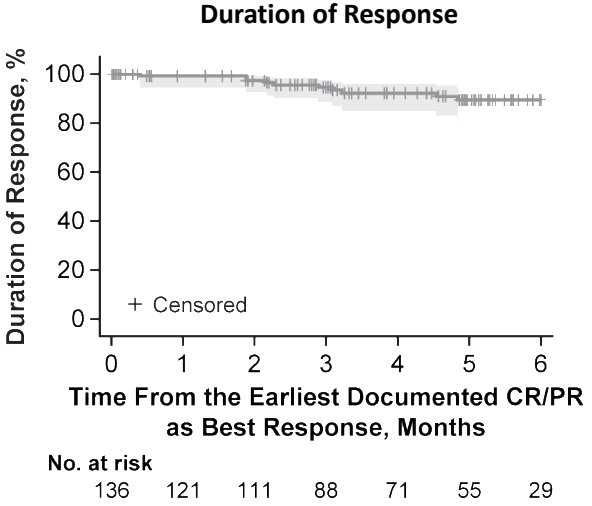
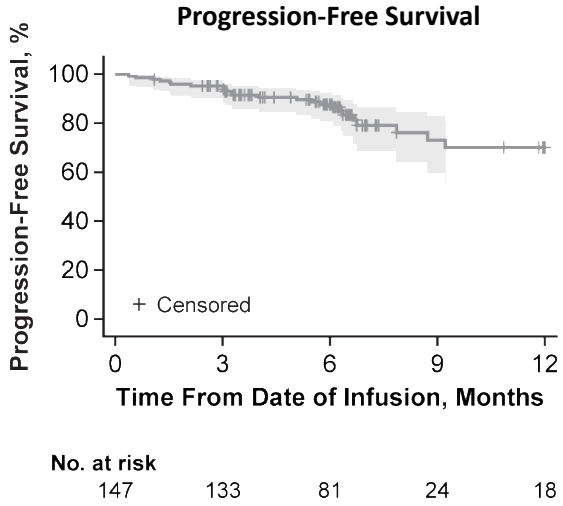
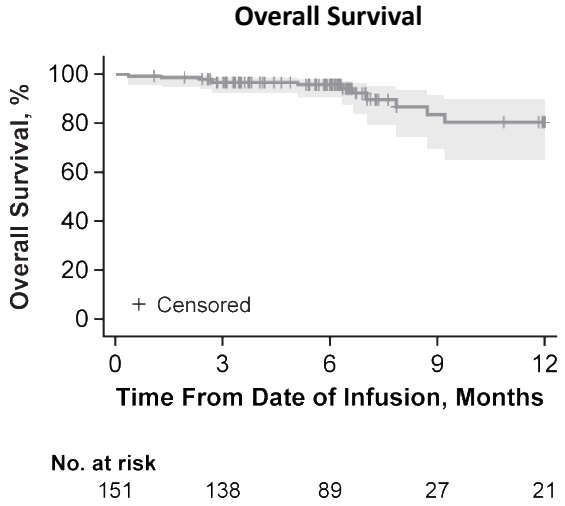
CIBMTR Axi-cel FL: Time Dependent Outcomes







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CIBMTR Axi-cel FL: CRS and ICANS

Parameter	Enrolled Patients in Analysis Set (N=151)	ZUMA-5 Eligibility		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Any-grade CRS,[a,b] n (%)	109 (73)	70 (79)	39 (64)	70 (74)	39 (70)
Grade ≥3 CRS,[a,b] n (%)	3 (2)	1 (1)	2 (3)	2 (2)	1 (2)
Median time from infusion to CRS, any-grade, days (range)	5 (1-15)	6 (2-12)	5 (1-15)	5 (1-12)	6 (2-15)
Corticosteroids to treat CRS,[c] n(%)	43 (39)	26 (37)	17 (44)	23 (33)	20 (51)
Tocilizumab to treat CRS,[c] n(%)	84 (77)	53 (76)	31 (79)	52 (74)	32 (82)
Any-grade ICANS,[a,d] n (%)	58 (39)	38 (43)	20 (33)	33 (35)	25 (45)
Grade ≥3 ICANS,[a,d] n (%)	18 (12)	8 (9)	10 (16)	12 (13)	6 (11)
Median time from infusion to ICANS, any-grade, days (range)	8 (2-19)	8 (2-16)	8 (6-19)	8 (3-16)	8 (2-19)
Corticosteroids to treat ICANS,[c] n(%)	48 (83)	33 (87)	15 (75)	26 (79)	22 (88)
Tocilizumab to treat ICANS,[c] n(%)	7 (12)	2 (5)	5 (25)	5 (15)	2 (8)

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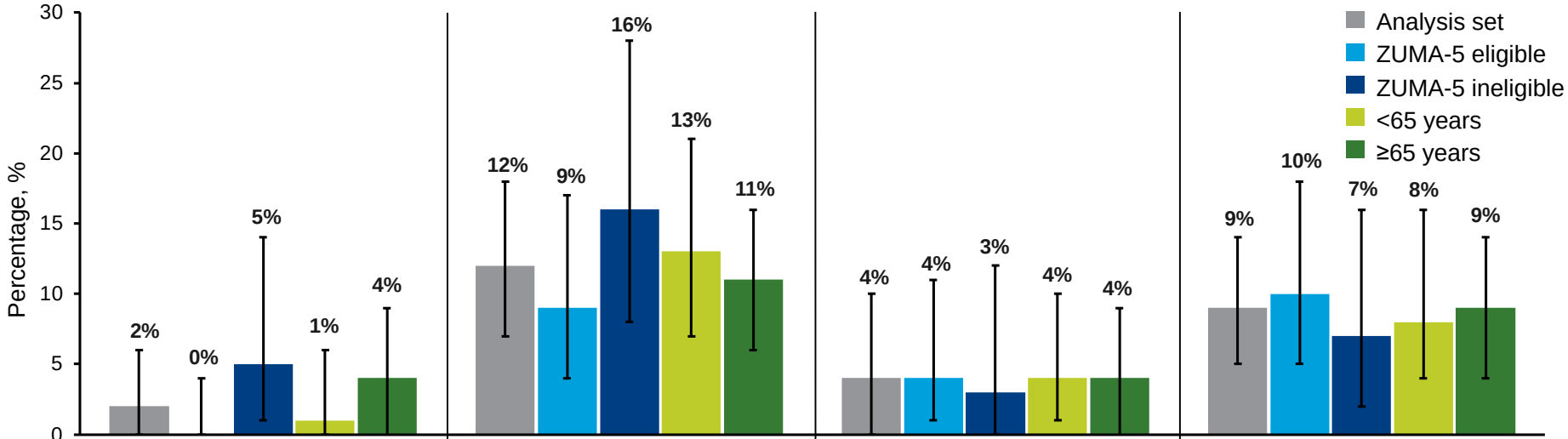
CIBMTR Axi-cel FL: Notable Toxicities



	CRS[a] of Grade ≥3					ICANS[a,b] of Grade ≥3					Prolonged Neutropenia[c]					Prolonged Thrombocytopenia[d]				
No. of patients with event	3	0	3	1	2	18	8	10	12	6	6	4	2	4	2	13	9	4	8	5
No. of patients evaluable	150	89	61	94	56	149	88	61	93	56	149	89	60	95	54	149	89	60	95	54

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CIBMTR Axi-cel FL: AEs of Interest

Parameter	Enrolled Patients in Analysis Set (N=151)	ZUMA-5 Eligibility		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Clinically significant infection,[a] n (%)	51 (34)	29 (32)	22 (36)	35 (37)	16 (29)
Bacterial	19 (13)	13 (14)	6 (10)	11 (12)	8 (14)
Fungal	2 (1)	0	2 (3)	1 (1)	1 (2)
Viral	38 (25)	17 (19)	21 (34)	28 (29)	10 (18)
Subsequent neoplasms,[b] n (%)	3 (2)	1 (1)	2 (3)	3 (3)	0
Deaths, n (%)	12 (8)	6 (7)	6 (10)	8 (8)	4 (7)
Primary disease	3 (2)	2 (2)	1 (2)	3 (3)	0
CRS	2 (1)	0	2 (3)	1 (1)	1 (2)
COVID-19	4 (3)	3 (3)	1 (2)	3 (3)	1 (2)
Organ failure[c]	2 (1)	1 (1)	1 (2)	0	2 (4)
Prior malignancy	1 (1)	0	1 (2)	1 (1)	0

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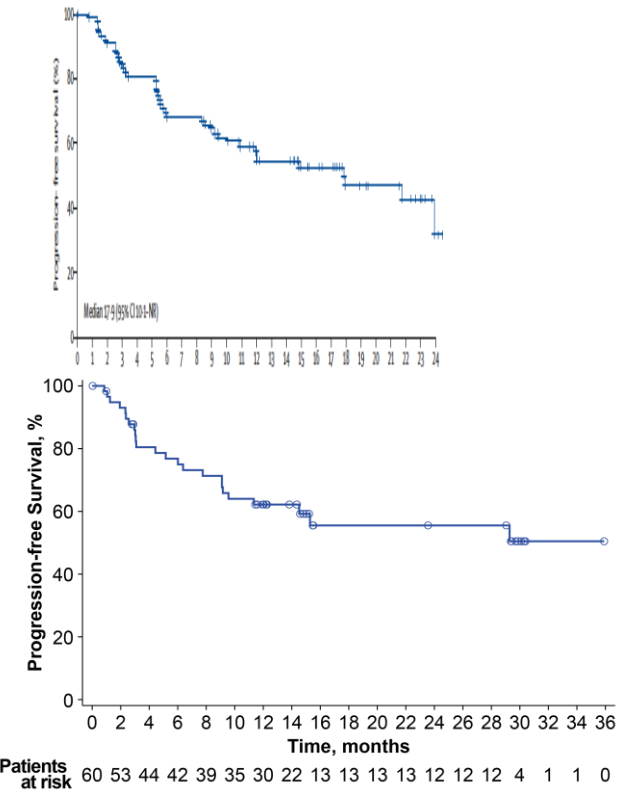
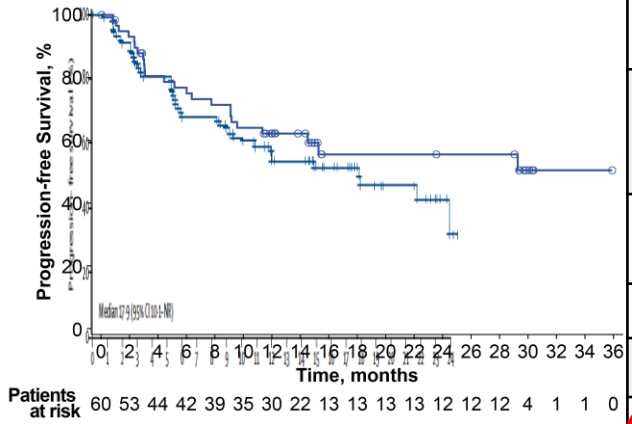
CAR vs Bispecifics in FL?



	CD20 Bispecifics	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Trial	**Multiple**	ZUMA-5	**ELARA**	**TRANSFORM FL**
Status	Phase I/II	Phase II	Phase II	Phase II
FL Patient Population	N = 11-121	N = 326	N = 75	N = 101
Median Prior Therapies	3	3	3	3
PFS	Median: 12-24m	Median: 40.2m (80% at 12m)	Median NR @ 24m (75% at 12m)	Median NR @ 16m (81% at 12m)
ORR	71-90%	94%	86%	97%
CRR	48-75%	79%	68%	94%
Any grade CRS/NT	44-59%/1-6%	78%/56%	49%/4%	58%/15%
Grade ≥ 3 CRS	1-7%	6%	0%	1%
Grade ≥ 3 NT	0-3%	15%	1%	2%

CAR vs Bispecifics in FL?



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Conclusions

- CD19 CAR T-cells lead to deep and durable responses in high-risk FL (multiply relapsed, POD24) with superior PFS compared with other available therapies

- CD19 CAR T-cells have lower rates of any and high-grade CRS and ICANS in FL compared with DLBCL but the risk is still notable for this population of patients

- CD19 CAR T-cells perform equally well in the real-world including non-trial eligible and older populations in terms of safety and efficacy

- Debate about how to sequence CAR vs CD20 bispecifics is still being shaped
  - Are CD20 bispecifics really safer than 4-1BB CARs?
  - Are some patients with FL cured with CAR T-cells?
  - What is the long-term PFS of bispecifics in FL?
  - Should patient-driven factors and preferences influence choice?