8th POSTGRADUATE
Lymphoma
Conference

FOLLICULAR LYMPHOMA: BISPECIFICS OR CAR T?

CARON JACOBSON

Dana-Farber Cancer Institute, Boston, MA

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Grand Hotel Santa Lucia

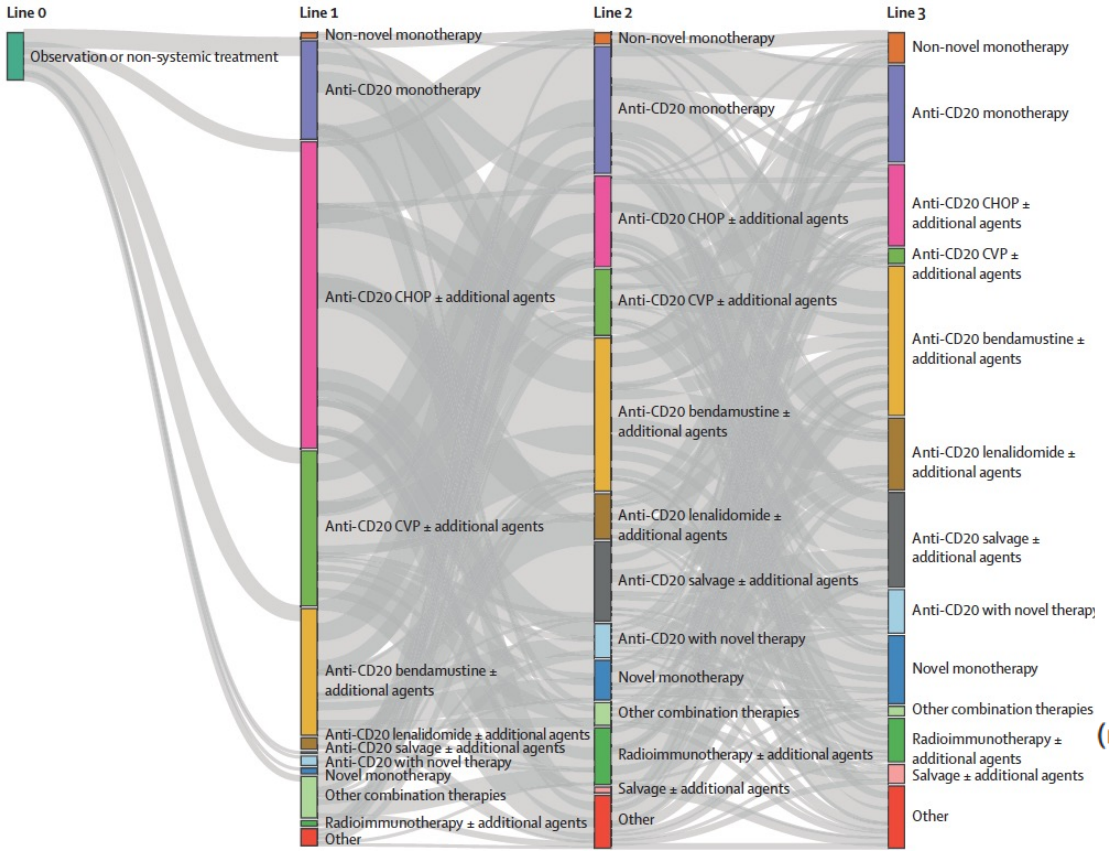
President:
P.L. Zinzani

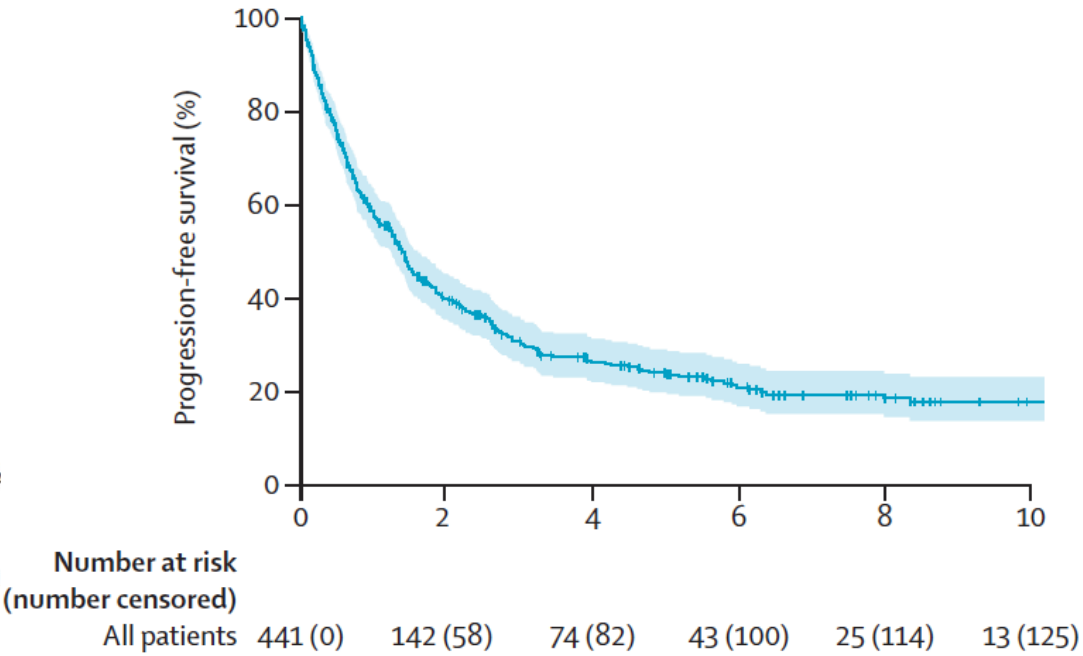
Disclosures of Caron Jacobson

- 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

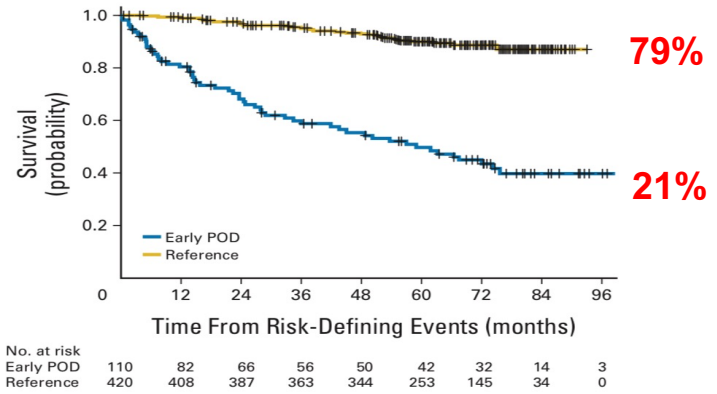
Outcomes in FL: Third Line and Beyond





Casulo et al Lancet Haematol 2022;9:e289;

Early Relapsing FL after Chemoimmunotherapy Identifies Patients with Inferior Overall Survival



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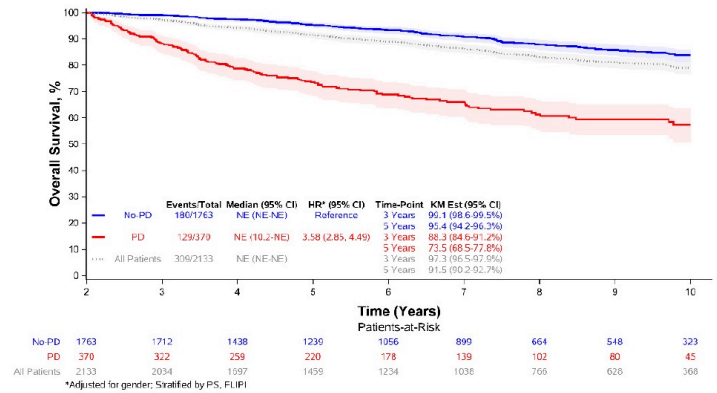

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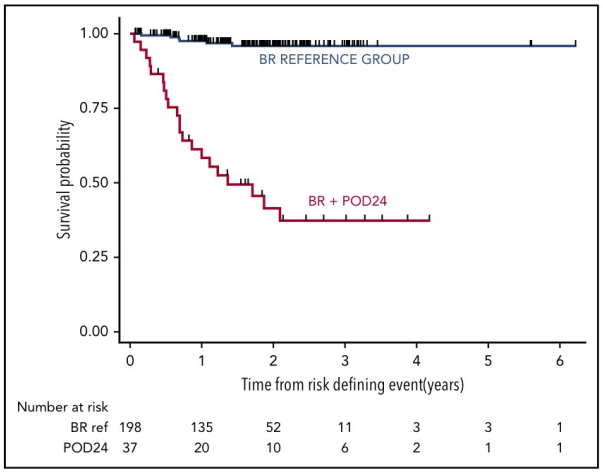

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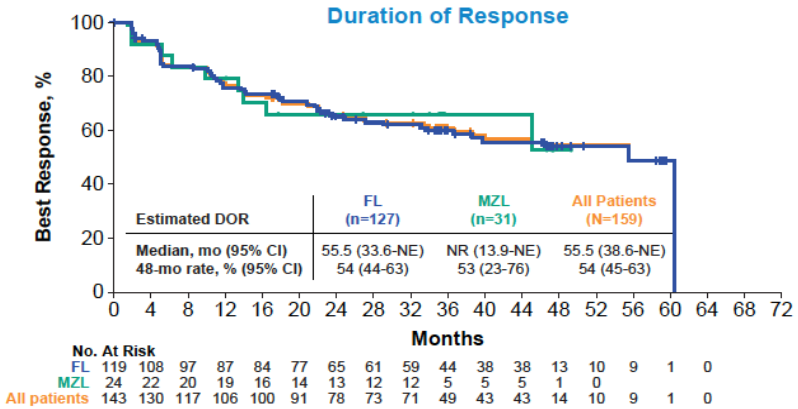
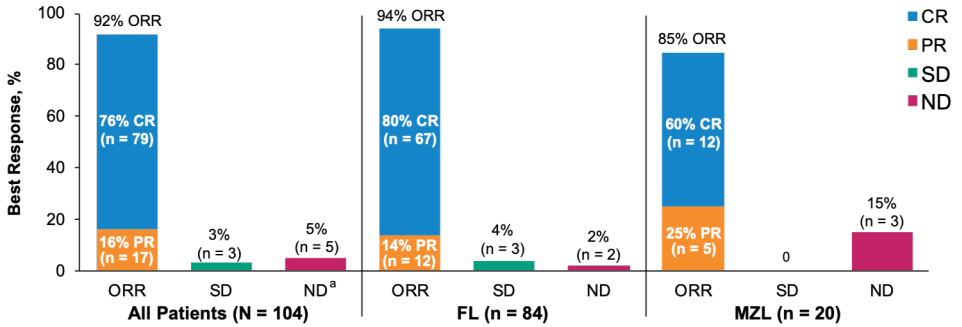
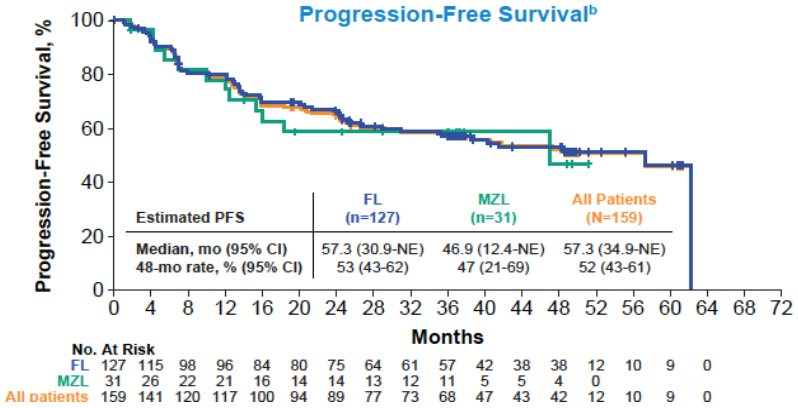
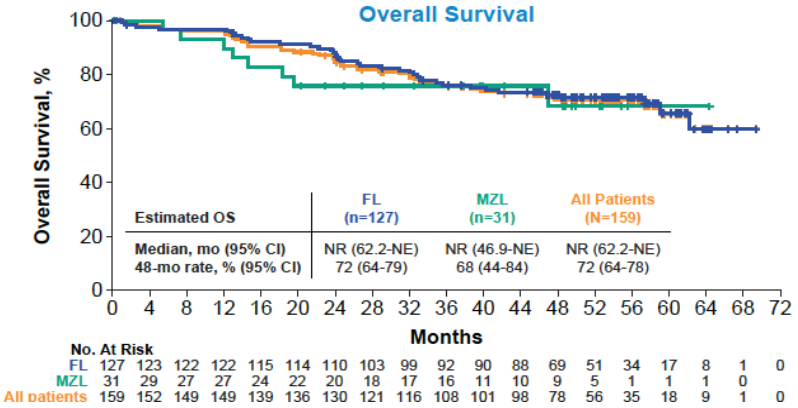
Casulo et al JCO 2015;33:2516; Casulo et al Blood 2022; 139:1684; Freeman et al Blood 2019;134:761

Axi-cel for iNHL: ZUMA-5



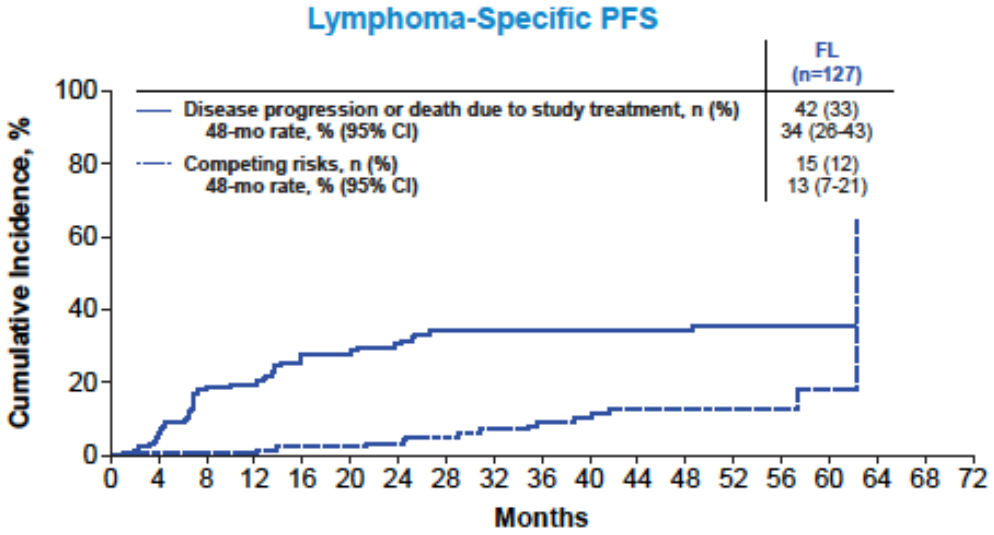


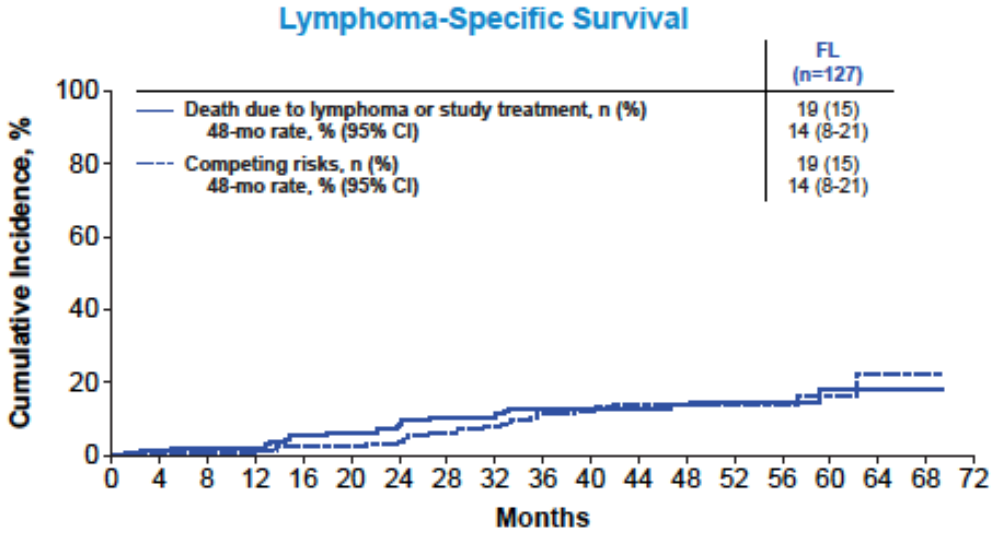




Jacobson ASH 2020; Neelapu ASH 2023

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 CRS and ICANS

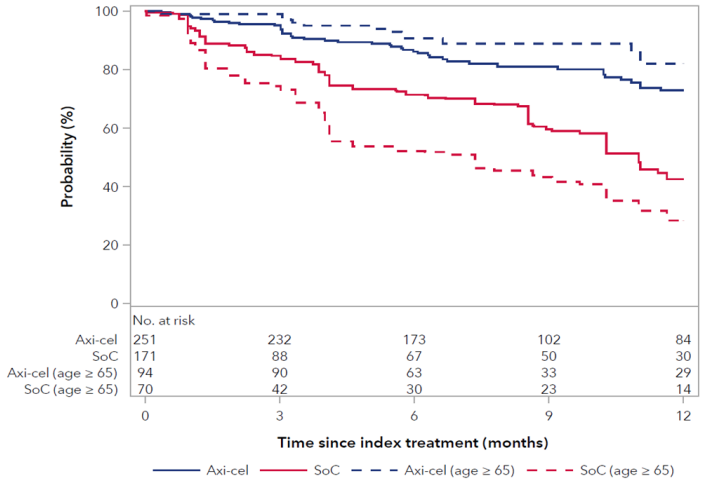
Parameter	CRS[a] FL (n=124)	CRS[a] MZL (n=22)	CRS[a] All Patients (N=146)	Neurologic Events[a] FL (n=124)	Neurologic Events[a] MZL (n=22)	Neurologic Events[a] All Patients (N=146)
Any grade	97 (78)	22 (100)	119 (82)	70 (56)	17 (77)	87 (60)
Grade ≥3	8 (6)	2 (9)	10 (7)	19 (15)	9 (41)	28 (19)
Most common 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)

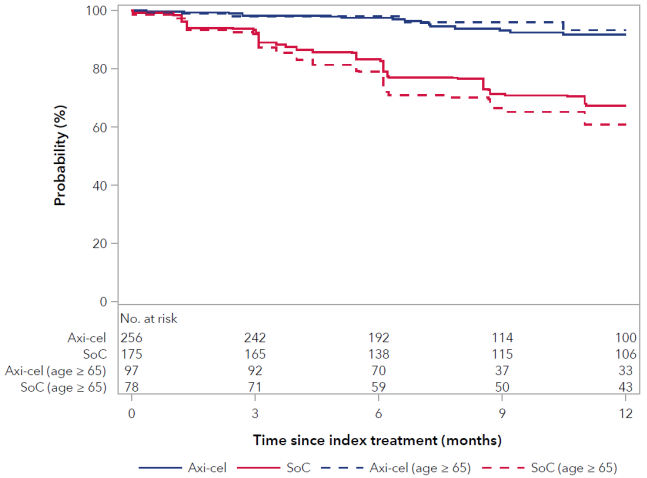
Jacobson ASH 2020

ZUMA-5 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

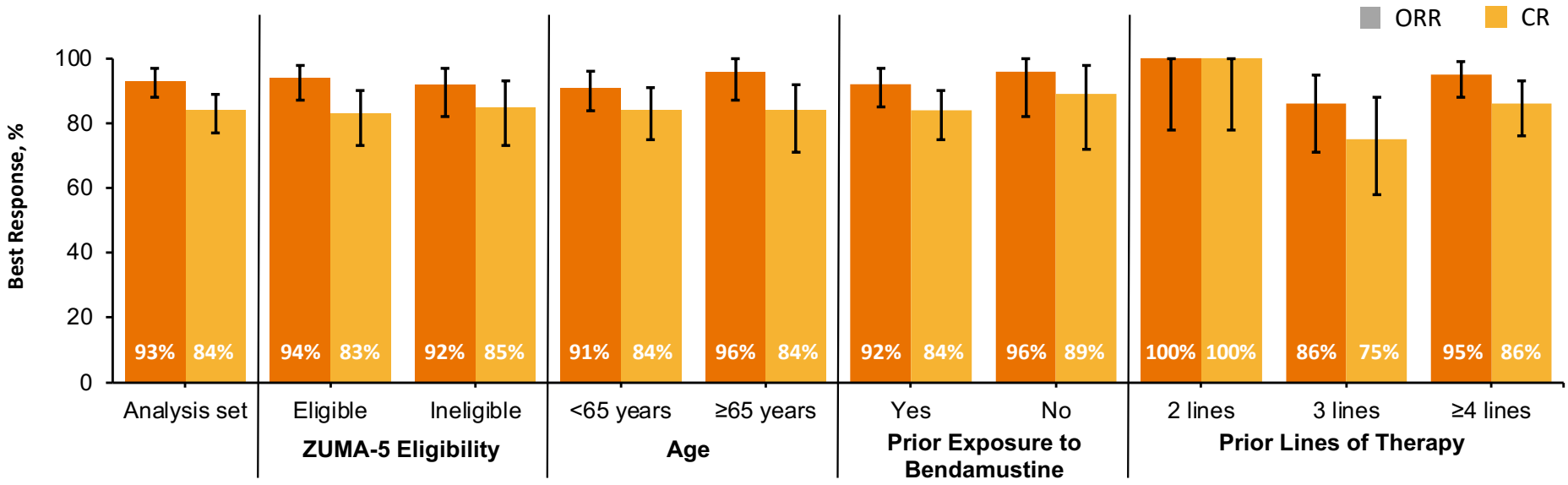




OS

Ghione EHA 2021; Kambhampti ASH 2023

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

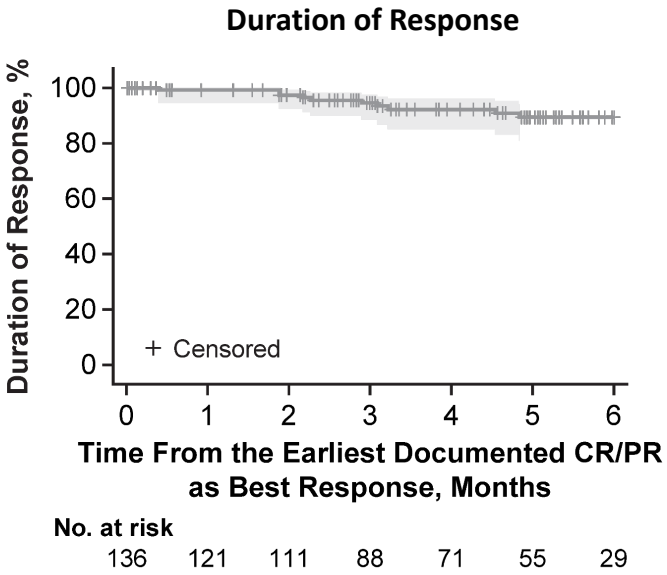


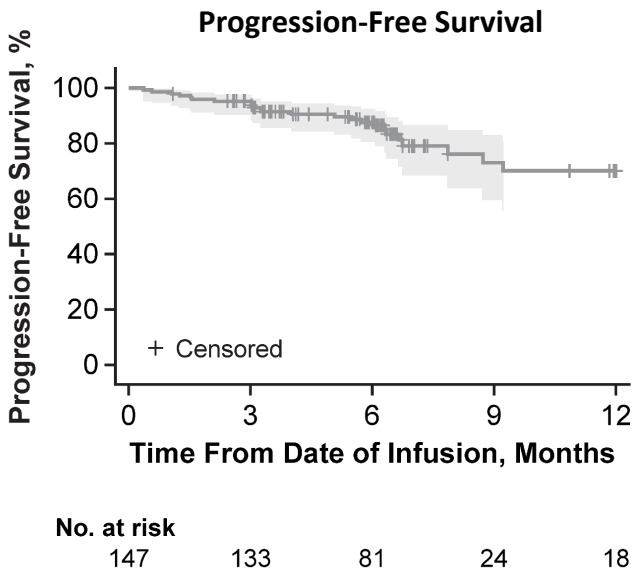
No. of patients	138	124	83	73	55	51	85	78	53	46	96	87	27	25	15	15	31	27	75	68
N	148	148	88	88	60	60	93	93	55	55	104	104	28	28	15	15	36	36	79	79

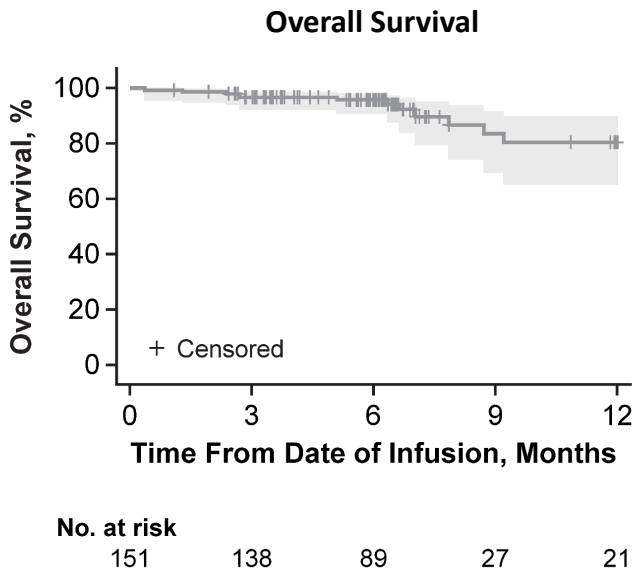
- Among 148 patients evaluable for response, for whom the median follow-up was 6.2 months, **138 patients (93%; 95% CI, 88-97) had an overall response, with 124 patients (84%; 95% CI, 77-89) achieving a CR**
- Overall response was comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine,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

Jacobson et al EHA 2023

Axi-cel in the Real World for FL: Time Dependent Outcomes







Jacobson et al EHA 2023

Axi-cel in the Real World for FL: CRS and ICANS

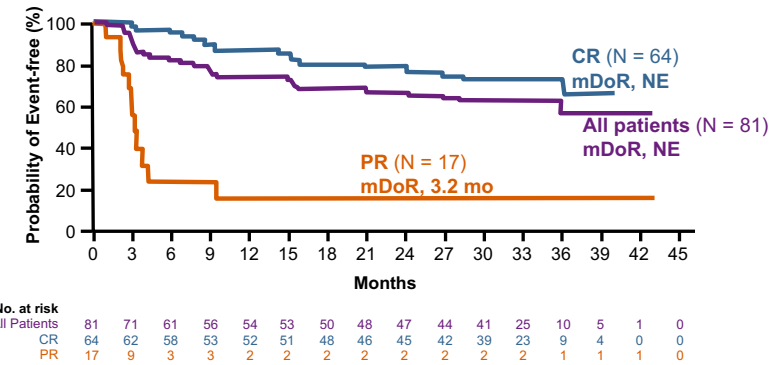
Parameter	Enrolled Patients in Analysis Set (N=151)	ZUMA-5 Eligibility		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Any-grade CRS,[a,b] n (%)	109 (73)	70 (79)	39 (64)	70 (74)	39 (70)
Grade ≥3 CRS,[a,b] n (%)	3 (2)	1 (1)	2 (3)	2 (2)	1 (2)
Median time from infusion to CRS, any-grade, 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)

Jacobson et al EHA 2023

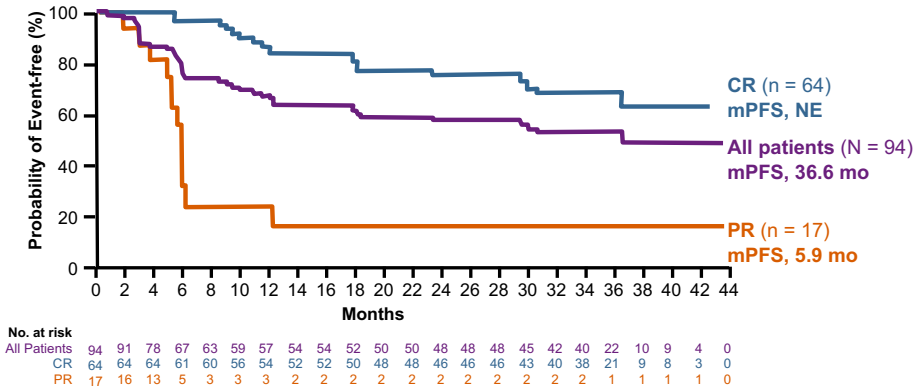
Tisa-cel in FL: ELARA

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

DOR



PFS



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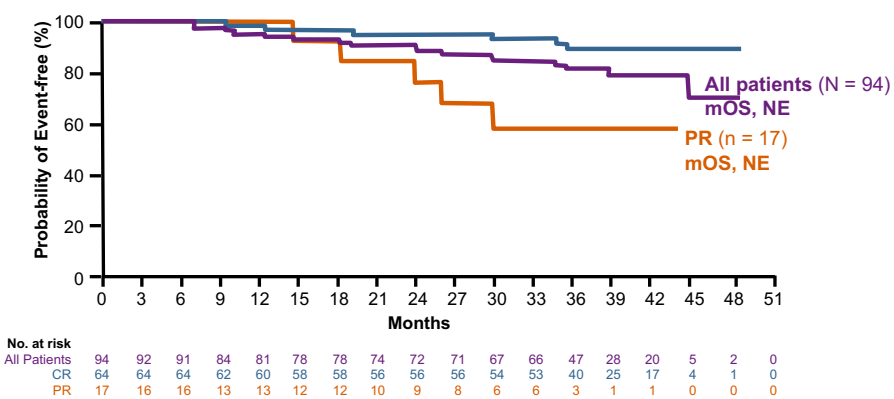
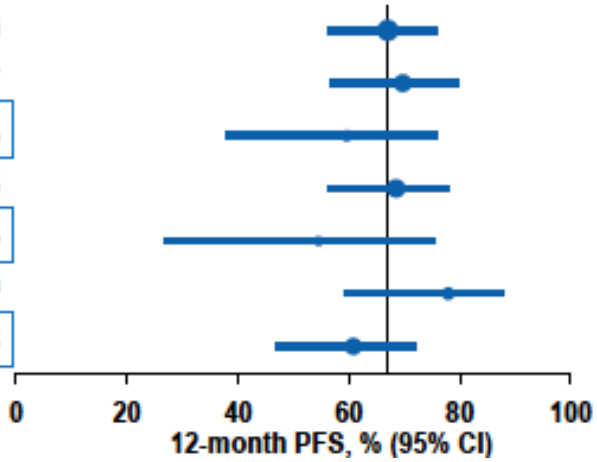


Schuster S, et al. *Blood*. 2023;142 (suppl 1):601

ELARA: Predictors of Outcome

		n	PFS %
Overall		94	67.0
Prior therapy	<5 lines	67	69.7
	≥5 lines	27	59.6
High TMTV (>510 ml)[a,b]	No	72	68.5
	Yes	20	54.5
POD24	No	33	77.9
	Yes	61	60.8



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)

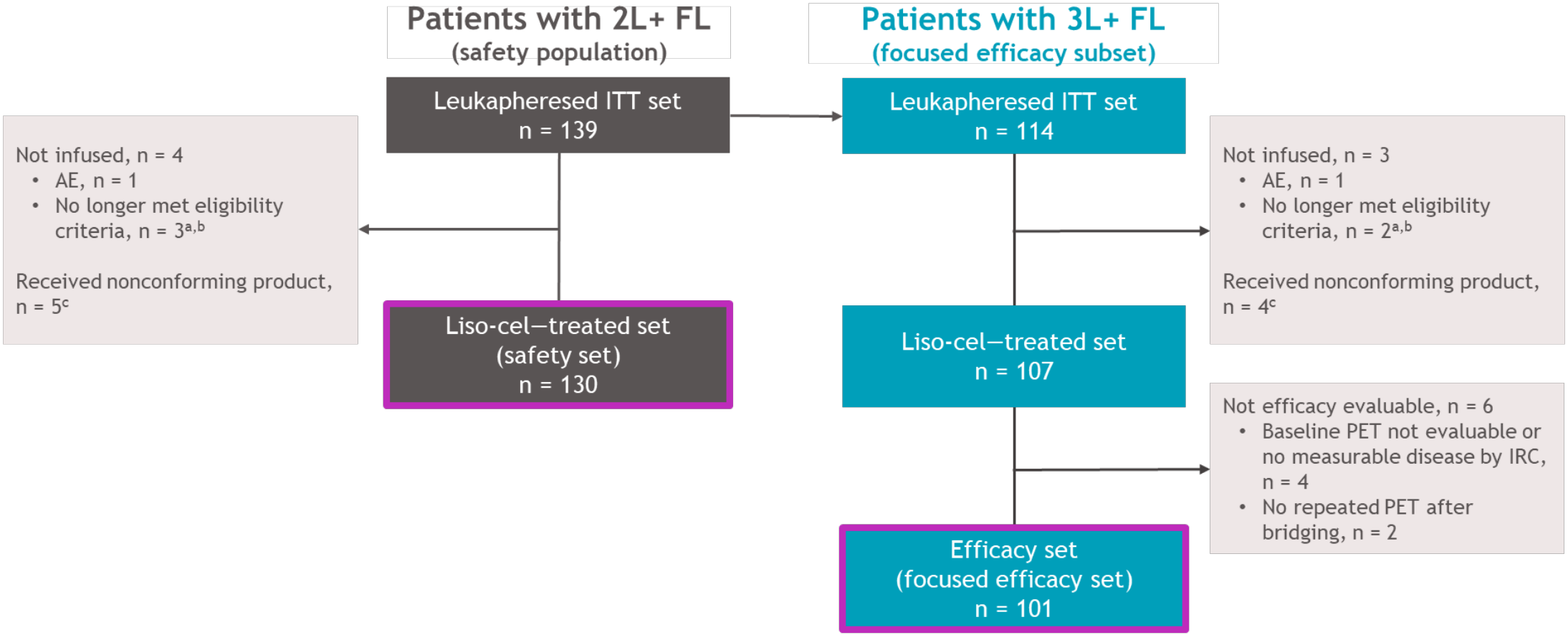
Thieblemont ASH 2021

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

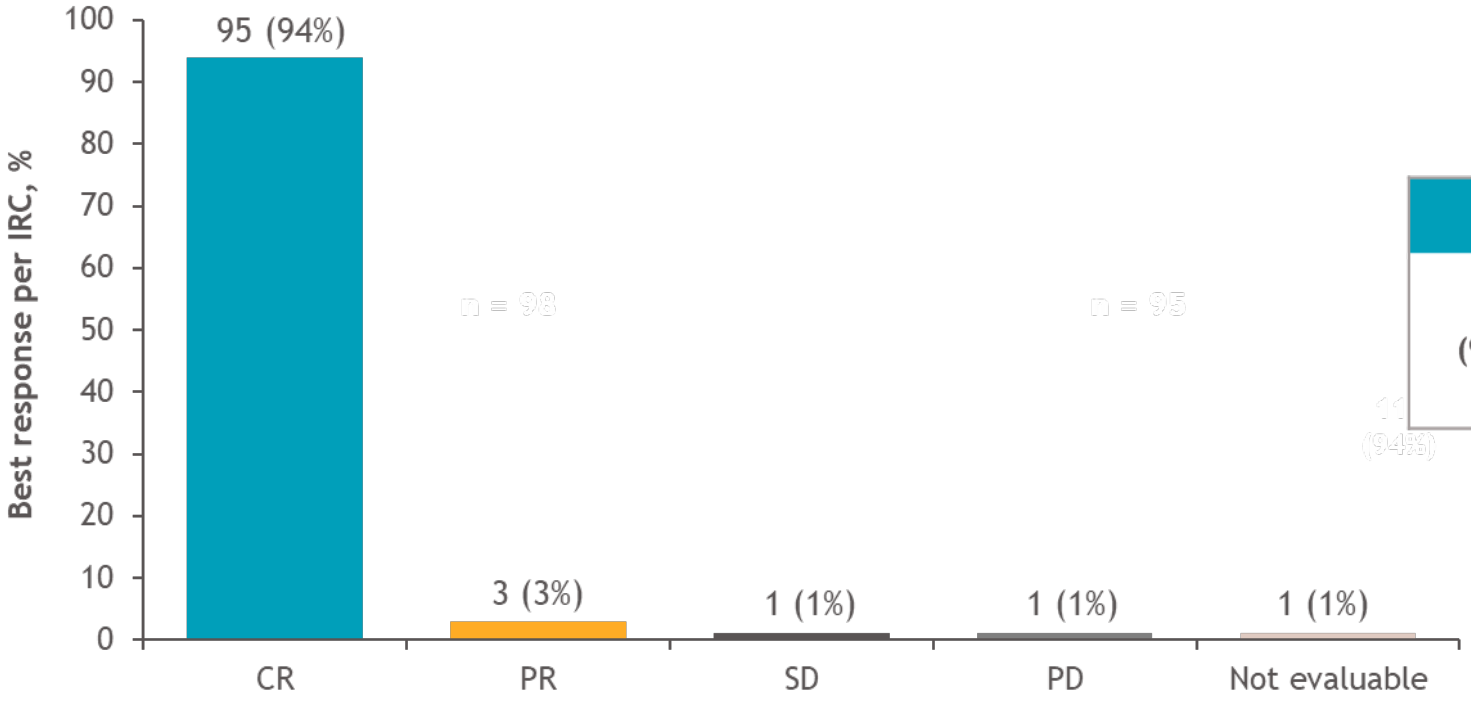
TRANSCEND-FL: Liso-cel in r/r FL



Morschhauser et al ICML 2023

TRANSCEND-FL: Outcomes

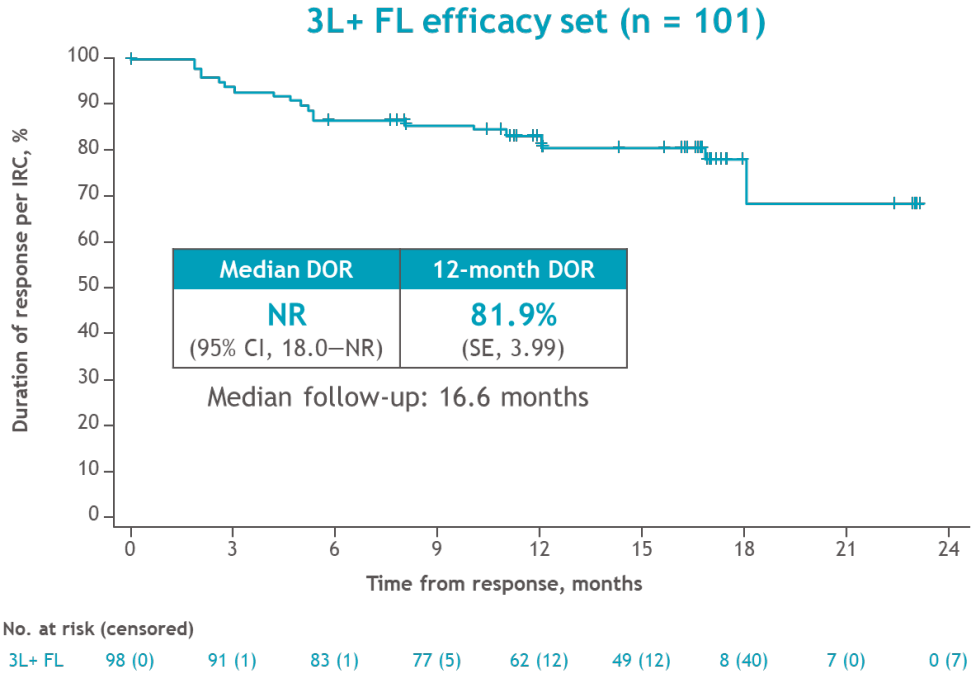
3L+ FL efficacy set (n = 101)

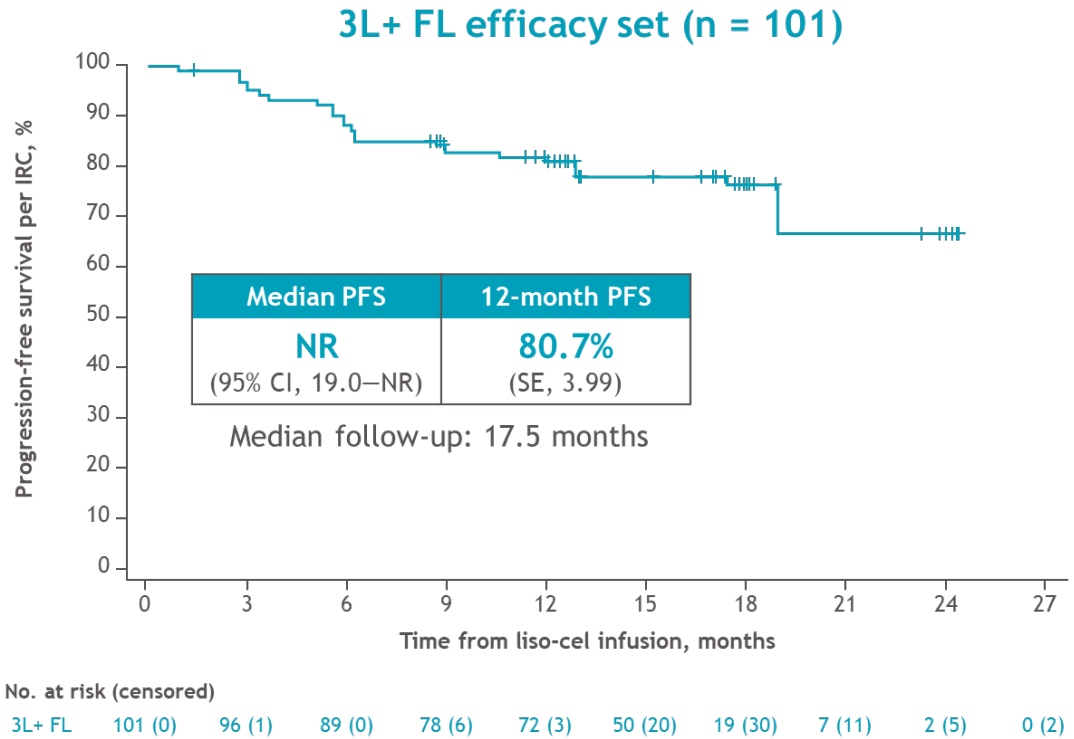


ORR	CR rate
97% (95% CI, 91.6–99.4) $P < 0.0001$[a]	**94%** (95% CI, 87.5–97.8) $P < 0.0001$[a]

Morschhauser et al ICML 2023

TRANSCEND-FL: DOR and PFS





Morschhauser et al ICML 2023

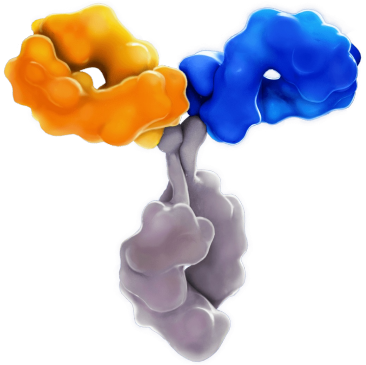
TRANSCEND-FL: Toxicities

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)

Morschhauser et al ICML 2023

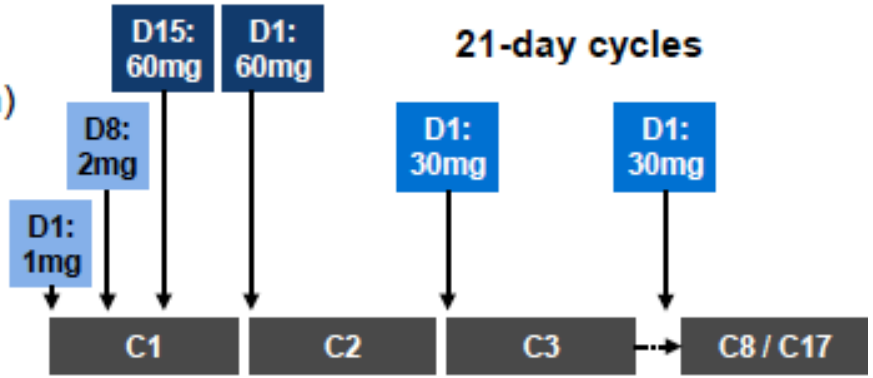
Mosunetuzumab in r/r FL



		N=90
Median number of prior lines, n (range)		3 (2–10)
Prior systemic therapy	Anti-CD20 therapy	90 (100%)
	Alkylator therapy	90 (100%)
	PI3K inhibitor	17 (18.9%)
	IMiD	13 (14.4%)
	CAR-T	3 (3.3%)
Prior ASCT		19 (21.1%)
Refractory to last prior therapy		62 (68.9%)
Refractory to any prior aCD20 therapy		71 (78.9%)
Refractory to any prior aCD20 therapy and alkylator therapy (double refractory)		48 (53.3%)
POD24		47 (52.2%)

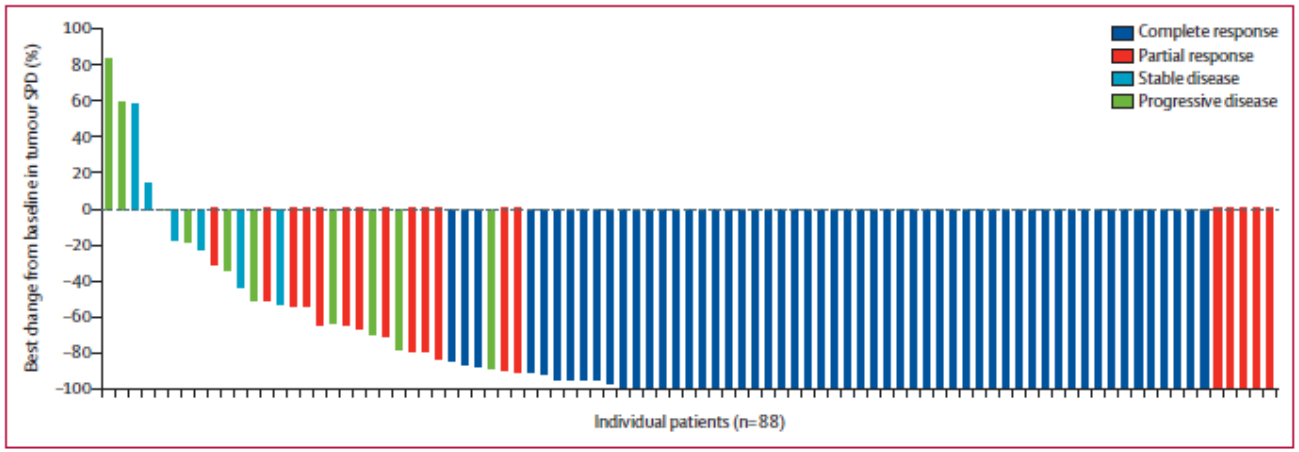
Mosunetuzumab administration

- Q3W intravenous administration
- C1 step-up dosing (CRS mitigation)
- **Fixed-duration treatment**
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8
- **No mandatory hospitalization**



Budde E et al. ASH 2021

Mosunetuzumab in r/r FL



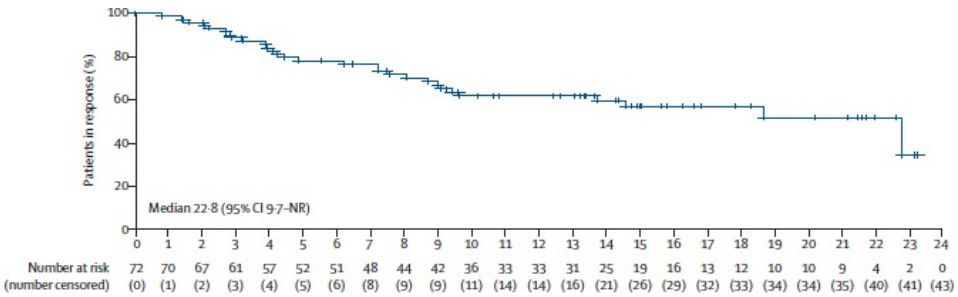
Efficacy Endpoint	Mosunetuzumab (N = 90)	Last Prior Therapy (N = 90)
ORR, %	78	56
CR, %	60	36
Median PFS, mos	24	12
Median DOCR†, mos	NR	15

	Grade 1–2	Grade 3	Grade 4
Cytokine release syndrome	38 (42%)	1 (1%)	1 (1%)
Fatigue	33 (37%)	0	0
Headache	27 (30%)	1 (1%)	0
Neutropenia or decreased neutrophil count	2 (2%)	12 (13%)	12 (13%)
Pyrexia	25 (28%)	1 (1%)	0
Hypophosphataemia	9 (10%)	15 (17%)	0
Pruritus	19 (21%)	0	0
Hypokalaemia	15 (17%)	2 (2%)	0
Cough	16 (18%)	0	0
Constipation	16 (18%)	0	0
Diarrhoea	15 (17%)	0	0
Nausea	15 (17%)	0	0
Rash	13 (14%)	1 (1%)	0
Dry skin	14 (16%)	0	0
Anaemia	5 (6%)	7 (8%)	0
Chills	11 (12%)	1 (1%)	0
Hypomagnesaemia	11 (12%)	0	0
Increased alanine aminotransferase	6 (7%)	4 (4%)	1 (1%)
Insomnia	11 (12%)	0	0
Arthralgia	10 (11%)	0	0
Peripheral oedema	10 (11%)	0	0
Abdominal pain	8 (9%)	1 (1%)	0
Back pain	8 (9%)	1 (1%)	0
Dizziness	9 (10%)	0	0
Urinary tract infection	8 (9%)	1 (1%)	0
Skin exfoliation	9 (10%)	0	0
Thrombocytopenia or decreased platelet count	5 (6%)	0	4 (4%)

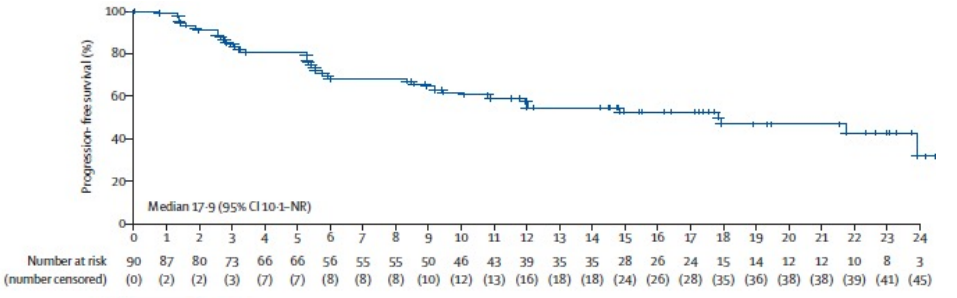
Budde E et al. Lancet Oncol 2022;23:1055; Bartlett NL et al ASH 2022 Abstract 610

Mosunetuzumab in r/r FL

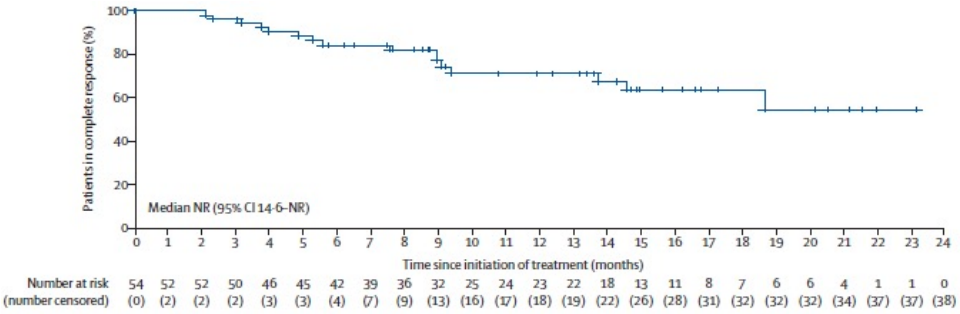
Duration of Response



Progression-free Survival



Overall Survival



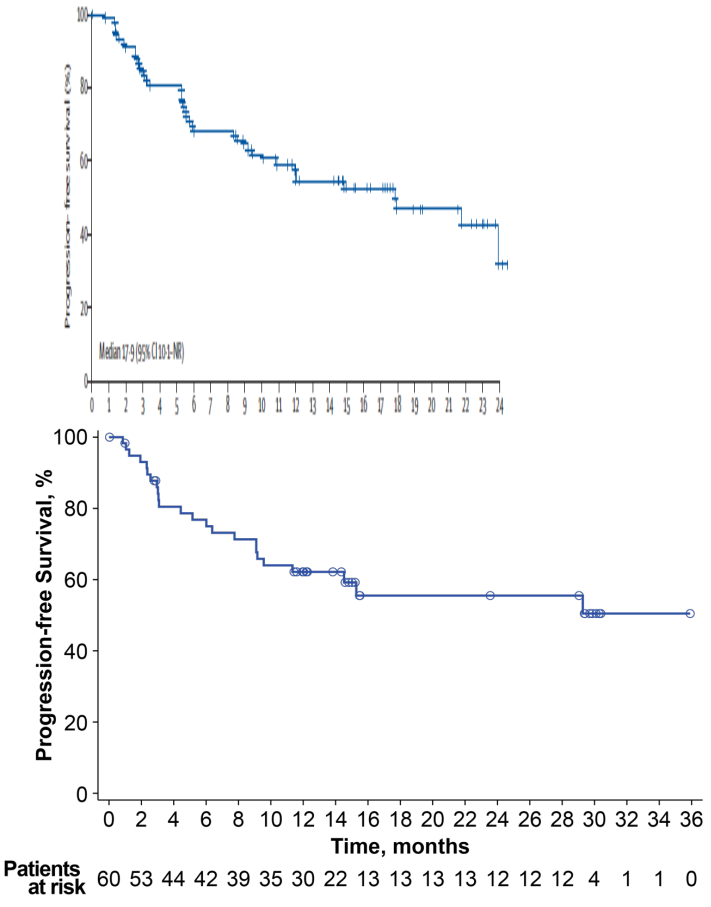
Budde E et al. Lancet Oncol 2022;23:1055

Follicular Lymphoma: CD20 Bispecific Ab Therapies

	Mosunetuzumab	Glofitamab	Epcoritamab (Epco)		Odronextamab
Trial	**GO29781** (NCT02500407)	**NP30179** (NCT03075696)	**GEN3013** (NCT03625037)	**EPCORE FL-1** + R^2 (NCT05409066)	**ELM-2** (NCT03888105)
Design	Phase I/II	Phase I	Phase I/II	Phase I/II	Phase II
FL Patient Population	N = 90	N = 44	N = 11	N=76	N = 121
Median Prior Therapies	3	3	4.5	1	3
PFS	Median: 24m	Median: 11.8m	NR	1y: 78%	Median: 20.2m
ORR	78%	71%	90%	95%	82%
CRR	60%	48%	50%	80%	75%
Any grade CRS/NT	44%/6%	50%/5%	59%/6%	43/1%	57%/NR
Grade ≥ 3 CRS	2%	4%	0%	0%	2%
Grade ≥ 3 NT	0%	0%	3%	0%	NR

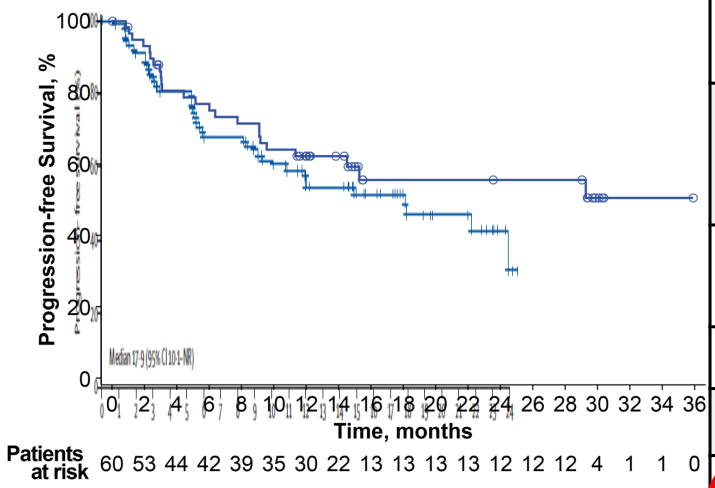
Budde LE, et al. *J Clin Oncol*. 2022;40(5):481-491; Hutchings M, et al. *J Clin Oncol.* 2021;39(18):1959-1970; Hutchings M, et al. *Lancet*. 2021;398(10306):1157-1169; Falchi L et al ASH 2022; Bannerji R, et al. *Lancet Haematol*. 2022;9(5):e327-e339;

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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Grade ≥ 3 NT	0-3%	15%	1%	2%

CAR T-cell Advantages and Disadvantages

Advantages

- Single infusion with a discrete toxicity period
  - Toxicities are manageable and reversible
  - Toxicity incidence is improving with time and experience
  - Toxicity is overall decreased and more favorable in FL
- Offers the most durable response and treatment free interval of any available therapy for a broad range of high-risk disease features
  - Unclear if it could be a definitive therapy for a subset of patients
- Resistance mechanisms beginning to be understood and engineering permutations are endless

Disadvantages

- Requires referral to a specialized center for at least 1m around the time of infusion
- Risk profile remains considerable over other available therapies
- Long-term toxicities of hypogammaglobulinemia, CD4 T-cell lymphopenia, and prolonged cytopenias is associated with ongoing infectious risk for some patients.

CD20 Bispecific Advantages and Disadvantages

Advantages

- Lower risk of significant CRS and almost no risk of ICANS, and risk limited to first cycle
- Can be administered at a wider number of oncology clinics and hospitals allowing for more universal and ready access
- Improved depth and duration of response over other available non-cell therapy options and in some cases can be time limited therapy

Disadvantages

- May still require referral to a specialized center for at least 1m around the time of first cycle and first full dose as risk profile remains limiting for some centers
- Requires prolonged dosing
  - Frequent clinic visits for infusions
  - Ongoing risk of immune dysfunction and infection

Conclusions

- Both CD19 CAR T-cells and CD20 bispecifics are a considerable advancement in the management of multiply relapsed and refractory FL over available therapies and we are fortunate to have them
- CAR T-cells have the longest follow-up and now real-world evidence and offer the deepest and most durable remissions of any therapy for these patients to date, and safety is much improved over that seen in LBCL
- Bispecifics still offer a considerable advantage over other non-cellular therapies for r/r FL and have a safer toxicity profile with regards to CRS and ICANS, and can be offered in more locations across the globe
- Ultimately, it will come down to patient discussion of pros and cons of each and patient preference