Updates CAR-T for Lymphomas

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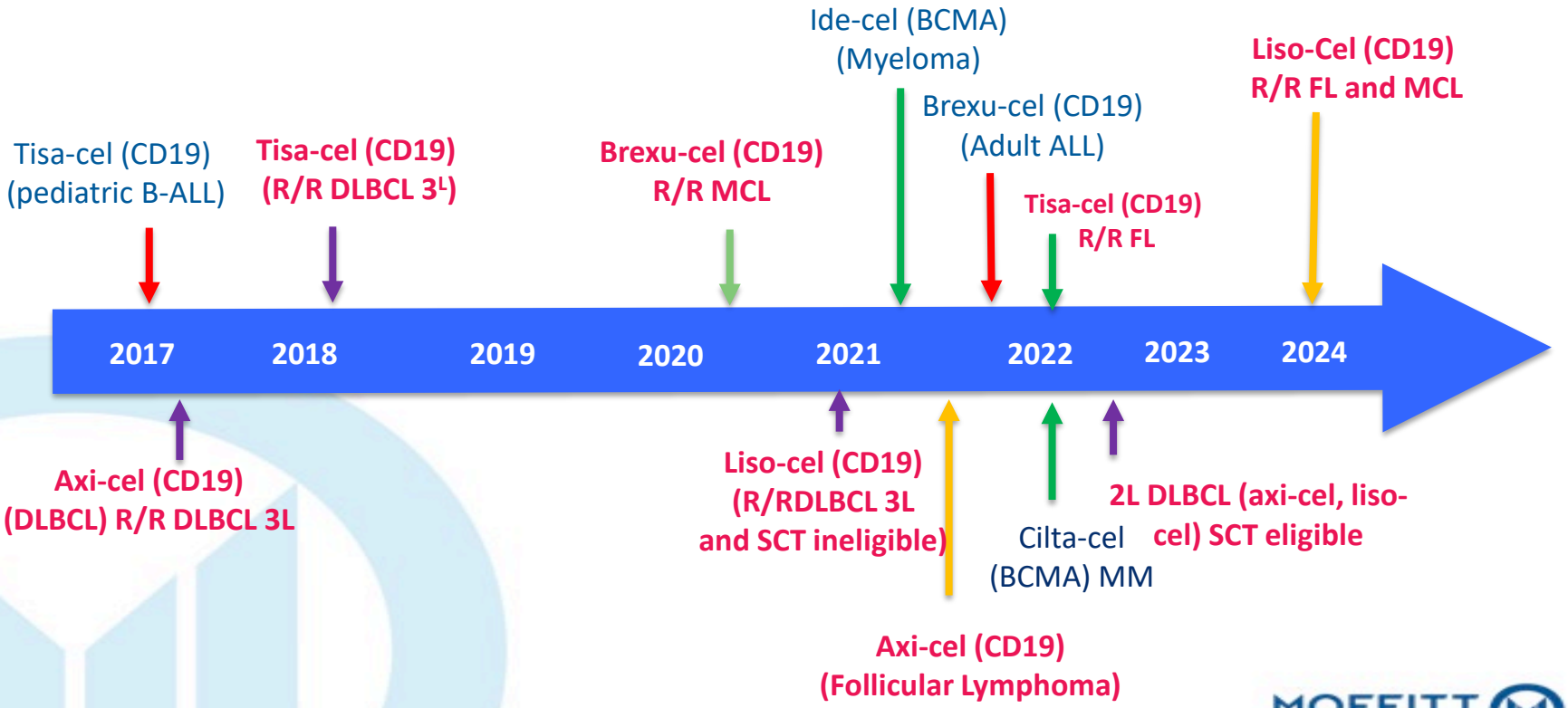
Disclosures

- *Research Support*: Merck, Janssen
- *Advisory Board*: Kite, Novartis, Bayer, Morphosys, Karyopharm, Abbvie, Janssen
- *Speaker Bureau*: BeiGene, AstraZeneca, Morphosys, Epyzime

CAR-T advances in DLBCL: US FDA approvals



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Diffuse Large B-cell Lymphoma

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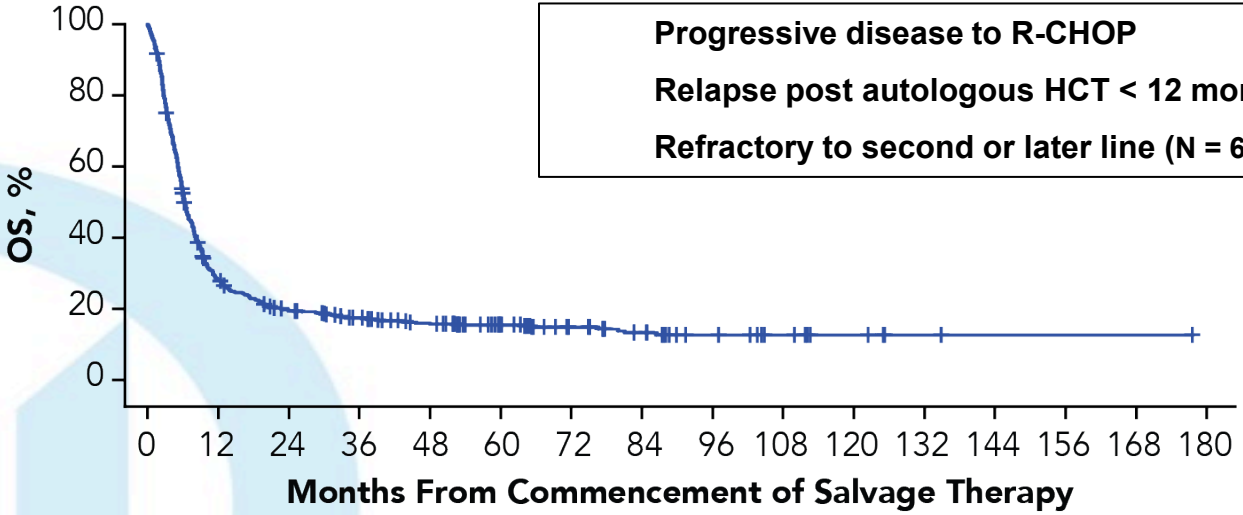
Refractory Diffuse Large B cell Lymphoma carries a poor prognosis

- SCHOLAR-1 patient level meta-analysis of refractory Aggressive NHL
  - ORR of 26% (CR of 7%, PR of 19%)
  - **Median OS of 6.6 months**



Crump M, et al. *Blood.* 2017; blood-2017-03-769620.

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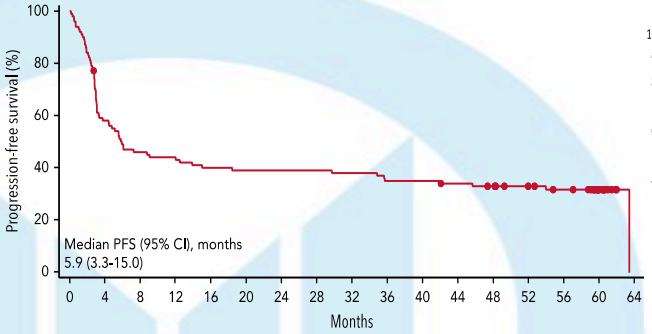
Pivotal Anti-CD19 CAR T-Cell Therapy Trials: Long term follow-up

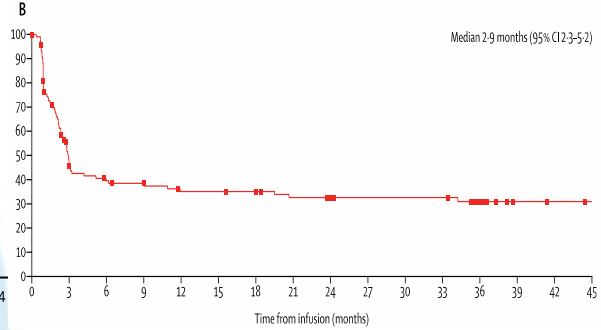
ZUMA-1
Axicabtagene Ciloleucel

Median F/U 5 years
Median age: 58 (23 – 76)
Enrolled (treated): 111 (101)
Best ORR: 83%
Best CR: 54%
PFS: 5.9 months
Ongoing CR: 39%



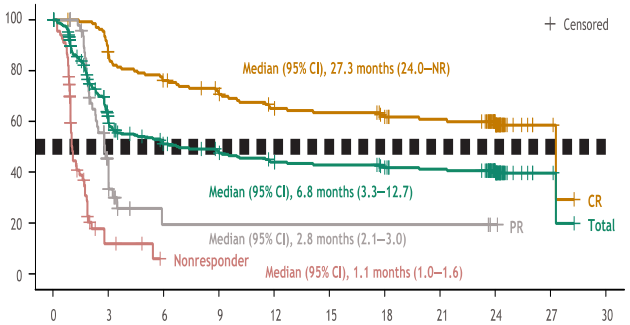
JULIET
Tisagenlecleucel

Median F/U 40.3 months
Median age: 56 (22 – 76)
Enrolled (treated): 165 (111)
Best ORR: 52%
Best CR: 40 %
PFS: 2.9 months
Ongoing CR: 37%



TRANSCEND NHL 001
Lisocabtagene Maraleucel

Median F/U 24 months
Median age: 63 (18 – 86)
Enrolled (treated): 244 (269)
Best ORR: 73%
Best CR: 53 %
PFS: 6.8 months
Ongoing CR: 45%



Neelapu et Al. Blood 2023. Schuster et Al. Lancet Oncol 2021. Abramson et Al. Blood 2023

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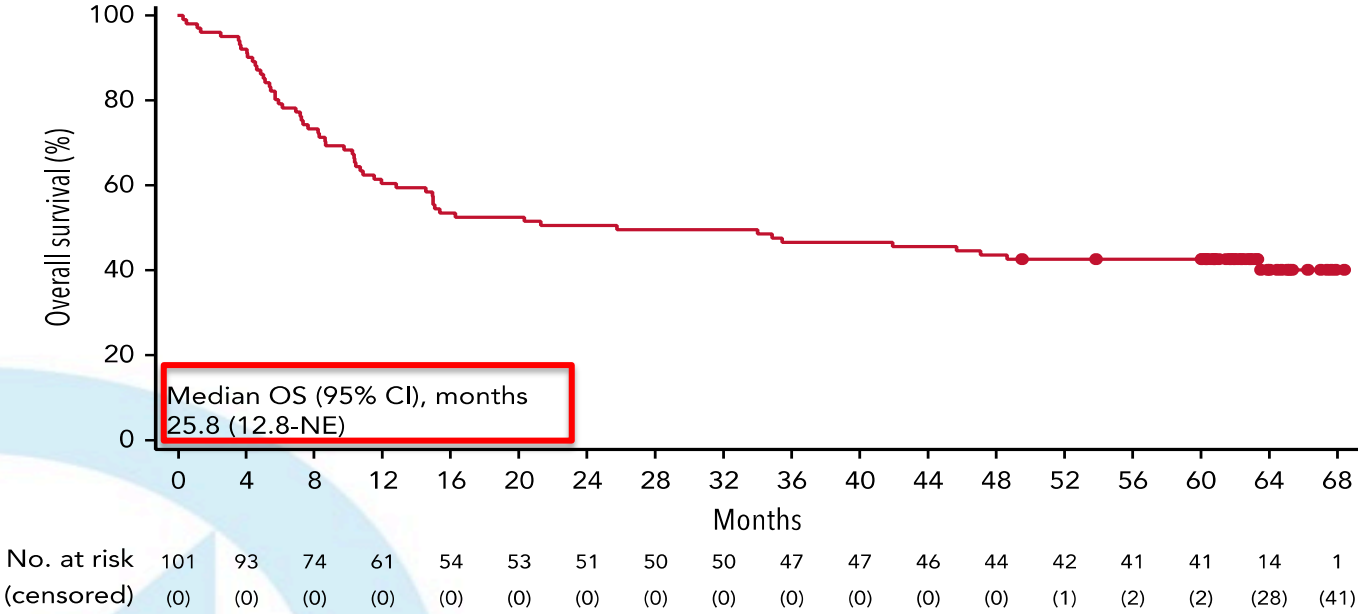
CAR-T cures patients with R/R DLBCL in 3L setting: Results of the 5-year OS update of the ZUMA-1



- With ≥ 5 years of follow-up, median OS was **25.8 months**, and the KM estimate of the 5-year OS rate was 42.6%
- Since the 4-y cut-off there was 1 dead (month 63) and 1 PD (month 54)

Jacobson et al. ASH Meeting 2021: 1760, Neelapu et al. Blood 2023

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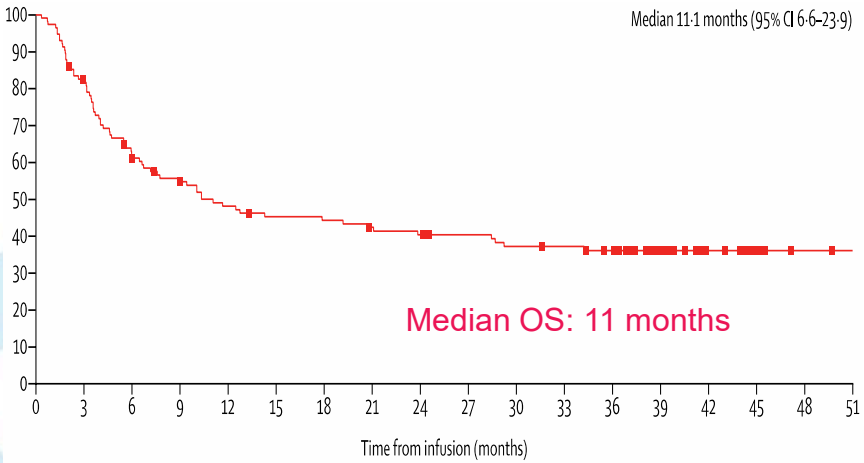
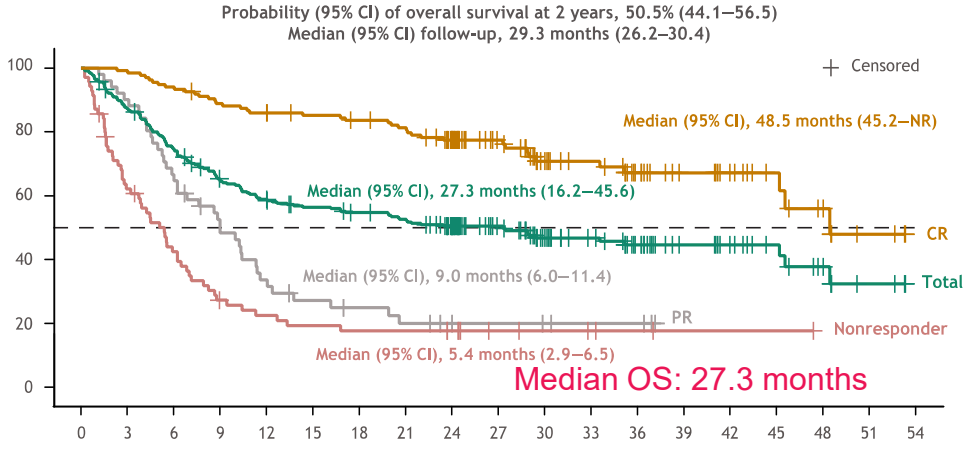
OS update in JULIET (Tisa-Cel) and TRANSCEND (Liso-cel): 3L DLBCL

JULIET



Median follow up: 40.3 months

TRANSCEND



Median follow up: 23.9 months

Schuster S et al. *Lancet Oncol* 2021; Abramson et Al. *Blood* 2023

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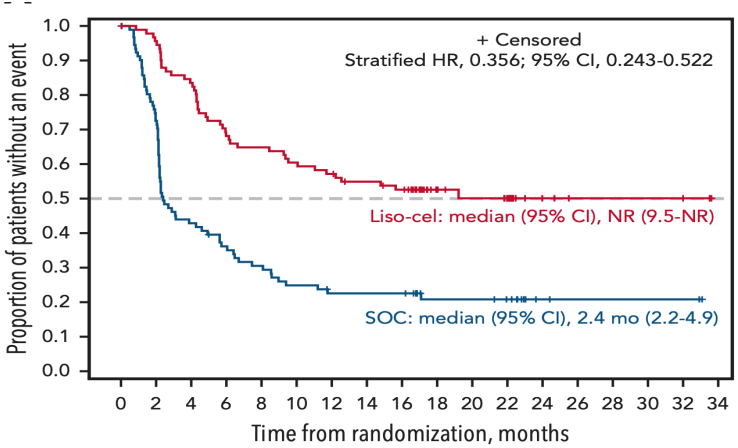
CAR-T improves outcomes in Transplant Eligible DLBCL in 2L Setting: Results of ZUMA-7 and TRANSFORM

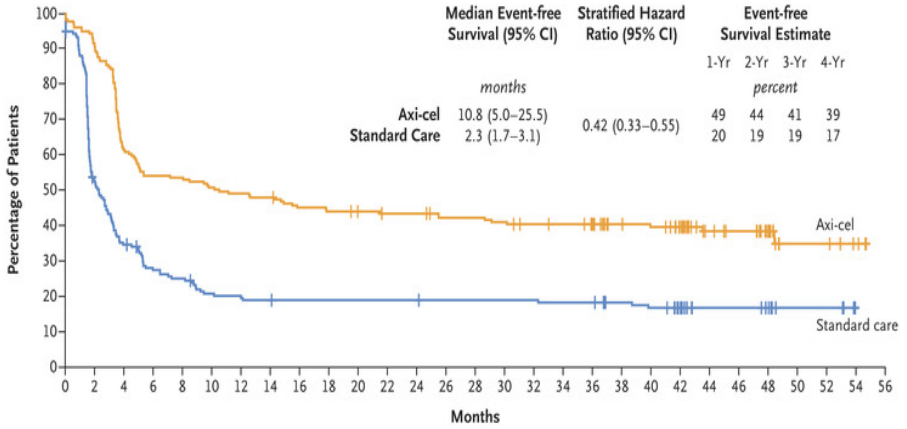
TRANSFORM
Lisocabtagene maraleucel vs SOC

Median F/U: 24.9 months
Median age: 60 (20 – 74)
Enrolled (CAR-T) 92
Best ORR: 87%
Best CR: 74%
PFS: NR



ZUMA-7
Axicabtagene Ciloleucel vs SOC

Median F/U 47.2 months
Median age: 58 (21 – 80)
Enrolled (CAR-T): 180
Best ORR: 83%
Best CR: 65%
PFS: 14.7 months



Abramson et al. Blood 2023; Locke et al. NEJM 2021

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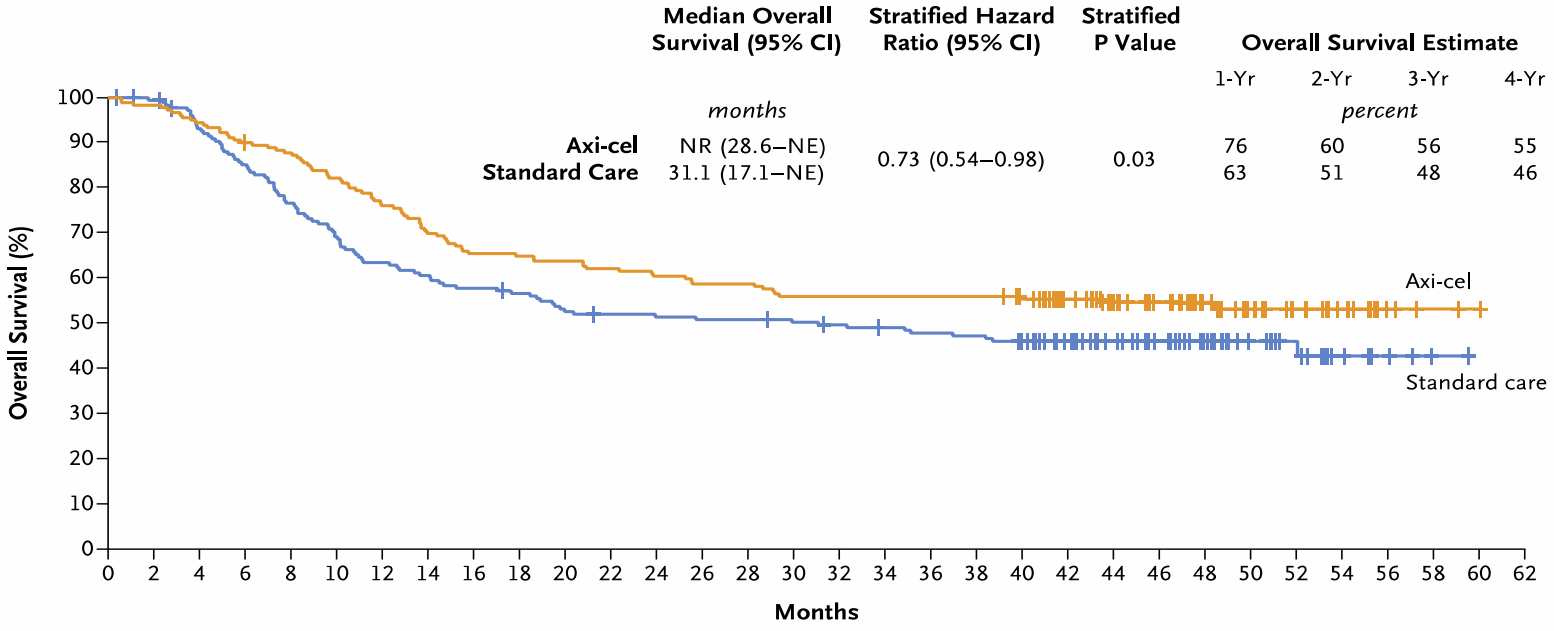
ZUMA-7 Improved OS with CAR-T as second line therapy



Westin J et Al. N Eng J Med 2023

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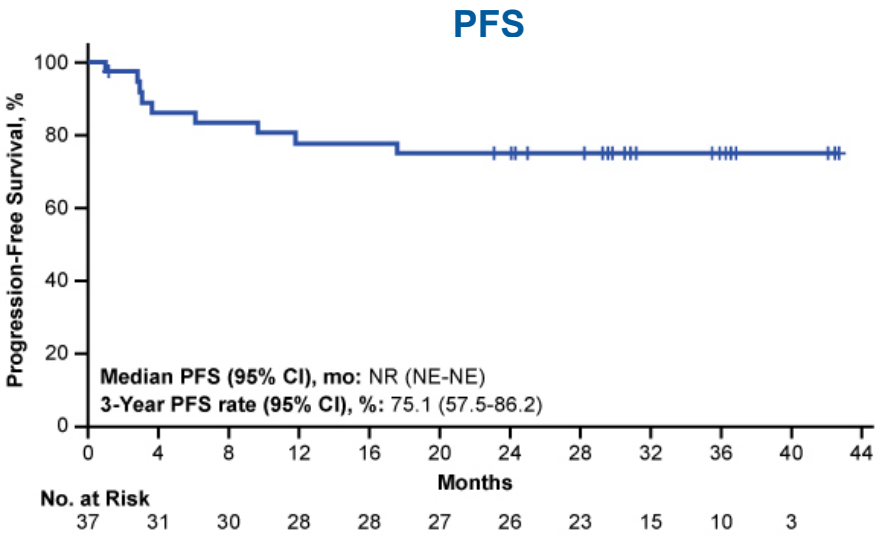
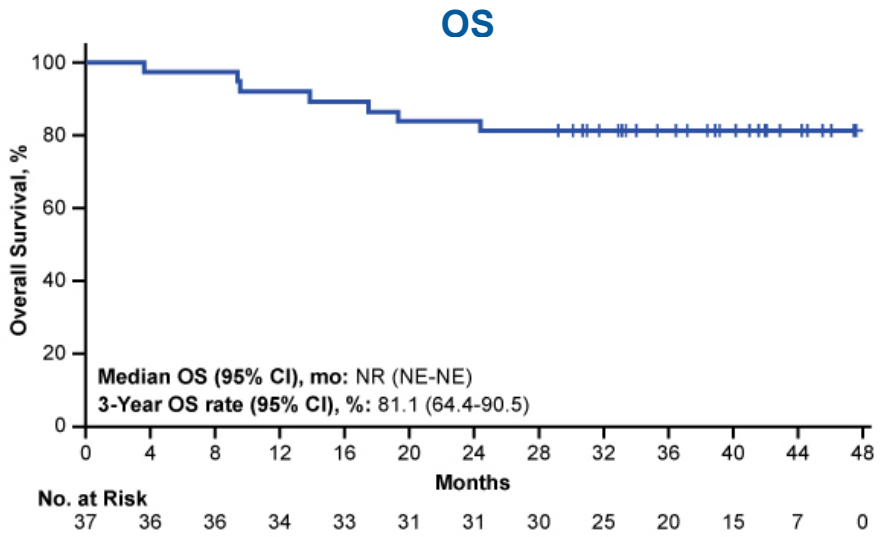
ASH 2023 update: ZUMA-12- Axi-Cel as Frontline Therapy for High Risk DLBCL: 3-year follow up Phase 2 study





- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates **were 84.4%** (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

Chavez JC et Al. ASH Meeting Abstracts 2023

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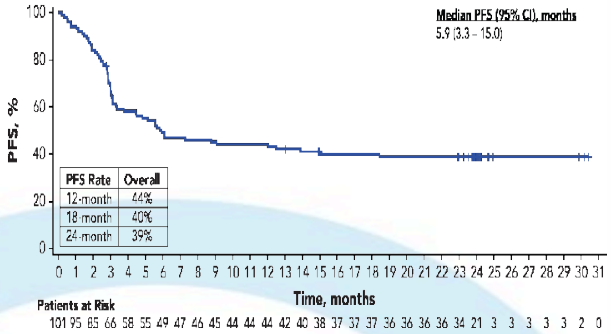
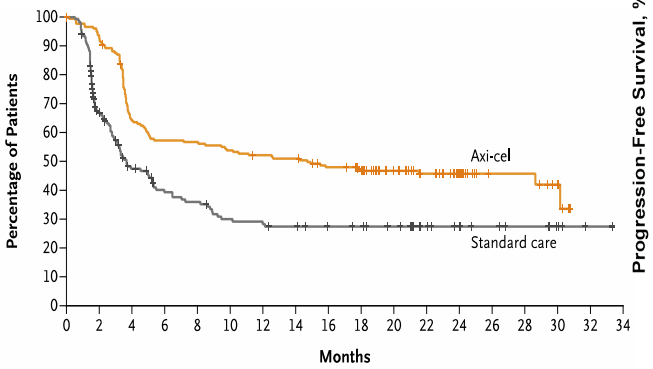
Earlier use of CART may improve outcomes

ZUMA-1



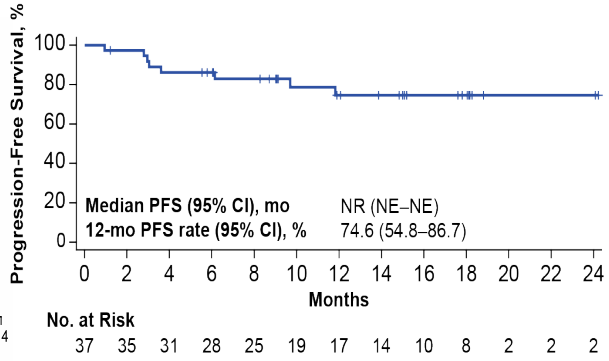
3rd L DLBCL
Median PFS 5.9 months

ZUMA-7



2nd L DLBCL
Median PFS (axi-cel arm): 14.6 months

ZUMA-12



1st L HR DLBCL
Median PFS: Not reached

Locke et al. *Lancet Oncol* 2018, Locke et al. *N Eng J Med* 2021, Neelapu ASH Meeting Abstracts 2021

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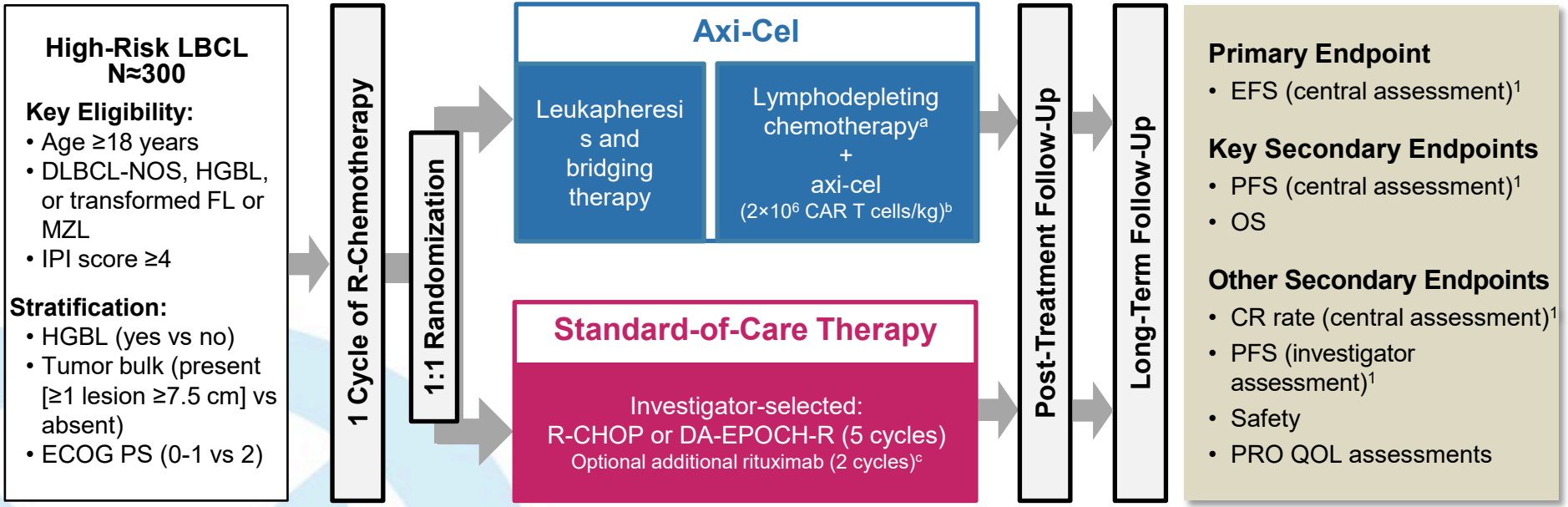
ZUMA-23 Phase 3 Study Design



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Efficacy of FDA approved CAR-T and BiAbs in R/R LBCL (3rd line)

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
Median F/U	60 months	24 months	40.3 months	10.7 months	12.6 months
ORR	83%	75%	52%	63.1%	52%
CR	54%	53%	40%	38.9%	39%
PFS	5.9 months	6.8 months	2.9 months	4.4 months	4.9 months
OS	25.8 months	27.3 months	11.1 months	NR	8.9 months

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *N Eng J Med* 2022.

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Key Immune-Related Toxicities: CAR-T and BiAbs

	ZUMA-1	TRANSCEND	JULIET	EPCORE	GO
Product	**Axi-Cel**	**Liso-Cel**	**Tisa-Cel**	**Epcoritamab**	**Glofitamab**
CRS (all grades)	93%	39%	58%	47.9%	63%
CRS $\geq$ 3	13%	1%	22%	2.5%	4%
ICANS (all grades)	64%	23%	21%	6.4%	8%
ICANS $\geq$ 3	28%	10%	12%	0.6%	3%

Neelapu et Al. *Blood* 2023, Abramson et Al. *Blood* 2023, Schuster et Al. *Lancet Oncology* 2021, Thieblemont at Al. *J Clin Oncol* 2022, Dickinson M et Al. *N Eng J Med* 2022.

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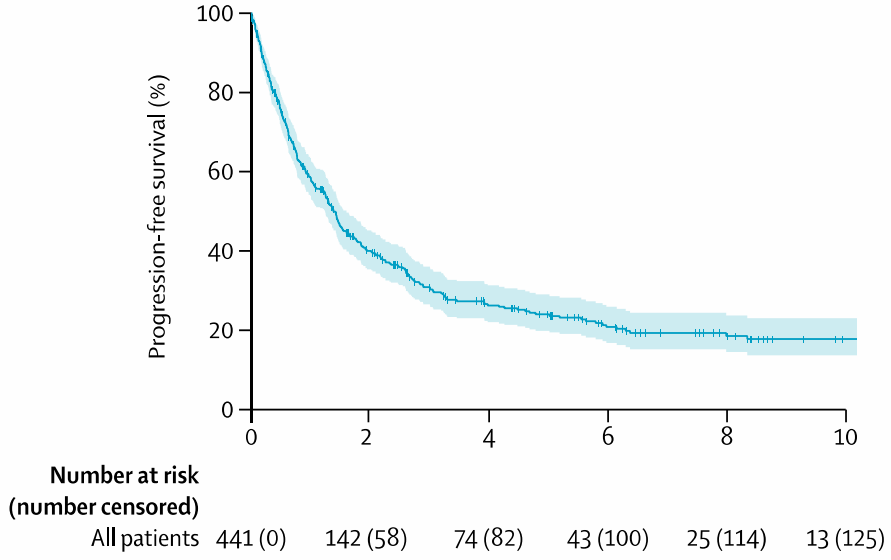
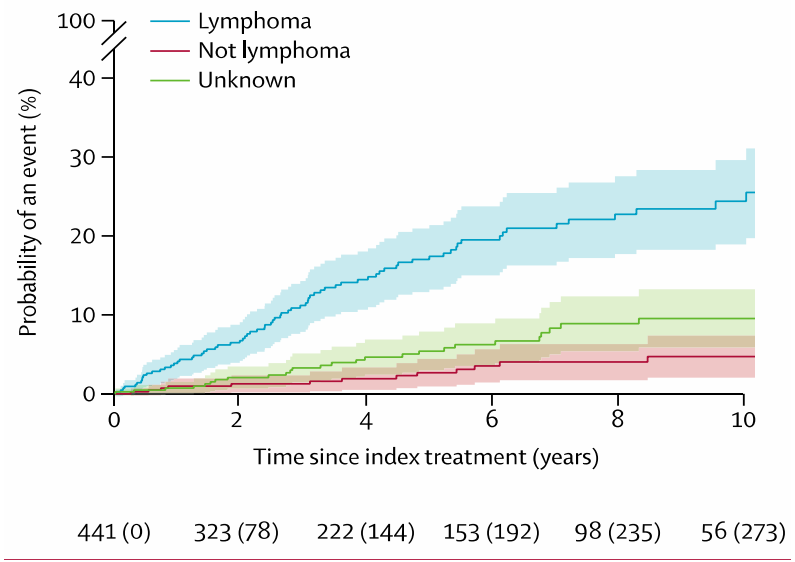
Follicular Lymphoma

LEO-CReWE: Outcomes at third line therapy for R/R FL

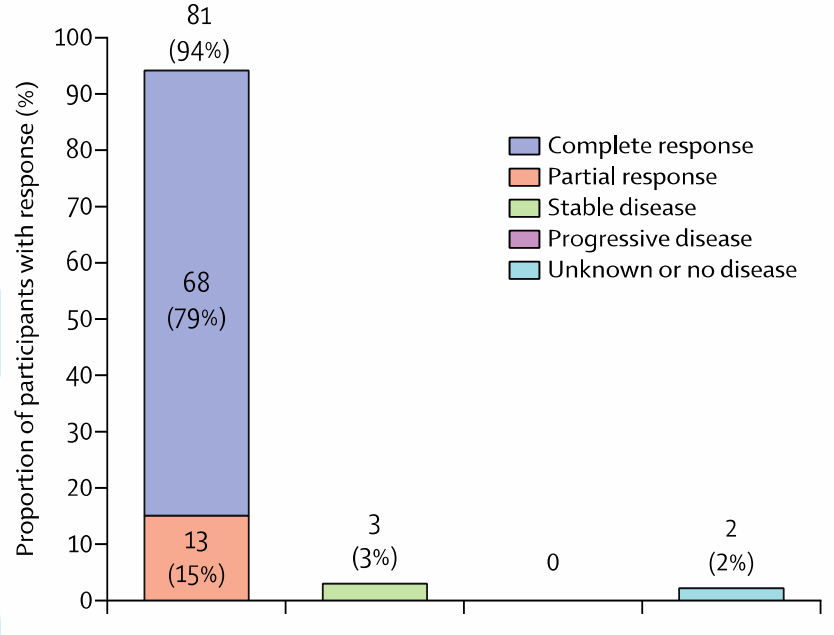




Casulo C et al. *Lancet Haematol* 2022

ZUMA-5 vs ELARA: High responses rates with CAR-T in R/R FL

ZUMA-5



ELARA

Efficacy Results of extended Follow-up Analysis (n=97 pts, median F/U 17 months)

Endpoint	% (95% CI)
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**86.5** (74.7-93.1)

Jacobson C et Al. Lancet Oncol 2021; Fowler N et Al. Nat Medicine 2022

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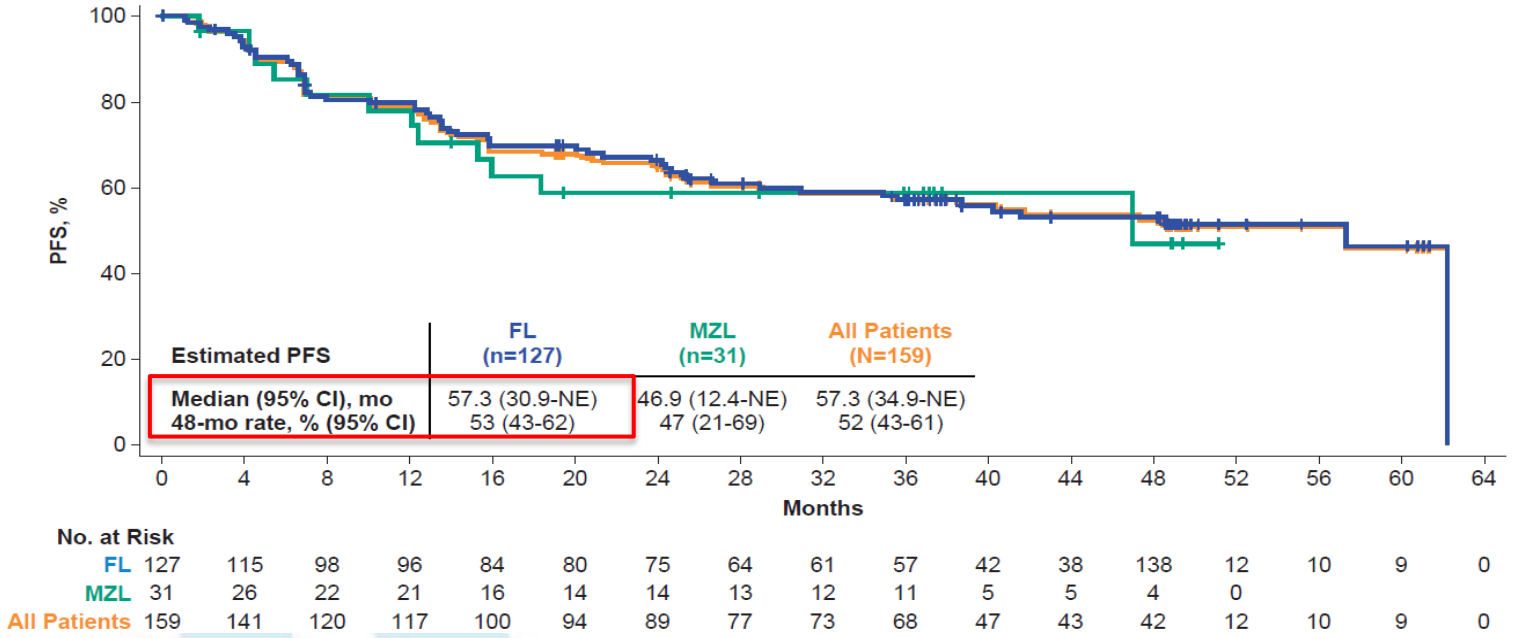
ASH 2023 Update: 4-year follow up ZUMA-5 Axi-Cel 3L R/R FL



Median follow- up 52 months
Median PFS for FL pts 57.3 months

Neelapu S et Al. *ASH Meeting* 2023.

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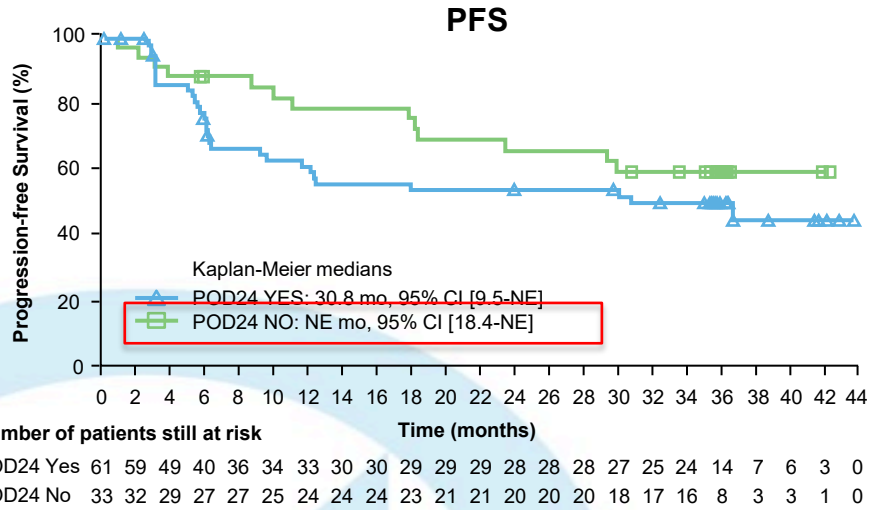
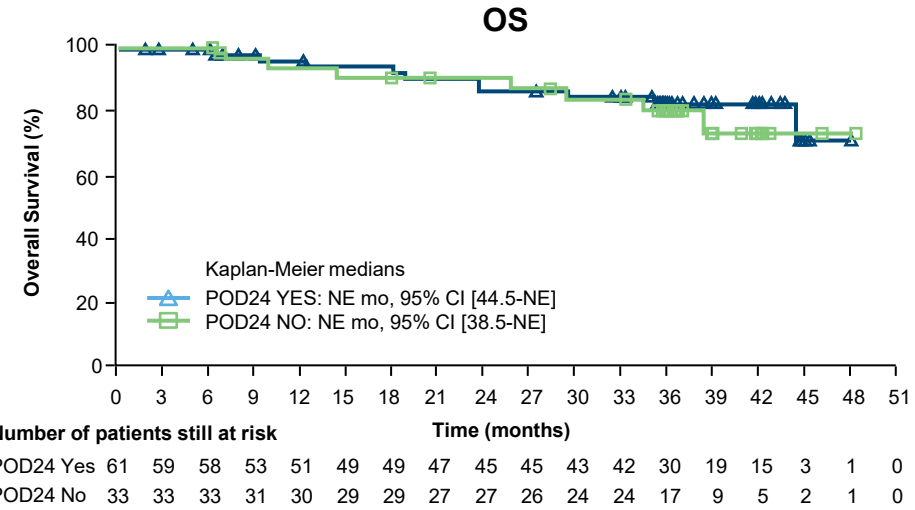
ASH 2023 Update: 3-y Follow Up ELARA-Tisagenlecleucel for R/R FL



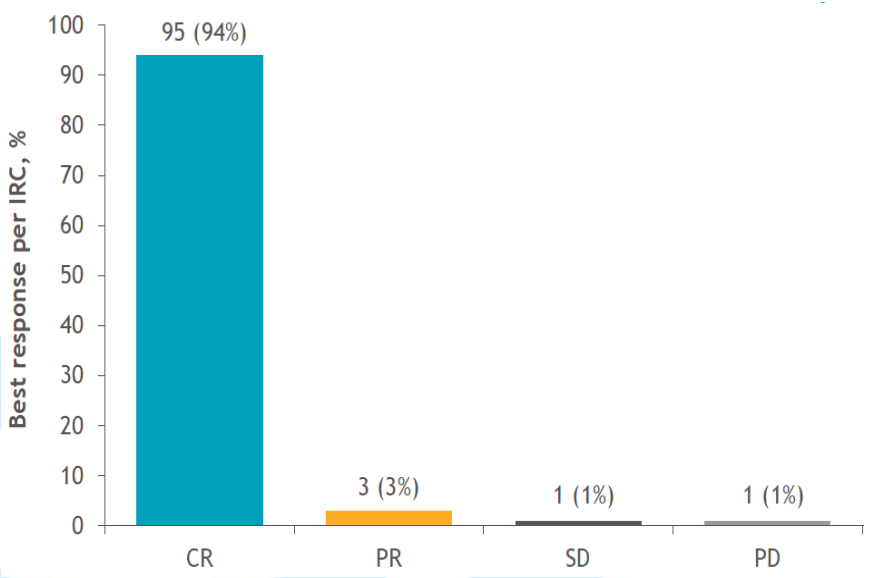


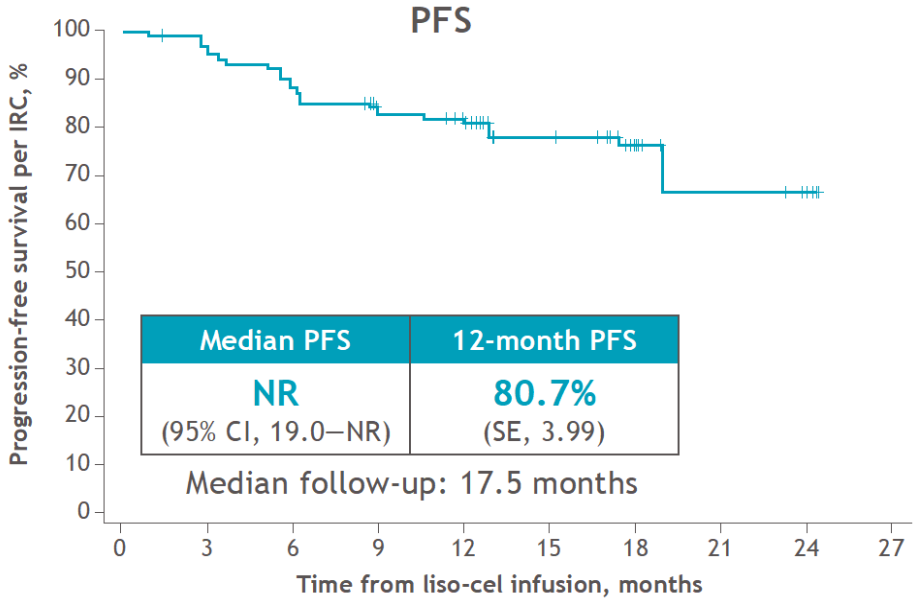
Median follow- up 30 months

Median PFS for FL pts **37 months** (not reached for non POD24 FL)

Schuster S et Al. *ASH Meeting* 2023.

SOHO 2023 update: Primary Analysis of TRANSCEND FL: Lisocabtagene Maraleucel for 3L R/R FL





Nastoupil L et al. SOHO 2023, Morschhauser F et al. Nat Medicine 2024

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CAR-T versus Bispecific Antibodies R/R FL

	ZUMA-5	TRANSCEND-FL	ELARA	EPCORE	GO
Product	**Axi-Cel (N= 140)**	**Liso-Cel (N= 114)**	**Tisa-Cel (N= 90)**	**Epcoritamab (N= 128)**	**Mosunetuzumab (N=90)**
Median F/U	52.5 months	17.6 months	30 months	17.4 months	37.8 months
Median Lines	3 (1 – 10)	3 (2 – 10)	4 (2 – 13)	3 (2 – 4)	3 (2 – 4)
POD24	55%	43 %	60%	42%	52%
Grade $\geq$ 3 CRS	8 %	1 %	0 %	2 %	1 %
ORR	94 %	97%	86 %	82 %	80%
CR	79 %	94%	68 %	63 %	60%
PFS	57.3 months	NR	37 months	15.4 months	24 months

Neelapu et Al. *Blood* 2023, Morschhauser F et Al. *Nat Medicine* 2024, Fowler N et Al *Nat Medicine* 2023, Schuster et Al. *ASH* 2023, Limton K. *Lancet Haematol* 2024, Budde E et AL. *Lancet Oncol* 2023

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ZUMA-22 Study Overview

R/R FL Subjects defined as: 1) POD24* after initiation of 1st line of therapy (2L POD24)
OR
2) All-comers after ≥ 2 prior lines of therapy (3L+ All-comers including POD24)

1:1 Randomization
n = Approximately 230, ~75 sites globally
Primary Endpoint: PFS

Stratification:
- 1 vs ≥ 2 prior lines
- POD24 vs Non-POD24
- US vs non-US site

Optional corticosteroid bridging

Axi-cel

Investigator Choice: R-CHOP, BR, or R2

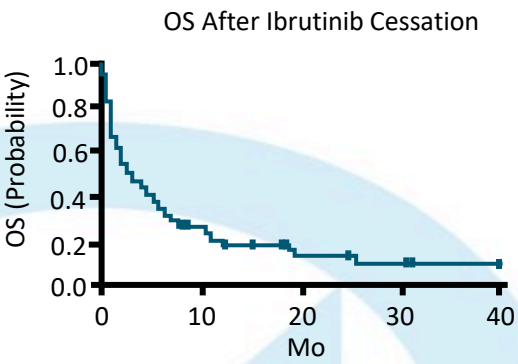
Mantle Cell Lymphoma

Poor Outcomes in MCL post BTKi pogression

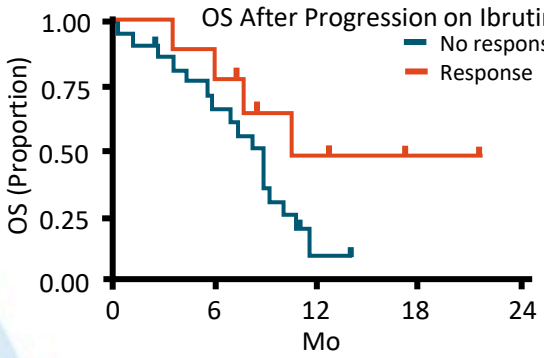
Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]

BTK C481-mutations are uncommon; bypass alterations and epigenetic changes implicated in some patients[7]

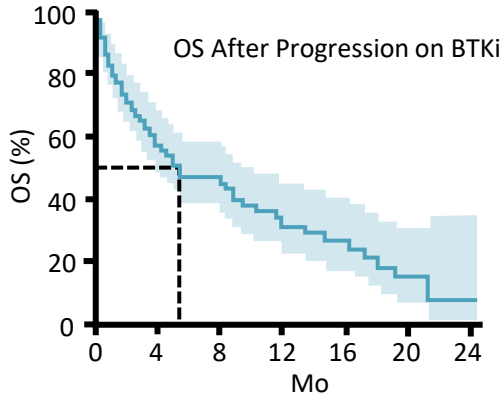
Overall Survival Following Covalent BTK Inhibitor Therapy[3,4,11]



N = 114 (global)[4]
Median OS: 2.9 mo



N = 31 (US)[3]
Median OS: 8.4 mo



N = 108 (Japan)[11]
Median OS: 5.46 mo

1. Hershkovitz-Rokah. Br J Haemtol. 2018;181:306. 2. Wang. NEJM. 2013;369:507. 3. Cheah. Ann Oncol. 2015;26:1175.
4. Martin. Blood. 2016;127:1559. 5. Dreyling. Lancet. 2016;387:770. 6. Epperla. Hematol Oncol. 2017;35:528.
7. Ondrisova. Front Oncol. 2020;10. 8. O'Brien. Clin Lymphoma Myeloma Leuk. 2018;18:648. 9. Byrd. Blood. 2019;130(suppl 1):4326.
10. Tam. Blood. 2020;136:2038. 11. Rai. Clin Lymphoma Myeloma Leuk. 2021;21(suppl 1):S407.

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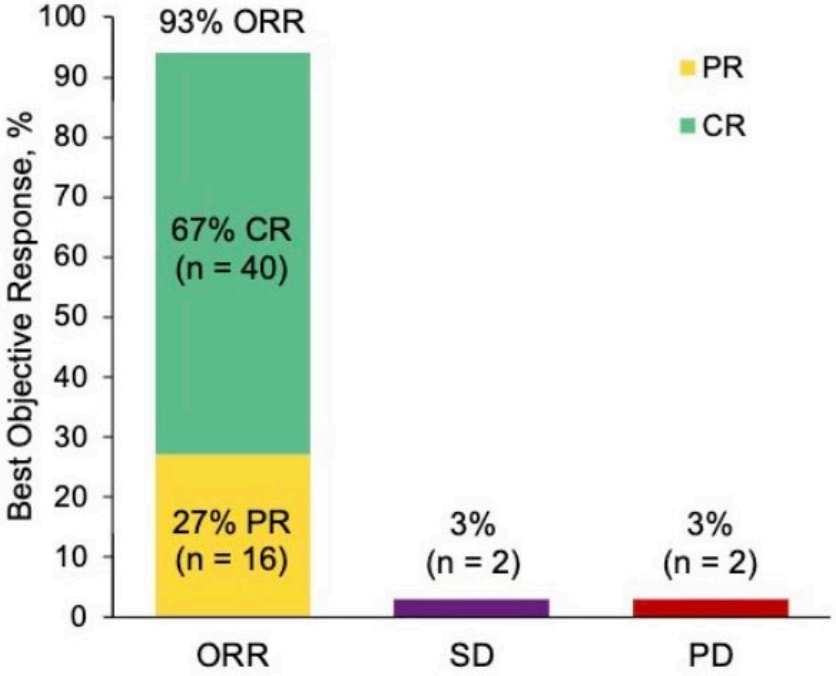
ZUMA-2: Brexucabtagene Autoleucel: ORR and CR rates in *BTKi refractory* MCL



Cytokine release syndrome
CRS (all grades): 91%
CRS > 3: 15%

Neurologic events
ICANS (all grades): 63%
ICANS > 3: 31%

Wang et al. *J Clin Oncol* 2022

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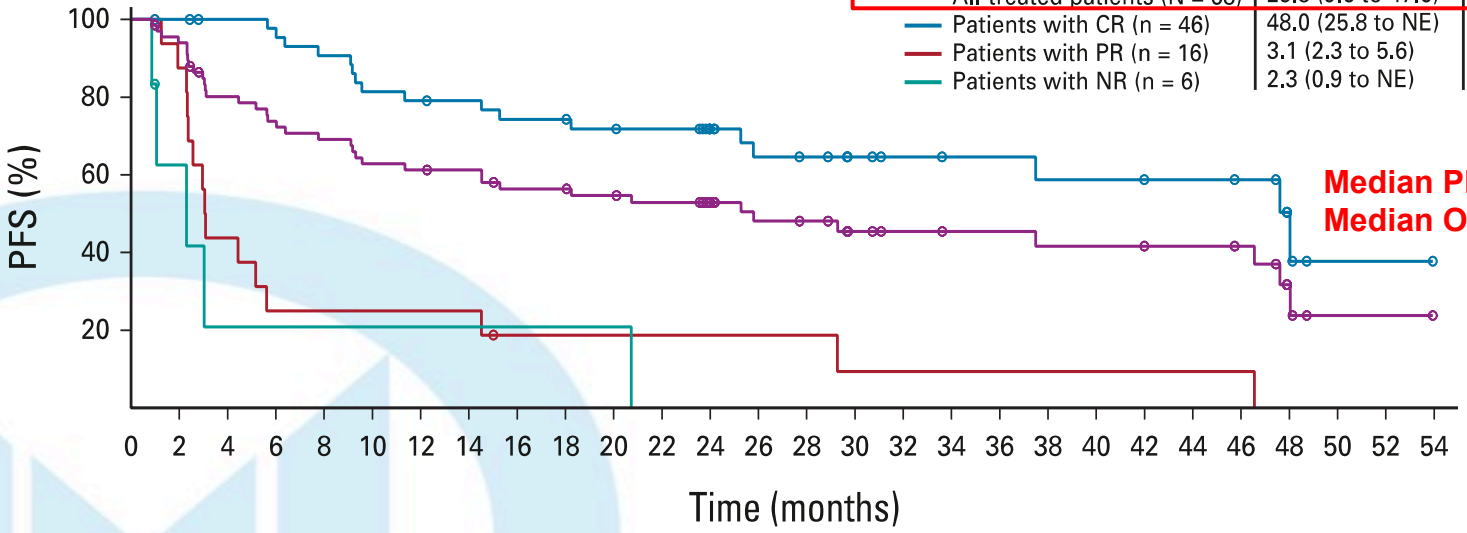
ZUMA-2: Brexu-Cel in BTKi Refractory MCL: PFS and OS at 3-y follow up

	Median PFS, Months (95% CI)	24-Month PFS Rate, % (95% CI)
All-treated patients (N = 68)	25.8 (9.6 to 47.6)	52.9 (39.9 to 64.3)
Patients with CR (n = 46)	48.0 (25.8 to NE)	71.8 (55.7 to 82.9)
Patients with PR (n = 16)	3.1 (2.3 to 5.6)	18.8 (4.6 to 40.2)
Patients with NR (n = 6)	2.3 (0.9 to NE)	ND



Median PFS= 25.8 months
Median OS= 46.6 months

Wang M et al. *J Clin Oncol* 2022

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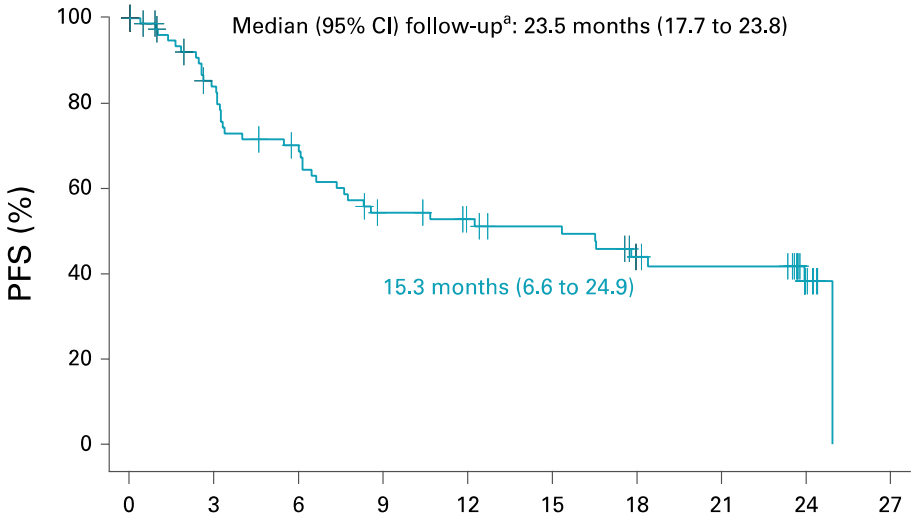
ASCO 2023 Update: Lisocabtagene Maraleucel for BTKi refractory MCL

Baseline Characteristics

Apheresed: 104; Infused: 88 pts
MIPI high risk: 6%
Median lines therapy: 3 (1-11)
Prior auto HCT: 30%
Prior BTKi: 94%
TP53 mut: 23%

Key results

Median follow up: 23.5 months
ORR: 86.5%
CR: 74.3%
CRS all (G>3): 61% (1%)
ICANS all (G>3): 31% (9%)



Wang M et al. *J Clin Oncol* 2023

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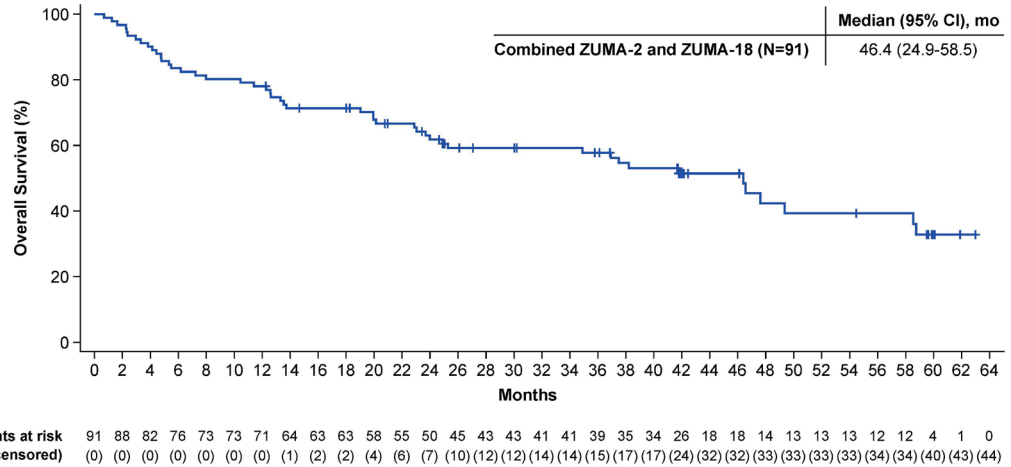
ASH 2023 Update: Brexu-Cel for R/R MCL (ZUMA-2 and ZUMA-18)

ZUMA-2 (n=68 pts)
Pivotal cohort
Median Follow-Up 47.5 months

ZUMA-18 (n=27 pts)
Expanded access cohort
Median Follow-Up: 33.5 months
ORR 87%, CR 57%

Figure 2. Combined Overall Survival in ZUMA-2 and ZUMA-18



Goy A et al. ASH Meeting 2023

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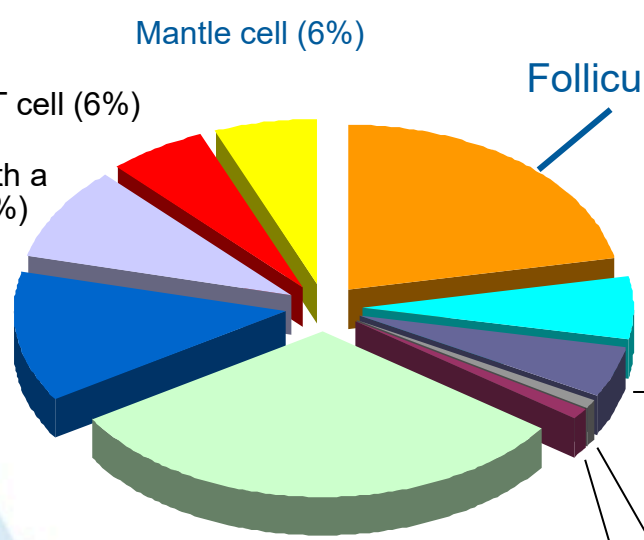
We have CAR-T Available (Essentially) for All B-cell Lymphomas



Brexu-Cel, Liso-cel

Mantle cell (6%)

Follicular (22%)

Tisa-cel, Liso-cel, Axi-cel

Peripheral T cell (6%)

Other subtypes with a frequency ≤2% (9%)

Unmet need

Small lymphocytic (6%)

Liso-cel

Composite lymphomas (13%)

Marginal zone, B cell, MALT type (5%)

Liso-cel, Axi-Cel

Marginal zone, B cell, nodal type (1%)

Diffuse large B cell, HGBCL (31%)

Tisa-cel, Liso-cel, Axi-cel

Lymphoplasmacytic (1%)

Armitage. J Clin Oncol. 1998;16:2780.

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CAR-T: Challenges

- Access
- Early referral
- Cost (shared: product and resource utilization)
- Toxicities (early and late- SPM)

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