Chimeric Antigen Receptor (CAR) T-Cell Therapy for Non-Hodgkin Lymphoma

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Commercial CD-19 CAR-T cell therapy for NHL

- **Aggressive NHL**
  - Tisagenlecleucel
  - Axicabtagene ciloleucel (Axi-cel)
  - Lisocabtagene maraleucel (Liso-cel)

- **Follicular Lymphoma**
  - Axicabtagene ciloleucel
  - Tisagenlecleucel

Mantle Cell lymphoma

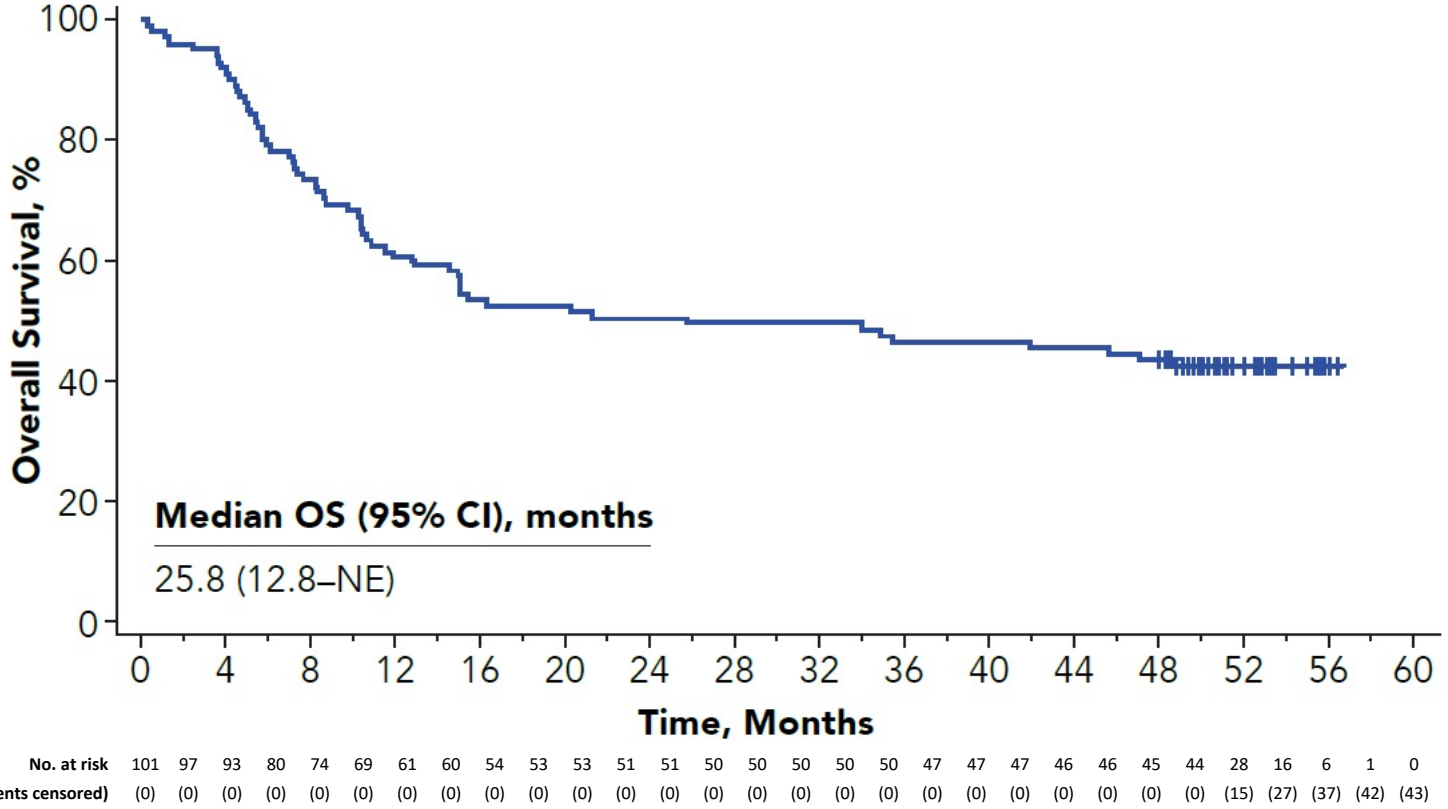
- Brexucabtagene autoleucel

Aggressive lymphoma: commercial CD19 CAR T cell products

Feature	Tisagenlecleucel	Axi-cel	Liso-cel
Construct	FMC-63 murine scFv 4-1BB co-stimulatory domain	FMC-63 murine scFv CD28 co-stimulatory domain	FMC-63 murine scFv 4-1BB co-stimulatory domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis Cryopreserved Bulk cells	Resting state apheresis Fresh only Bulk cells	Resting state apheresis Fresh only Selection CD4 and CD8
Manufacture	CD3/CD28 stimulation	CD3/CD28 stimulation	CD4, CD8 selection CD3/CD28 stimulation
Dose administered	0.6–6.0 × 10^8 CAR T cells CoA based on cell recovery	2 × 10^6/kg Max. 200 × 10^6 No CoA	100 × 10^6 (CD4/CD8) in separate vials (1:1) Dose based on recovery
Histology	DLBCL tFL	DLBCL PMBCL tFL	DLBCL, HGBCL PMBCL Indolent (FL, CLL, MZL)
CNS involvement	No	No	Yes, secondary

ZUMA-1: durable responses with axi-cel in patients with r/r DLBCL

Updated long-term data (median follow-up: 51.1 months)



Patients, n (%)	Axi-cel (N = 111)
Deaths	66 (59)
Primary cause of death	
PD	52 (47)
Other	8[a] (7)
AEs	5[b] (5)
Secondary malignancy	1 (1)

Data cut-off date: August 11, 2020.

[a] Three events had no causal relationship (MDS, cardiac arrest), 4 events occurred post subsequent therapy (sepsis, infection, and pulmonary nocardiosis), and 1 event was unknown.

[b] One event was related to conditioning chemotherapy, 2 events had no causal relationship, and 2 events were related to axi-cel.

AE, adverse event; CI, confidence interval; MDS, myelodysplastic syndrome; NE, not estimable; PD, disease progression; RR, relapsed/refractory.

Jacobson C, et al. Long-term survival and gradual recovery of B cells in patients with refractory large B-cell lymphoma treated with axicabtagene ciloleucel. Poster presented at TCT 2021;abstract 494.

CIBMTR Analysis of Commercial Axi-cel

Characteristics	RWE	ZUMA-1
n	1297 tx	111 101 tx (91%)
Median age (range)	62 (20-91)	58 (23-76)
ECOG PS >1	5%	0
High risk IPI (≥ 3)	NR	485
Median prior tx	3	3
Bridging therapy	22%	0
Prior ASCT	28%	21%
Histology DLBCL HGBCL PMBCL Other	 79% 16% 3% 1%	 76% NR 8% NA
Ineligible for pivotal trial	57%	0

Reasons for Zuma-1 Ineligible	N=76
Pulmonary disease	50%
Cardiac dysfunction	23%
Prior malignancy	23%
ECOG >1	8%
Rheumatologic disease/IBD	8%
Active infection	7%
Ineligible histology	6%
Prior checkpoint inhibitor	5%
Hepatic dysfunction	4%
Renal dysfunction	4%
CNS involvement	3%
Allo SCT	2%

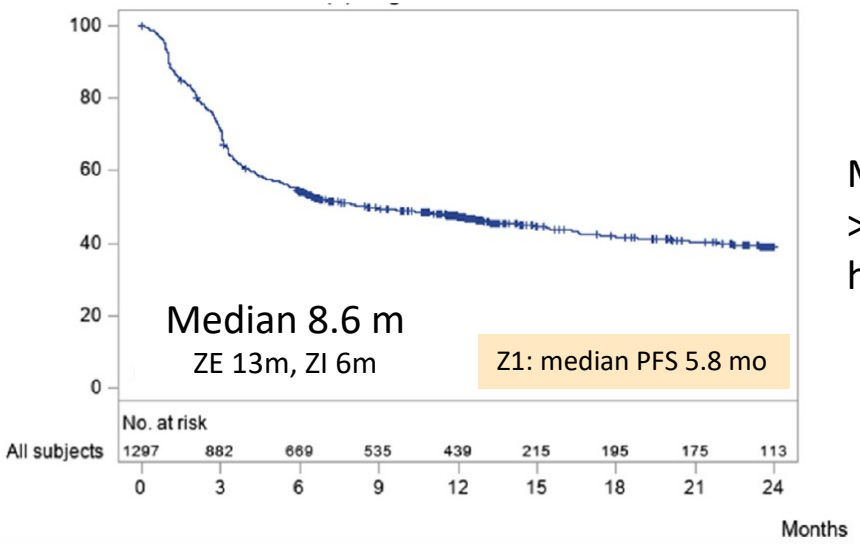
Median infusion time 28 days from apheresis

Jacobson, et al. JTCT 2022

CIBMTR Analysis of Commercial Axi-cel: Efficacy

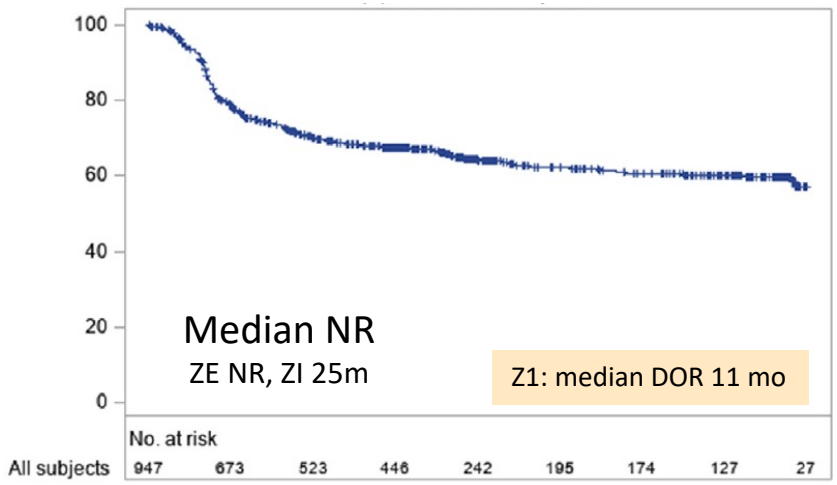
Response	Total N=1297	Z-1 eligible N=558	Z-1 inelig N=739	ZUMA-1
ORR	73%	76%	71%	83%
CR	56%	60%	52%	58%

Progression-free Survival

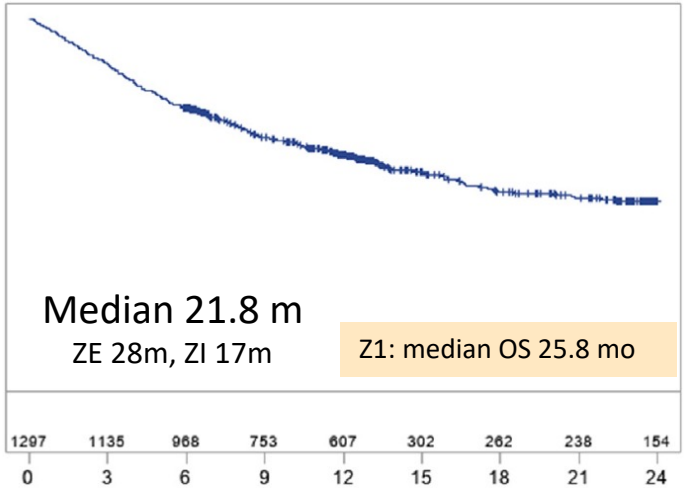


MVA: Inferior PFS with ECOG >1, chemoresistant, severe hepatic disease

Duration of Response (median f/u 23 m)



Overall Survival



MVA: Inferior OS with ECOG >1, chemoresistant

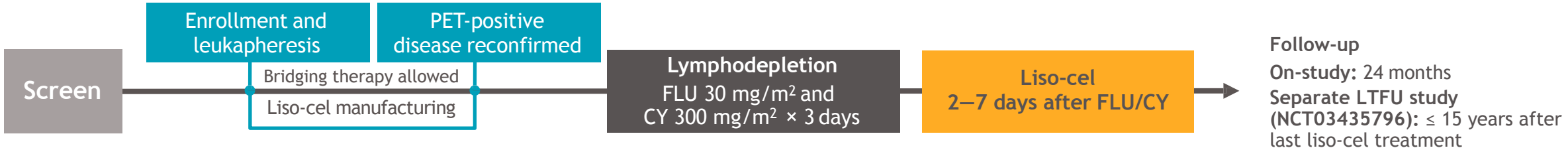
Jacobson, et al. JTCT 2022

CIBMTR Analysis of Commercial Axi-cel: CRS and ICANS

Toxicity	Total N=1297	Z-1 eligible N=558	Z-1 inelig N=739	ZUMA-1
Any grade CRS	83%	83%	83%	93%
≥Grade 3 CRS	8%	6%	10%	13%
Any grade neurotoxicity	55%	58%	72%	64%
≥ Grade 3 neurotoxicity	24%	26%	36%	28%
ICU transfer	28%	17%	34%	NR
Tocilizumab +/- steroid	58%	59%	57%	43%
Steroids alone	7%	8%	7%	27%

Jacobson, et al. JTCT 2022

TRANSCEND NHL 001, a seamless design, pivotal, phase 1 study[1,2]



Patient eligibility

- Age ≥ 18 years
- LBCL after ≥ 2 lines of therapy
  DLBCL NOS (de novo; transformed from FL, CLL, MZL, or other)
  HGBCL (double/triple hit), PMBCL, FL3B
- Prior HSCT allowed (autologous/allogeneic)
- ECOG PS of 0–2
- Patients with secondary CNS lymphoma were eligible
- CrCl > 30 mL/min/1.73 m², LVEF ≥ 40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

Endpoints

Primary: AEs, ORR by IRC

Secondary: CR rate by IRC, DOR, PFS, OS, PK

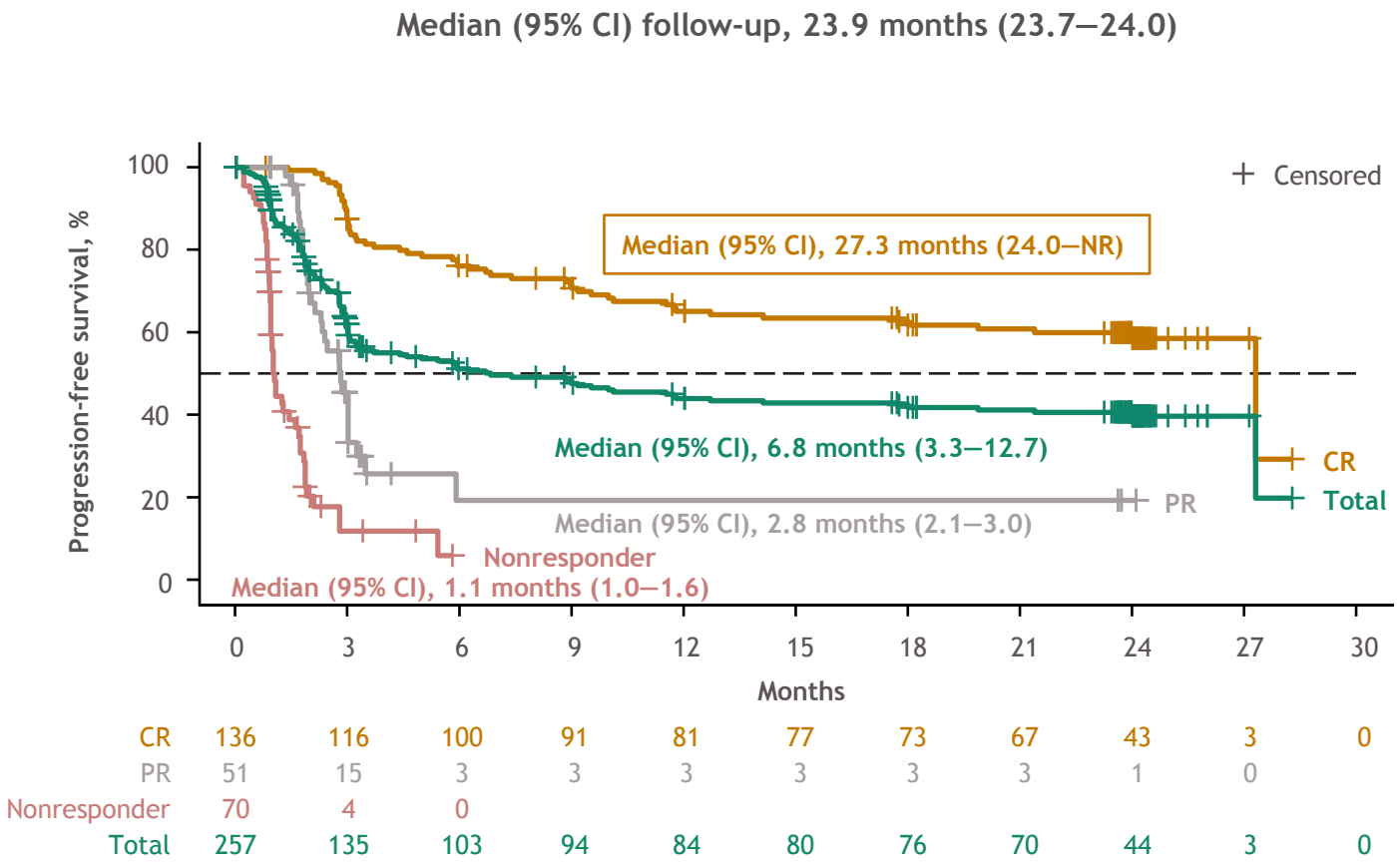
Analysis sets

- **Safety analysis set (N = 270):** patients who received ≥ 1 dose of liso-cel
- **Efficacy-evaluable set (N = 257):** patients with confirmed PET-positive disease who received ≥ 1 dose of liso-cel

- In TRANSCEND, patients were followed for 2 years after the last dose of liso-cel. As of the January 2021 data cut, study is ongoing; 268 patients had ≥ 24 months of follow-up, or died, or withdrew from the study
- Of 120 patients in the liso-cel—treated set who completed TRANSCEND, 81 consented to a separate long-term follow-up study of safety and OS for up to 15 years; however, no IRC response assessments were performed (NCT03435796)

1. Abramson JS, et al. *Lancet* 2020;396:839—852; 2. ClinicalTrials.gov identifier: NCT02631044.

Progression-free survival by IRC assessment per Lugano 2014 criteria[1,a]



- Median (95% CI) PFS was 6.8 months (3.3–12.7)
- Probability (95% CI) of PFS at 2 years was 40.6% (34.0%—47.2%)

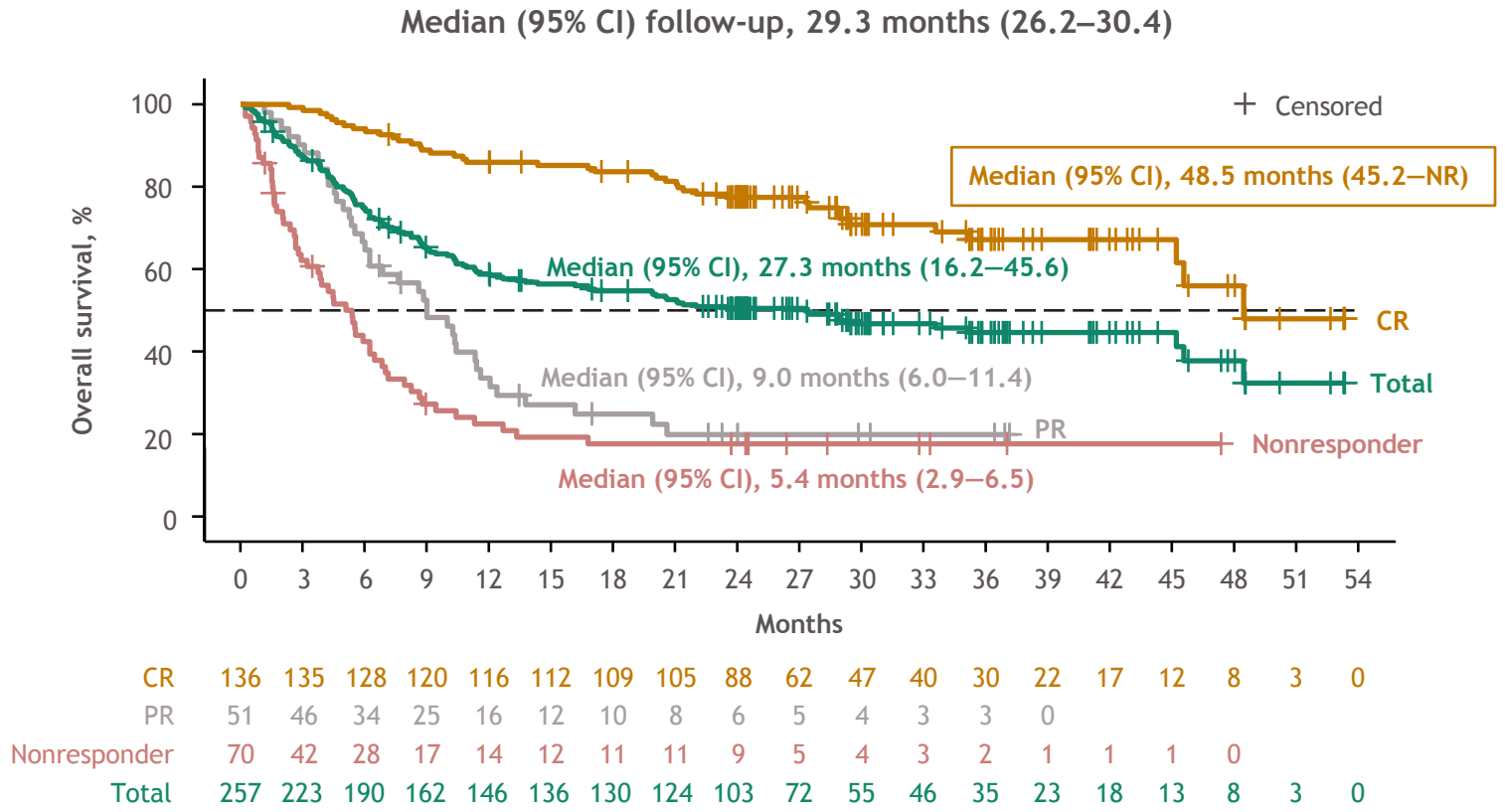
- At 27 months after liso-cel infusion, 1 patient (same as in the DOR curve at 26 months) died because of sepsis and had ongoing CR

[a]KM method was used to calculate median (95% CI) of PFS; reverse KM method was used to calculate median (95% CI) of follow -up. Only includes data from TRANSCEND.
PFS, progression-free survival.

1. Cheson BD, et al. *J Clin Oncol* 2014;32:3059—3068.

Abramson J, TCT, 2022

Overall survival[a]



- Median (95% CI) OS was 27.3 months (16.2–45.6)
- Probability (95% CI) of OS at 2 years was 50.5% (44.1%—56.5%)

- Three deaths occurred after 45 months
  - Two patients died because of unknown causes and had ongoing response
  - One patient died because of disease progression
- CAR T cell persistence was detected at 48 months in the LTFU study and in 37% (26 of 70 patients) of patients at 24 months in TRANSCEND

OS analysis incorporated survival data from the separate LTFU study (**NCT03435796**)

[a]KM method was used to calculate median (95% CI) of OS; reverse KM method was used to calculate median (95% CI) of follow -up. Includes survival data from patients who completed TRANSCEND and enrolled in the subsequent LTFU study.
LTFU, long-term follow-up.

Abramson J, TCT, 2022

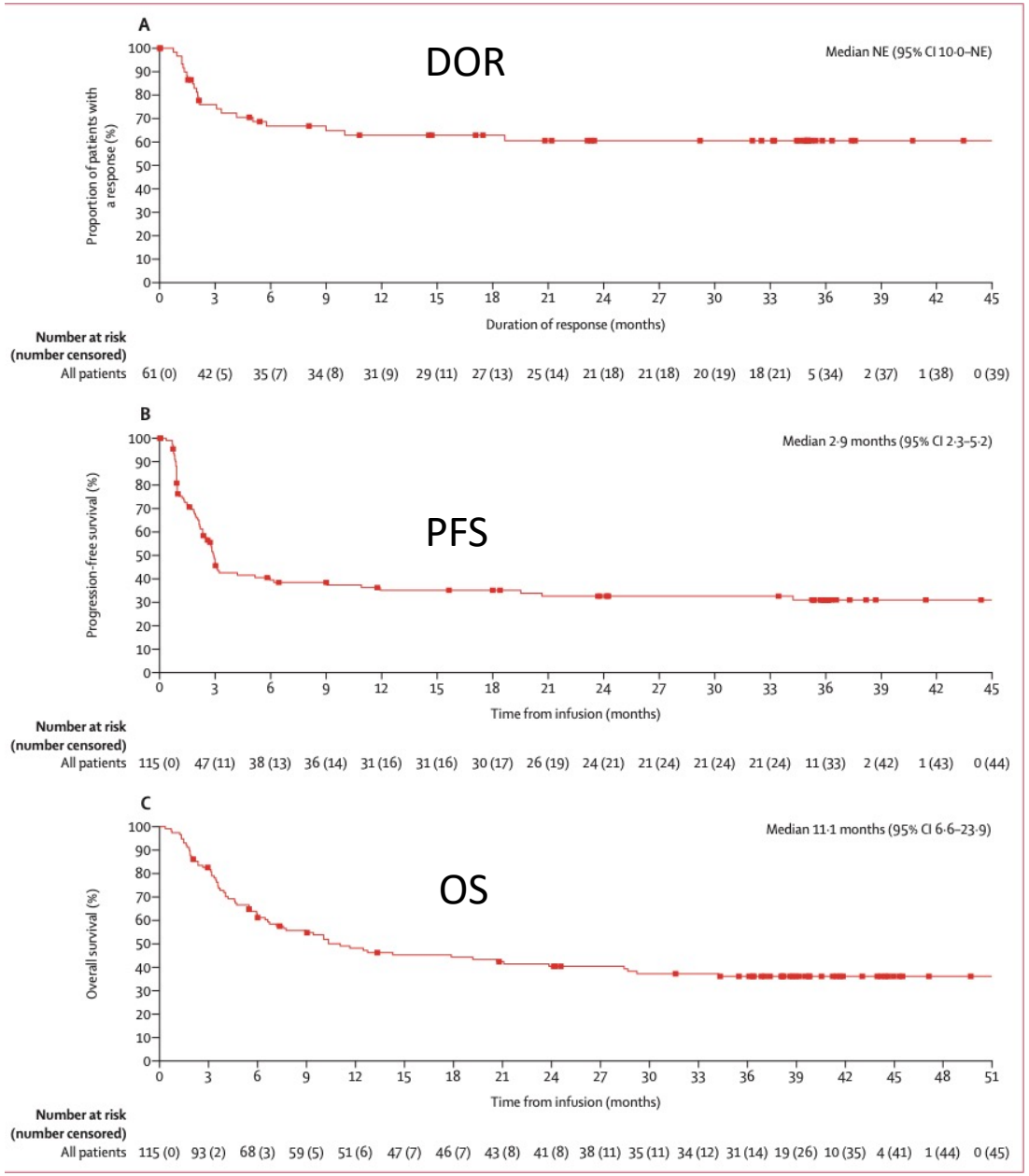
Tisagenlecleucel for Aggressive NHL: JULIET trial

Phase II trial, CD19 directed CAR-T

Enrolled = 167
Infused = 115

ORR = 53%
CR = 39%

CRS = 27%

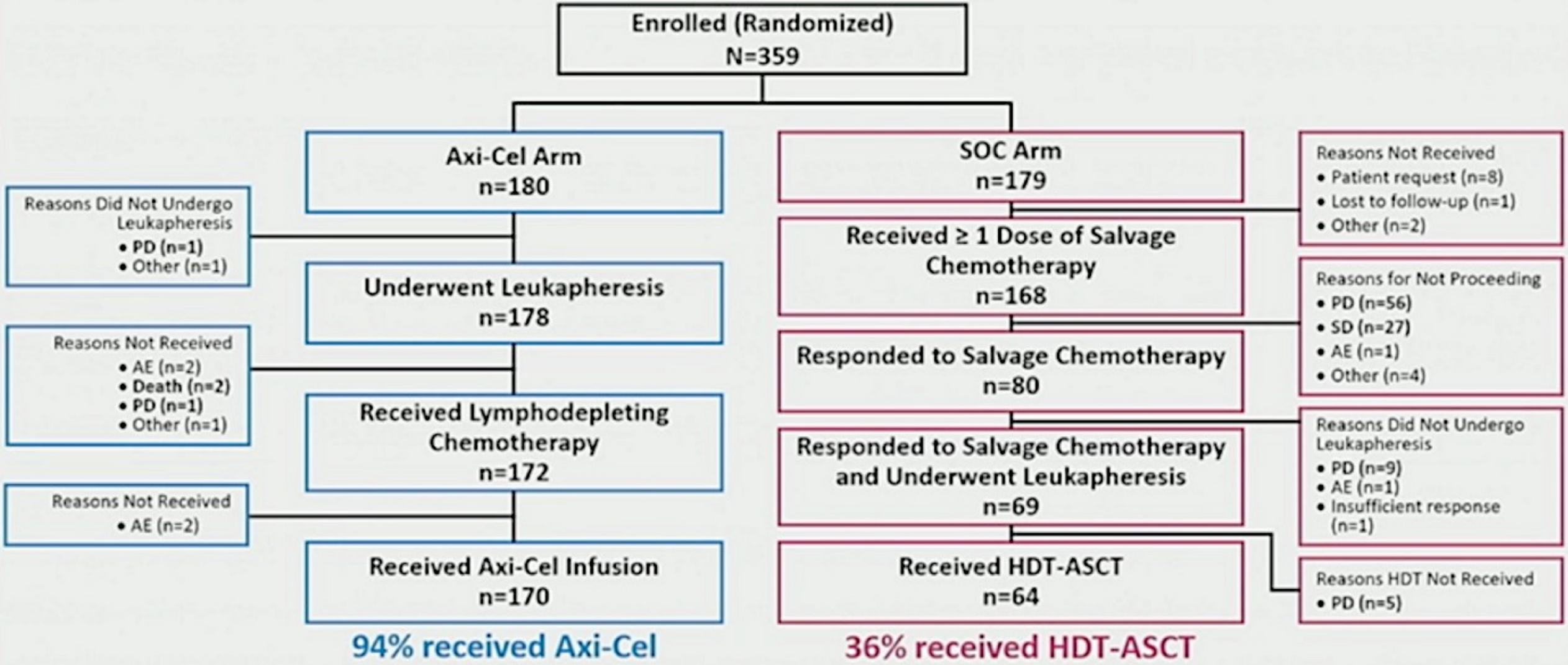


Schuster, SJ Lancet Oncology, 2021

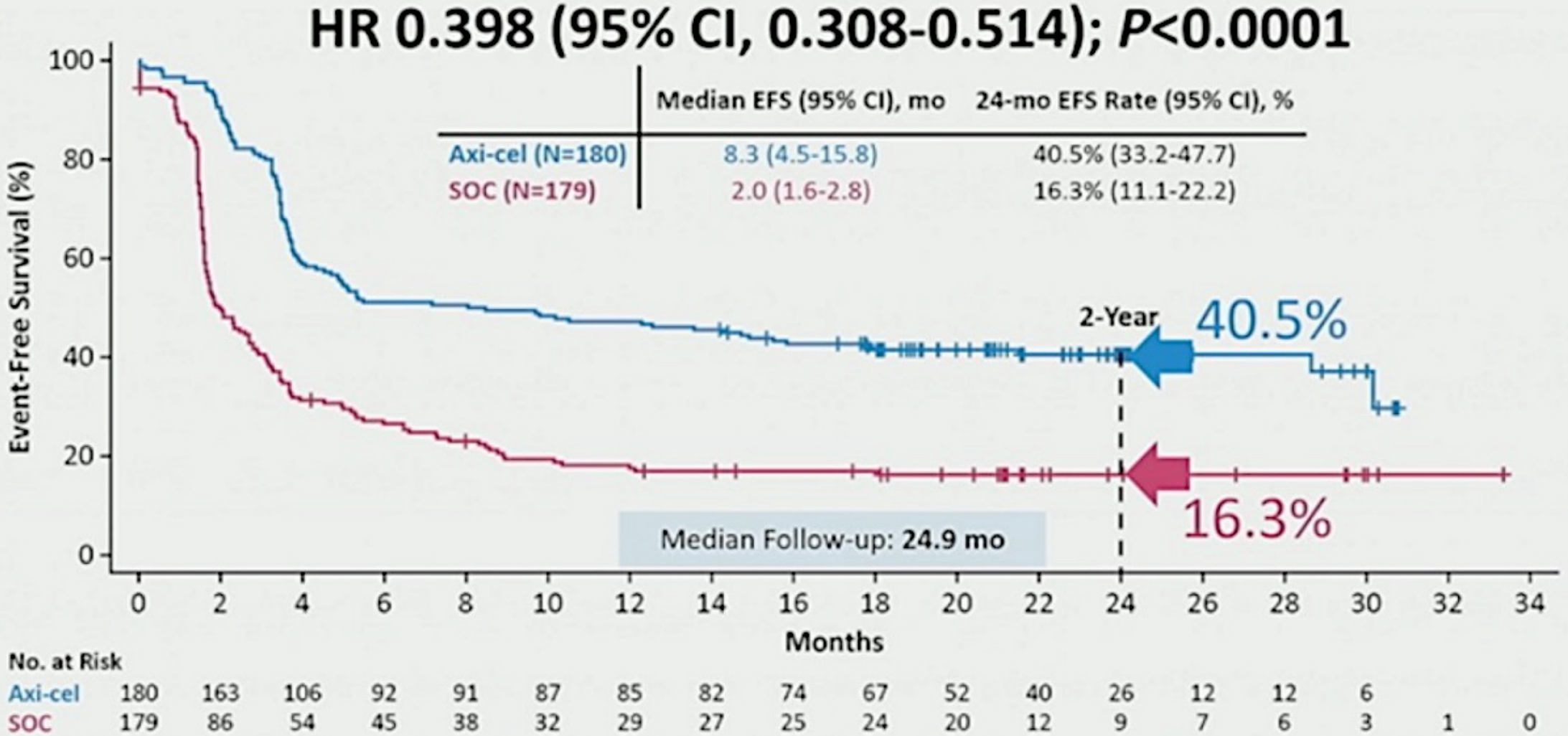
CD19 Directed CAR-T for Aggressive NHL in Second Line

- ZUMA-7
  - Axi-cel vs SOC for transplant eligible, early relapse
- TRANSFORM
  - Liso-cel vs SOC for transplant eligible, early relapse
- PILOT
  - Liso-cel for transplant ineligible patients

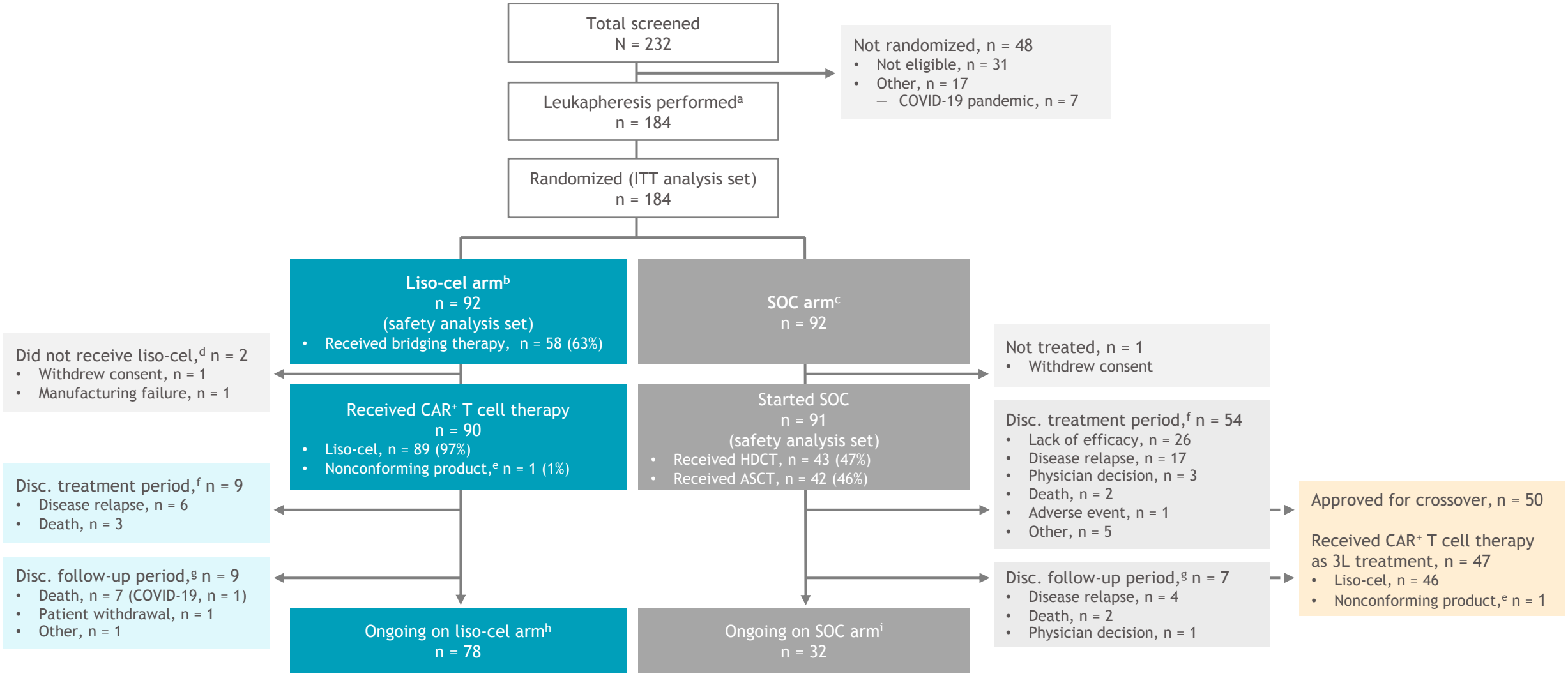
Patient Disposition: Nearly 3× as Many Axi-Cel Patients Received Definitive Therapy Versus SOC Patients



Primary EFS Endpoint: Axi-Cel Is Superior to SOC



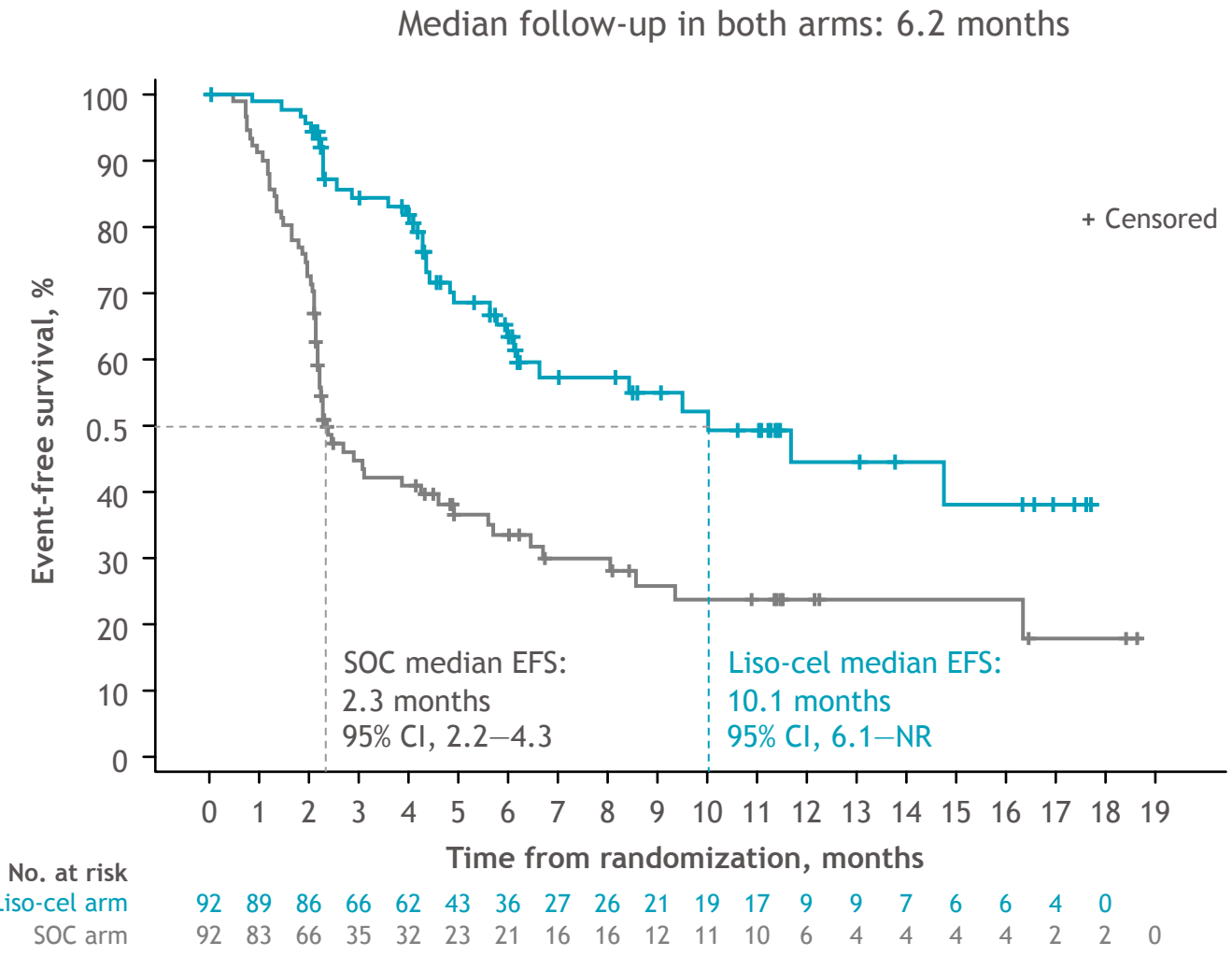
TRANSFORM: CONSORT diagram



[a]During screening, patients were assessed for eligibility, underwent unstimulated leukapheresis, and subsequent randomization; [b]Patients received LDC followed by liso-cel infusion; bridging therapy was allowed per protocol; [c]Patients received 3 cycles of SOC salvage CT (see Methods for details) followed by HDCT and ASCT; [d]Patients received bridging therapies and, therefore, were included in the safety analysis set; [e]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet release criteria for liso-cel but was considered safe for infusion; [f]Patients could discontinue the treatment period, defined as the period from randomization to Week 18, but continue to be followed up for OS; [g]Patients could discontinue the follow-up period, defined as the period from Week 18 to Month 36, but continue to be followed up for OS; [h]Six patients who discontinued the treatment period remained in the study follow-up period; [i]One patient who discontinued the treatment period remained in the study follow-up period.
Disc., discontinued.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	**0.349** (0.229—0.530)	
	***P* < 0.0001**	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0—74.7	23.0—43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4—59.6	13.4—34.1

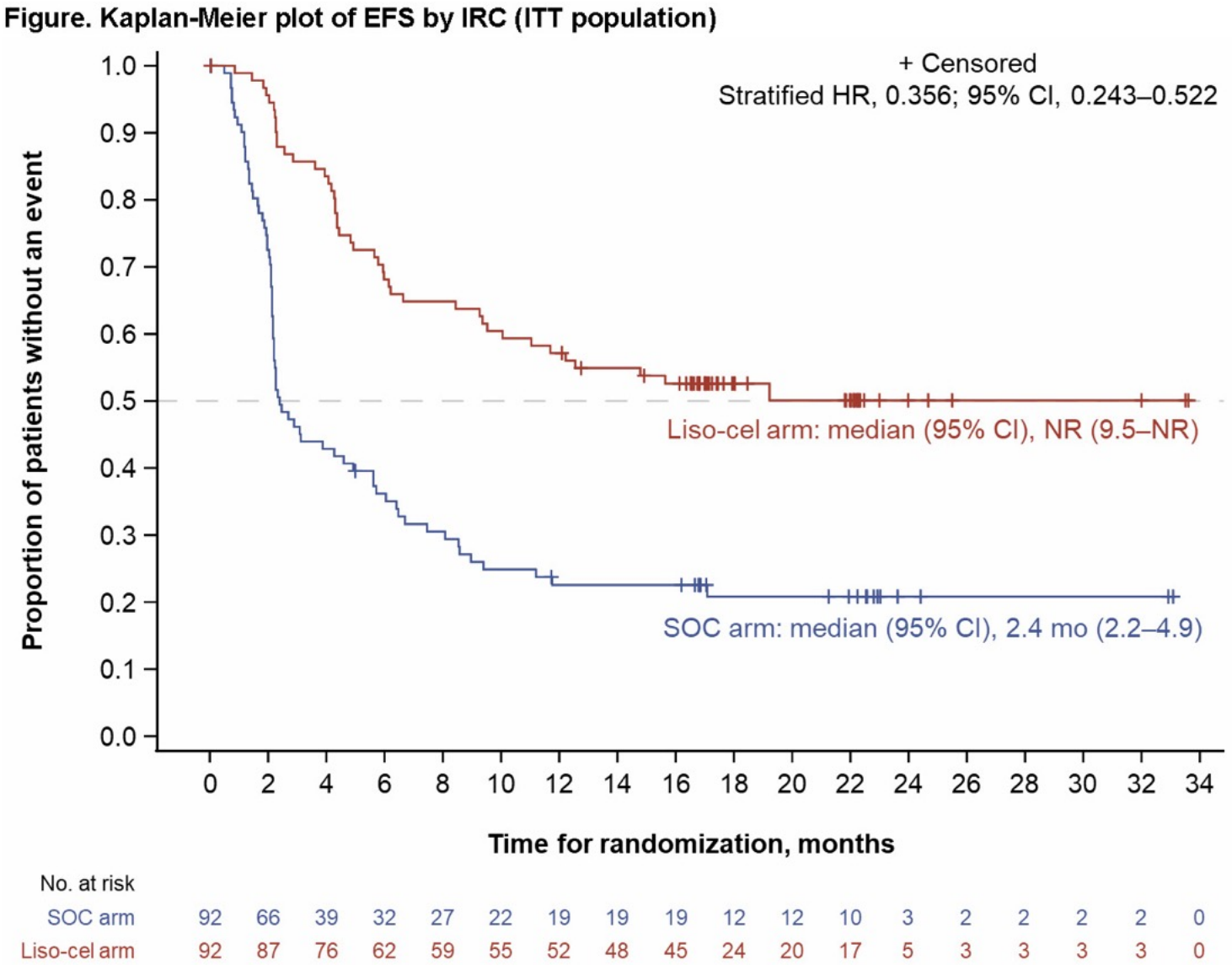
One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

TRANSFORM: Event-free survival per IRC –ASH update

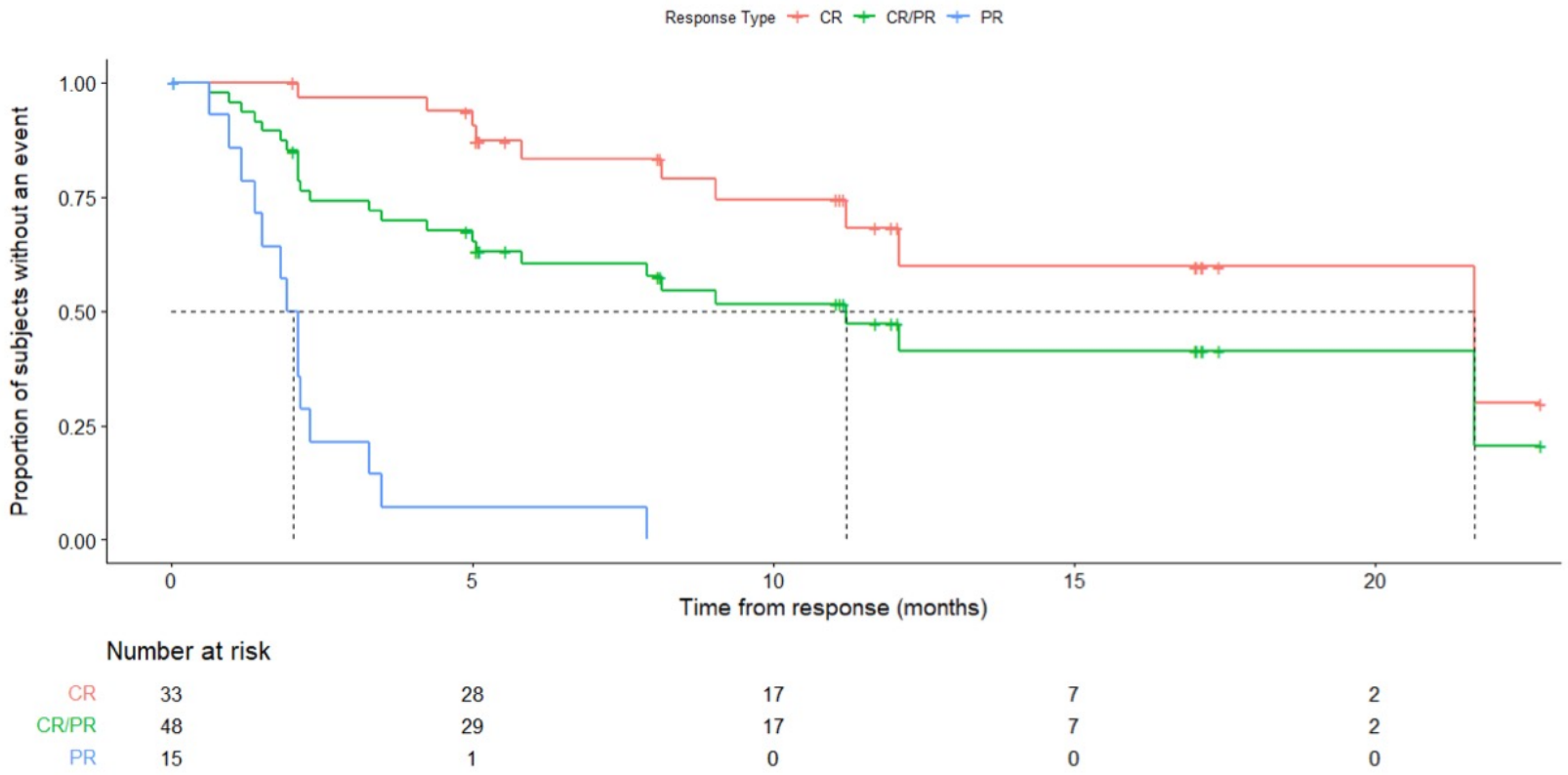
- Primary analysis at 17.5 mo
- N=184 randomized
  - 92 Liso-cel
  - 92 SOC
- Liso-cel CR= 74%
- SOC CR = 43%



Abramson, JS ASH 2022 #655

PILOT: Liso-cel for transplant ineligible aggressive NHL in Second line

- N= 61 treated, 74 apheresis
  - —Age = 74 years
  - —ECOG 2 = 26%
  - —Refractory = 54%
  - —Rel < 1 year = 21%
- ORR = 80%,
- CR = 54%
- CRS = 38%, 1 pt grade 3
- ICANS = 31%, 3 pt grade 3



(Source: FDA statistical reviewer's analysis)

ASCO 2022 #7062, FDA approval

Moving CAR T cell therapy to the first line?

ZUMA-12: a phase 2, multicenter, open-label, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL

Eligibility criteria

- Age ≥ 18 years
- High-risk LBCL
  - HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations, or
  - LBCL with IPI score ≥ 3 any time before enrollment
- 2 cycles of anti-CD20 plus anthracycline-containing regimen
- Positive interim PET (DS 4 or 5)
- ECOG PS score 0 or 1

Enrollment/leukapheresis → Optional nonchemotherapy bridging therapy[a] →

Conditioning chemotherapy + axi-cel infusion

- Conditioning
  - Flu 30 mg/m^2 i.v. and Cy 500 mg/m^2 i.v. on Days −5, −4, and −3
- Axi-cel
  - Single i.v. infusion of 2 × 10^6 CAR T cells/kg on Day 0

Primary endpoint

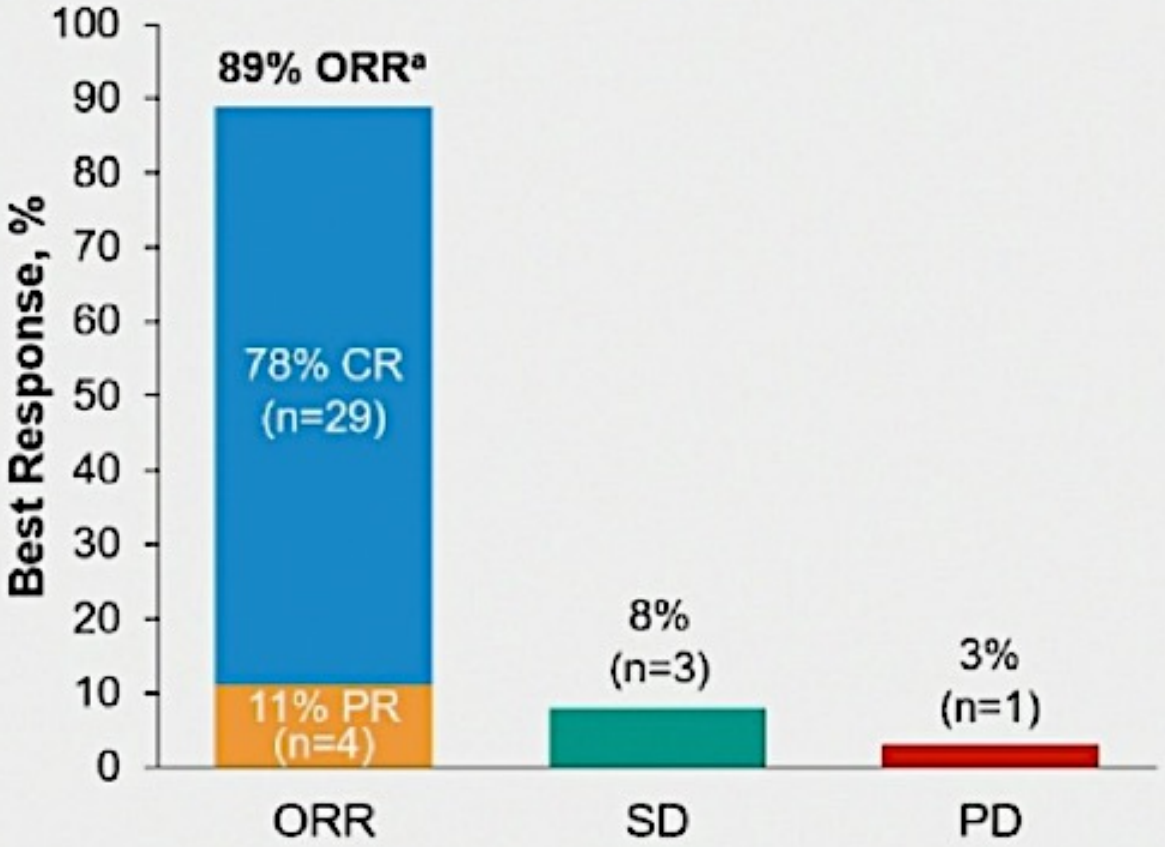
- CR[b]

Key secondary endpoints

- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

[a] Administered after leukapheresis and completed prior to initiating condition chemotherapy; PET-CT was required after bridging.
[b] Per 2014 Lugano criteria.
DS, Deauville score; IPI, International Prognostic Index; i.v., intravenous.
Neelapu SS, et al. Interim analysis of ZUMA-12: A phase 2 study of axicabtagene ciloleucel (axi-cel) as first-line therapy in patients (Pts) with high-risk large B cell lymphoma (LBCL). Oral presentation at ASH 2020;abstract 405.

ORR Was 89% (95% CI, 75–97) and CR Rate Was 78% (95% CI, 62–90) Among Efficacy-Evaluable Patients

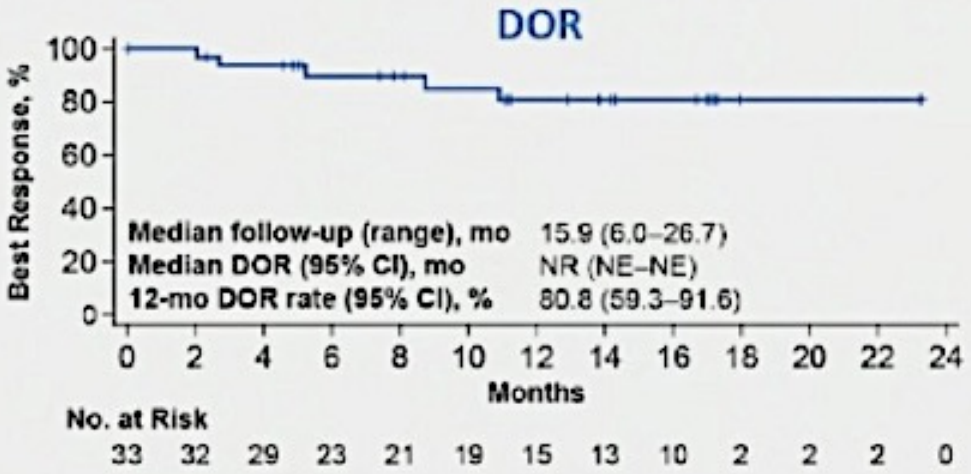


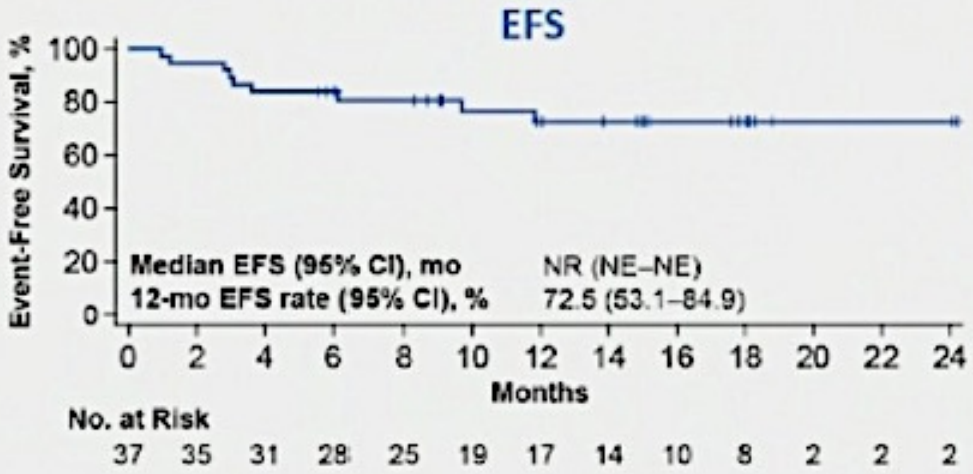
	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)[c]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

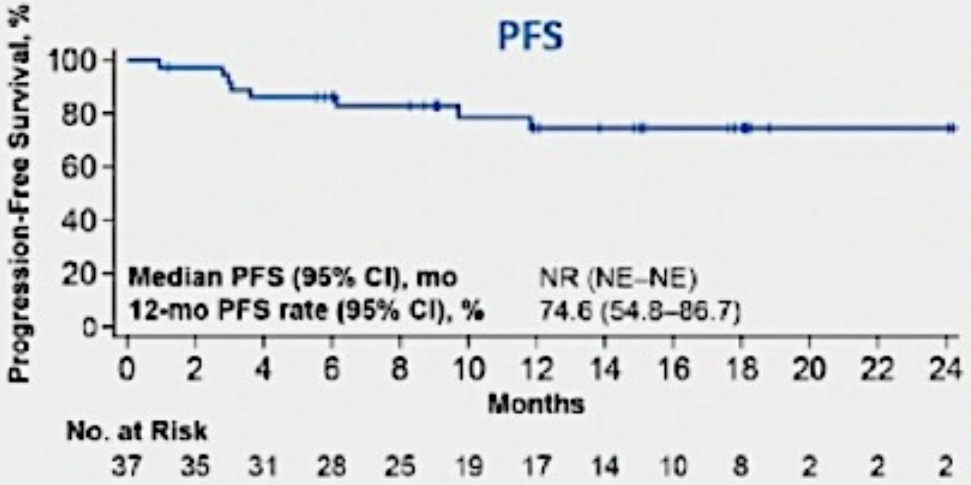
- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

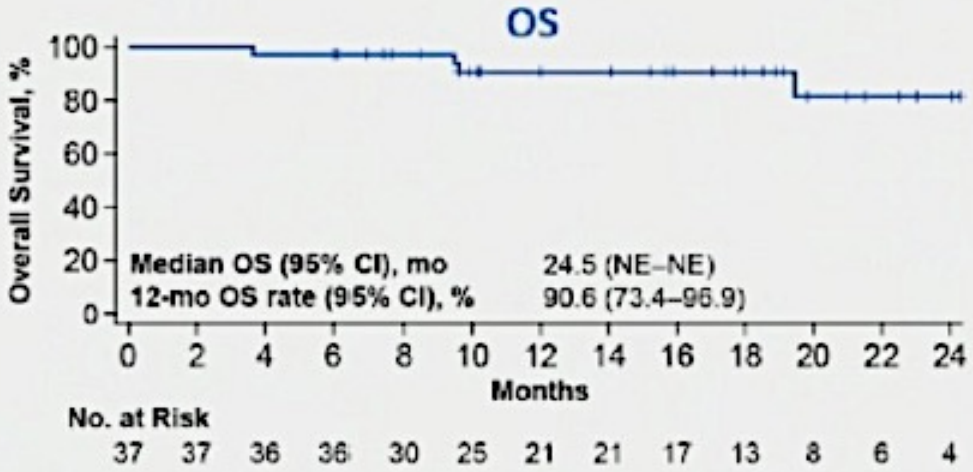
[a] Response assessments are based on best overall response. [b] Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
[c] All 7 patients converted to a CR by Month 6 postinfusion.
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response, Event-Free Survival, Progression-Free Survival, and Overall Survival[a]







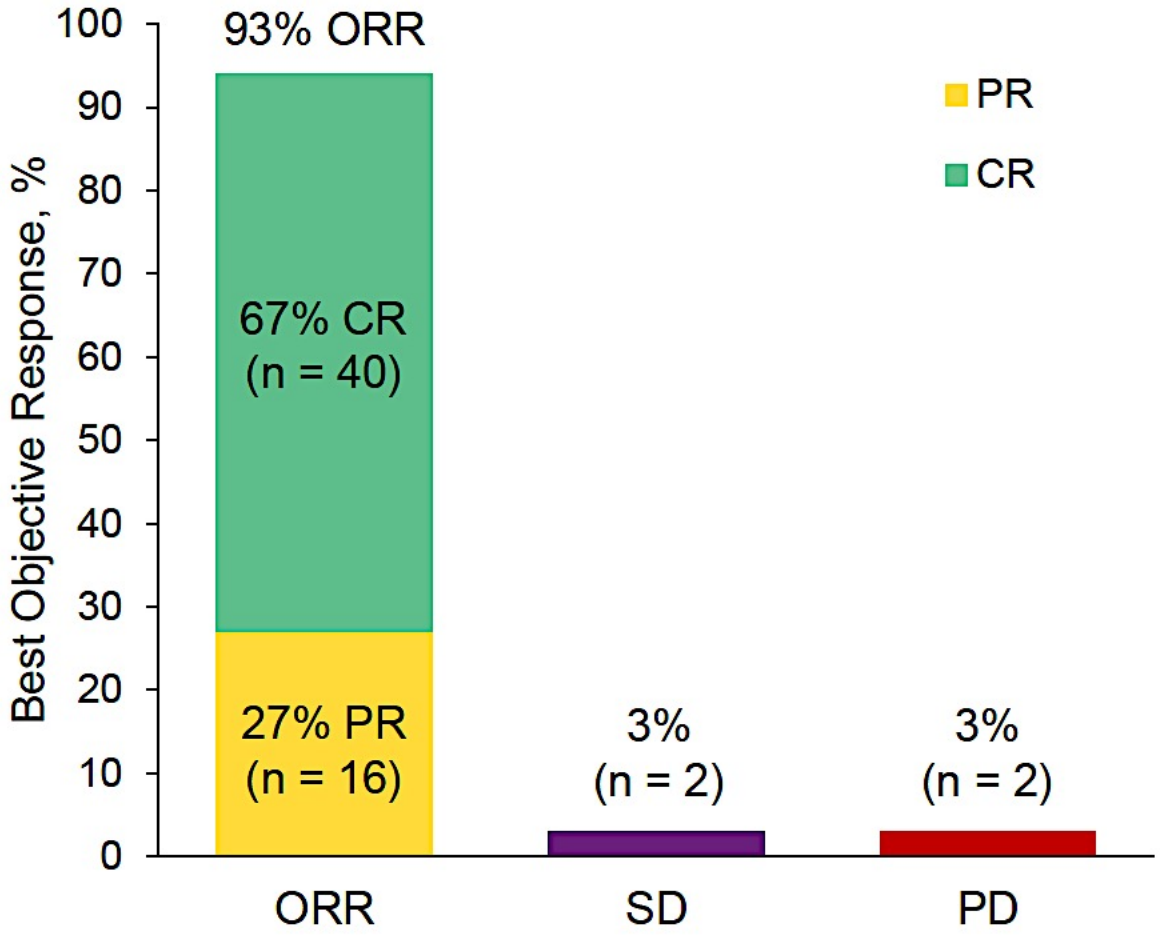


[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

CD19 CAR-T cells for Mantle cell and Indolent NHL

- Brexucabtagene autoleucel for Mantle cell Lymphoma
- Tisagenlecleucel for Follicular Lymphoma
- Axi-cel for Follicular Lymphoma and Marginal zone lymphoma

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)

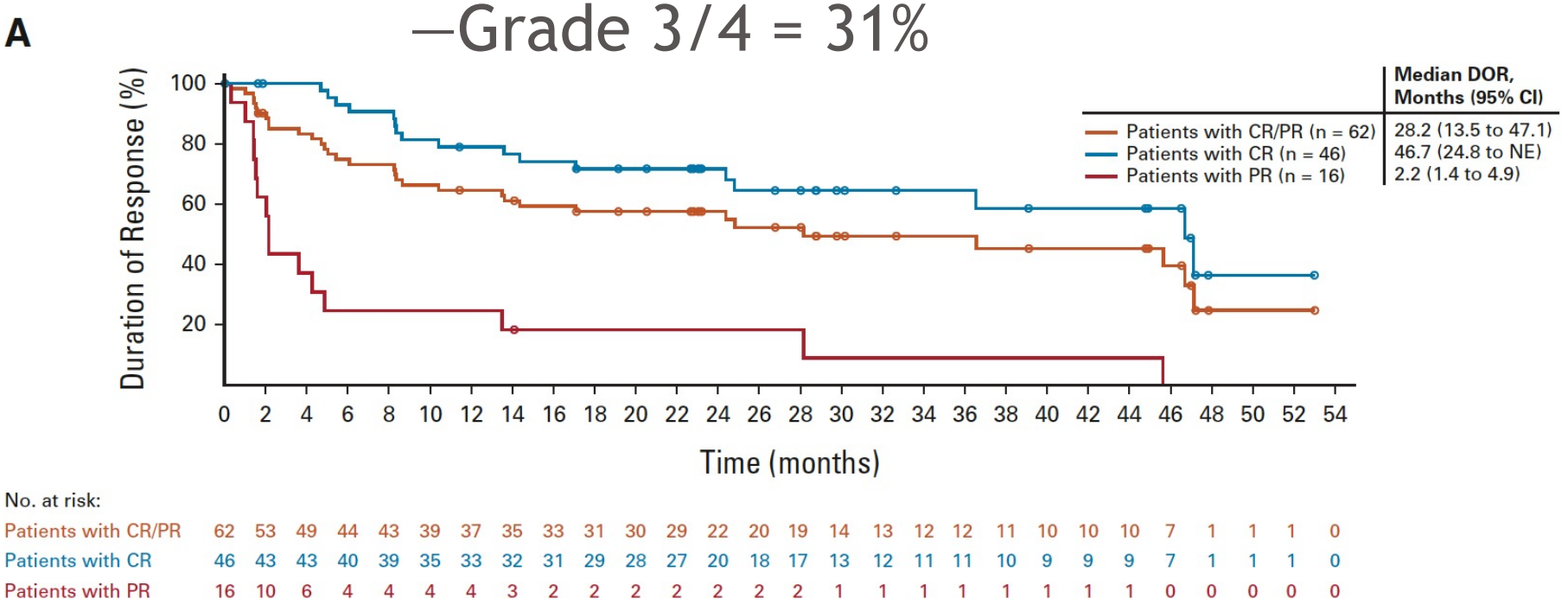


	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ZUMA-2: Brexu-cel CD-19 Directed CAR-T cell therapy for Mantle Cell NHL - 3 year update

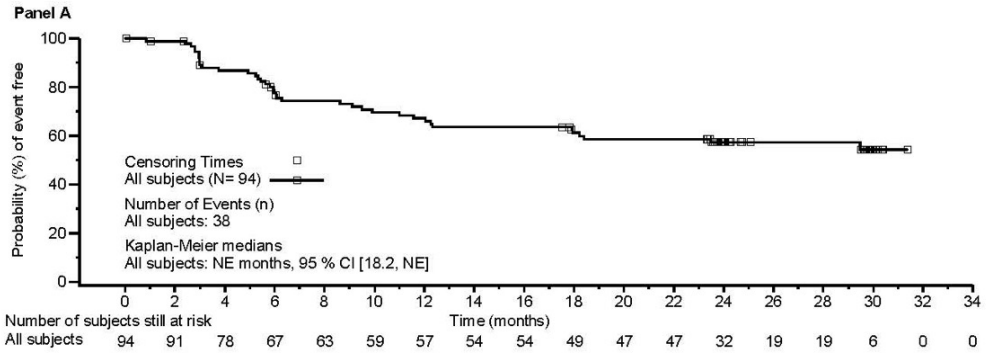
- N= 68 infused
- ORR = 91%
  - —CR = 68%
- DOR = 28.2 mo
- PFS = 25.8 mo
- OS = 46.6 mo
- BTKi exposed
  - —Similar outcome
- CRS = 91%
  - —Grade 3/4 = 15%
- ICANS = 63%
  - —Grade 3/4 = 31%

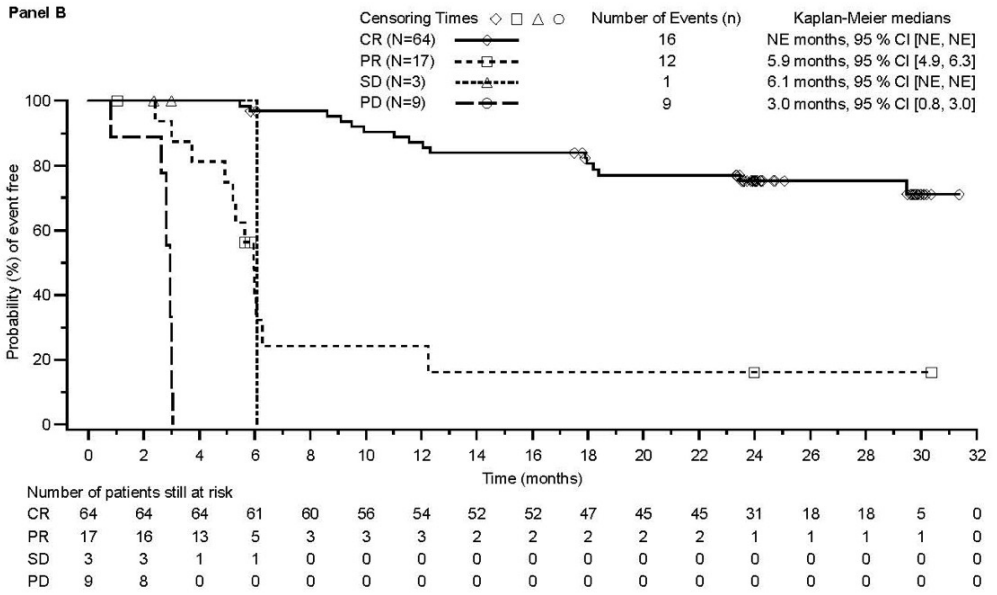


Wang M, JCO 2022

ELARA: Tisagenlecleucel for Follicular NHL- ASH 2022 update

- N= 94 (evaluable) with relapsed/ref FL
- ORR = 86.2%
- CR = 68%
- CRS = 48.5%
  - —Grade 3/4 = 0%
- NT = 37.1%
  - —Grade 3/4 = 3%
- Median f/u 28.9 mo
- 24% received subsequent Rx

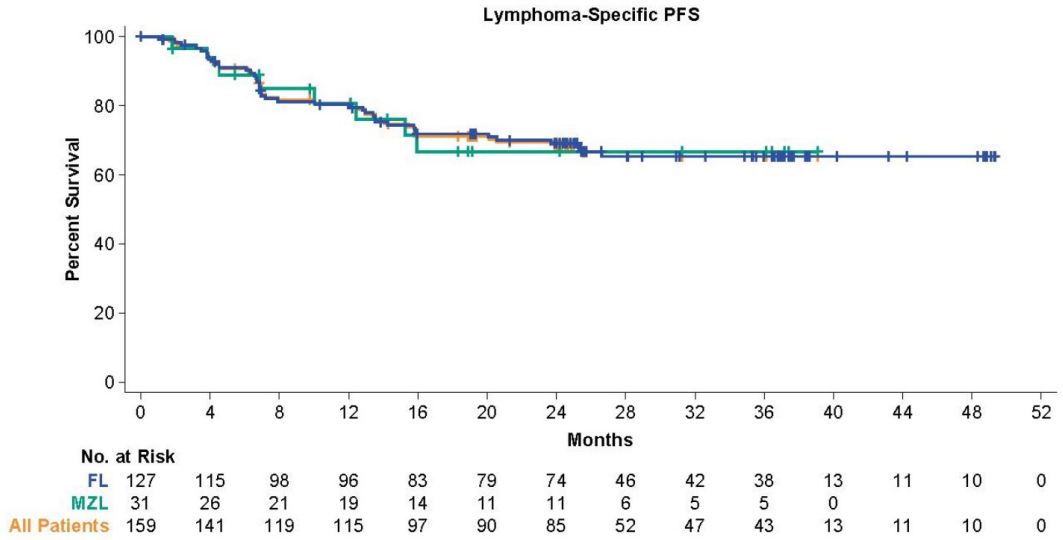


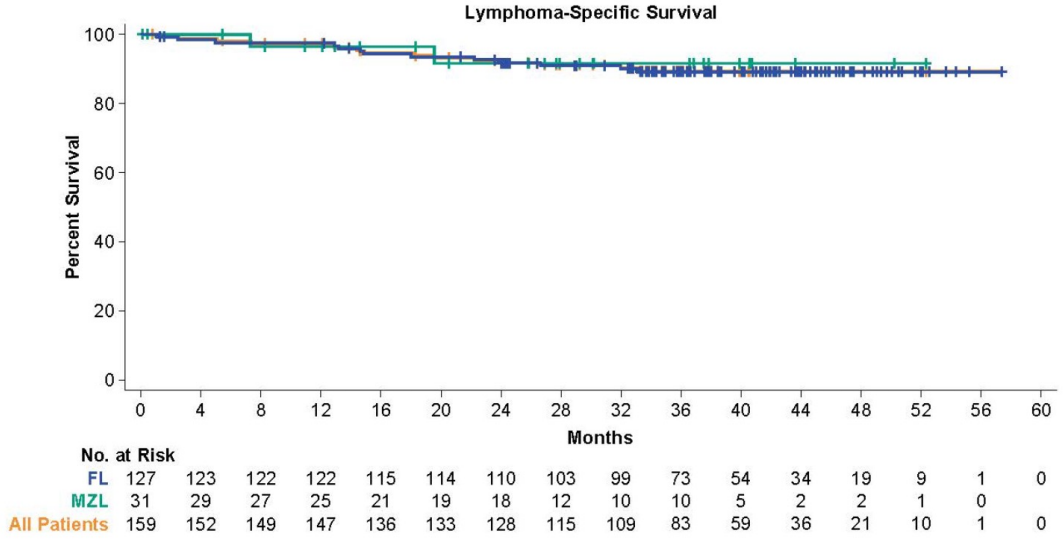


Dreyling M ASH 2022 #608, Fowler NH Nat Med 2022

ZUMA-5: Axi-cel CAR-T cell therapy for Follicular NHL and MZL- ASH 2022 3-year update

- N= 159 enrolled, 152 treated
- Follicular NHL = 124
- Marginal zone NHL 28
- Flu/Cy lymphodepletion and 2 x 10^6 CAR-T cells/kg
- ORR
  - FL = 94%, MZL = 83%
- CR
  - FL = 79%, MZL = 65%
- CRS ≥ grade 3 = 10 (7%)
- NT ≥ grade 3 = 28 (19%)



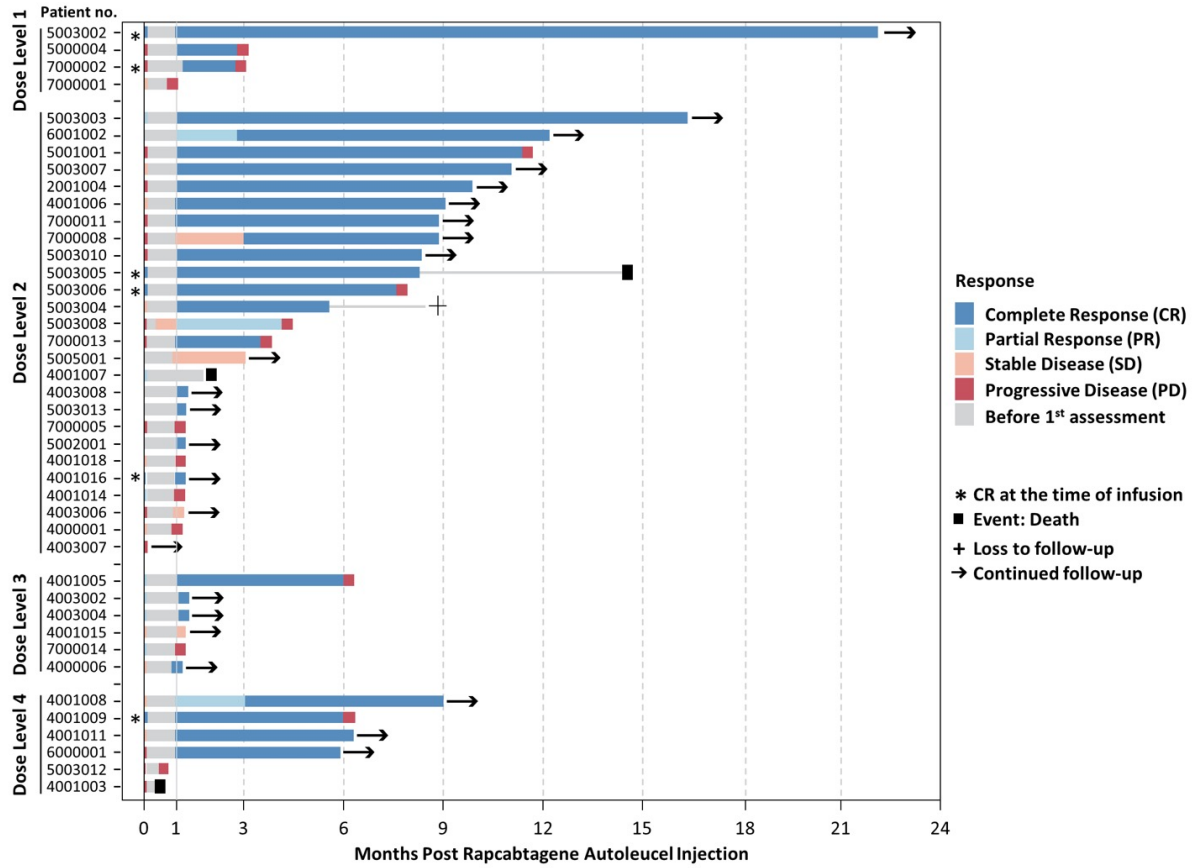


Neelapu SS ASH 2022 # 4660, Jacobson CA Lancet Onc 2022

YTB323 (Rapcabtagene Autoleucel) CD-19 Directed CAR-T cell therapy for Large B cell NHL

- Rapid 2 day manufacturing preserving T cell “stemness”
- Phase 1 study
- Dose level 2 (**12.5 x 10^6**) chosen as recommended Ph 3 dose
- N=28 treated at DL 2
  - —CR = 65%
  - —ICANS in 3 pts
  - —CRS in 10 pts, onset median d9

Figure 1. Response durability following rapcabtagene autoleucel injection.



Conclusions and Future Directions

- Approval of 4 CD19 CAR-T cell products for Aggressive NHL, FL and MCL
- Treatments appear to lead to long lasting remissions especially for patients with Complete Remissions
- Second line randomized trials for aggressive large B cell lymphoma superior to SOC/autologous HCT
- CAR-T now FDA approved in second line for transplant eligible (relapse < 1 year, axi-cel and liso-cel) and transplant ineligible patients (liso-cel).
- Product selection needs to consider **efficacy**, **safety**, as well as **production reliability** and **cost**
- Exciting new constructs and combinations being evaluated

Immunotherapy is changing the way cancer is treated!

BEZOS FAMILY IMMUNOTHERAPY CLINIC

Photograph courtesy of Ron hood, Fred Hutch

Fred Hutchinson Cancer Center

Appendix

Editorial Review

- Long-term findings with axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel for patients with multiply relapsed DLBCL
  - Slides 4-11, 26
- Available results with CAR T-cell therapy as second-line treatment for DLBCL, including among transplant-ineligible patients
  - Slides 12-18
- Early results with other CAR T-cell platforms (eg, rapcabtagene autoleucel) in DLBCL
  - Slide 27
- Key findings with brexucabtagene autoleucel and other CAR T-cell platforms in mantle cell lymphoma
  - Slides 23-24
- Principal outcomes from pivotal studies evaluating CAR T-cell therapy for FL (eg, ZUMA-5, ELARA)
  - Slides 19-21, 25-26

Appendix Slides – None