Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Lymphoma CAR T cells

Loretta J. Nastoupil, MD

Associate Professor

UT MD Anderson Cancer Center

lnastoupil@mdanderson.org

#LearnACI

Disclosures

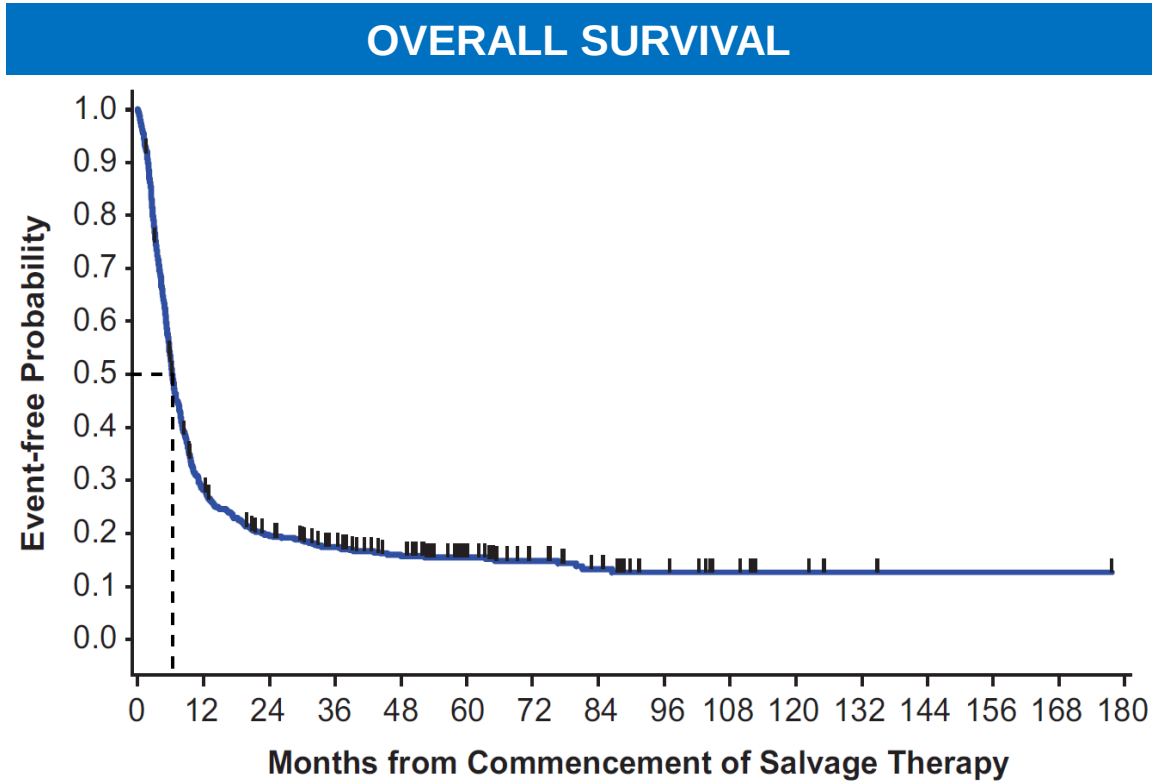
- I have the following disclosures:
  - Honorarium: ADC Therapeutics, Bayer, BMS/Celgene, Epizyme, Genentech, Gilead/Kite, Janssen, Morphosys, Novartis, Takeda, TG Therapeutics
  - Research support: BMS/Celgene, Epizyme, Genentech, Gilead/Kite, Janssen, Novartis, Takeda, TG Therapeutics

- I will be discussing non-FDA approved indications during my presentation.

SCHOLAR-1
(Retrospective Non-Hodgkin Lymphoma Research)

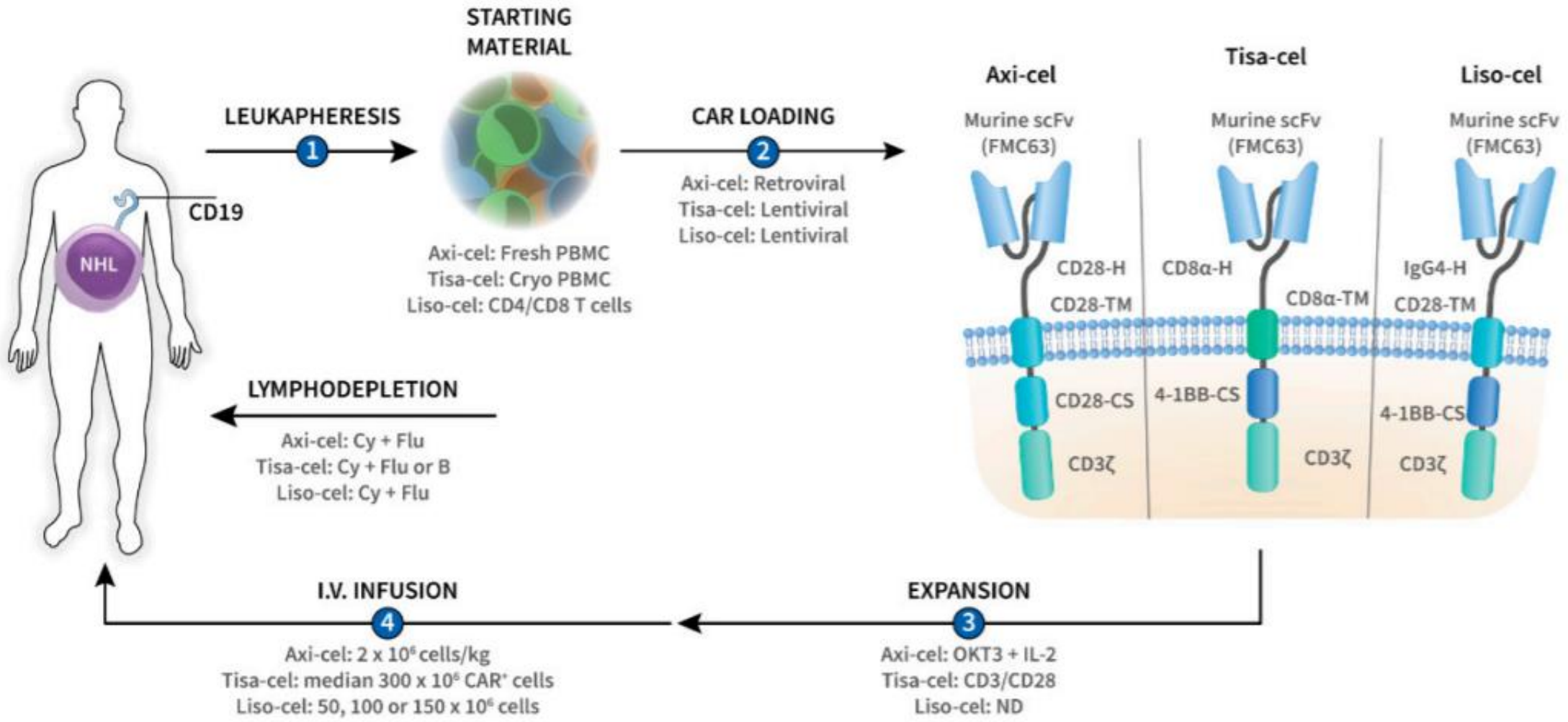
SCHOLAR-1, a retrospective, international, patient-level, multi-institution study with the largest reported analysis of outcomes in patients with refractory large B cell lymphoma

- N = 636 (post-rituximab era, 2000-2017)
- ORR = 26%
- CR rate = 7%
- Median OS = 6.3 months
- These results provided a benchmark for evaluation of new approaches



Crump, Blood 2017

Auto CD19 CAR T-cell Products



Roex G, et al. Pharmaceutics. 2020;12:194.

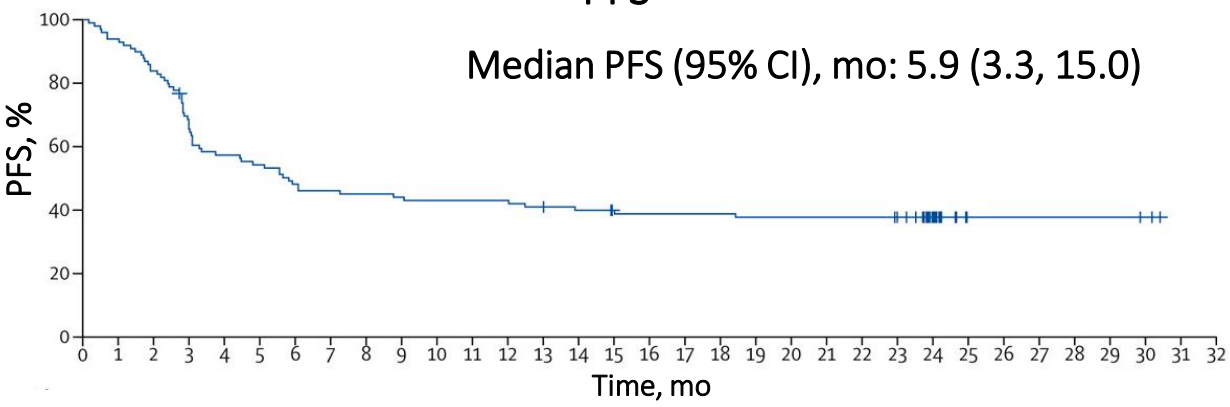
ZUMA-1
Axi-Cel in Patients With R/R LBCL

Patient Characteristic	Phase 1 and 2 (N = 108)
Median age, y	58
Age ≥ 65 y, No. (%)	27 (25)
Disease stage III/IV, No (%)	90 (83)
IPI risk score 3 or 4, No, (%)	48 (44)
≥ 3 prior therapies, No. (%)	76 (70)
Refractory to second- or later-line therapy, No. (%)	80 (74)
Best response as PD to last prior therapy, No. (%)	70 (65)
Relapse post-ASCT, No. (%)	25 (23)

- ORR (n = 101), % (by IRC): 83 (74)
- CR, %: 58
- CRS (%): Any (93); Grade ≥ 3 (11)
- Neurotoxicity (%): Any (64); Grade ≥ 3 (32)

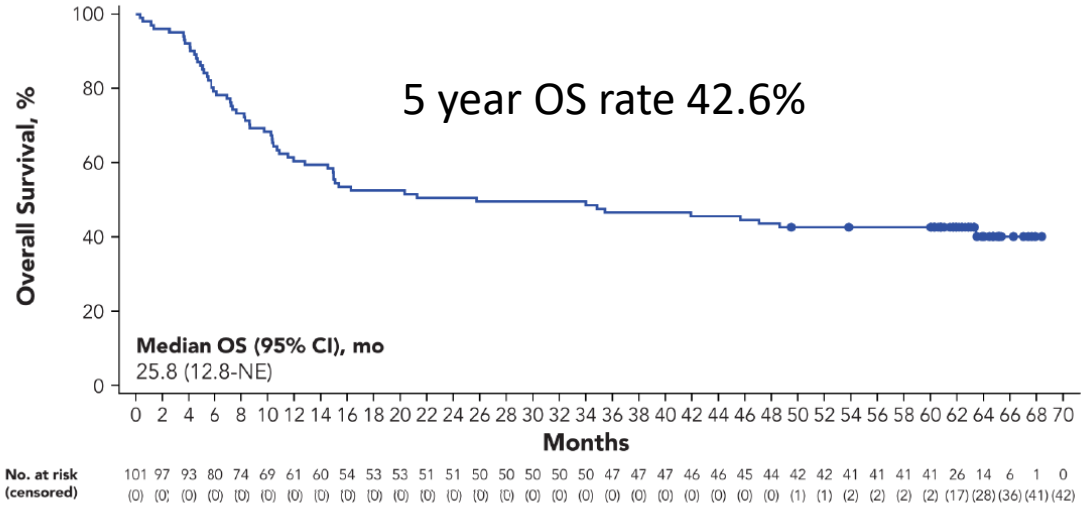
PFS

Median PFS (95% CI), mo: 5.9 (3.3, 15.0)



OS

Figure 3. 5-Year Overall Survival



One patient's event time was updated from Month 42 to 39 after data cutoff and is not reflected in this figure.
NE, not estimable; OS, overall survival.

Locke FL, et al. *Lancet Oncol*. 2019;20:31-42; Jacobson. ASH 2021. #1764

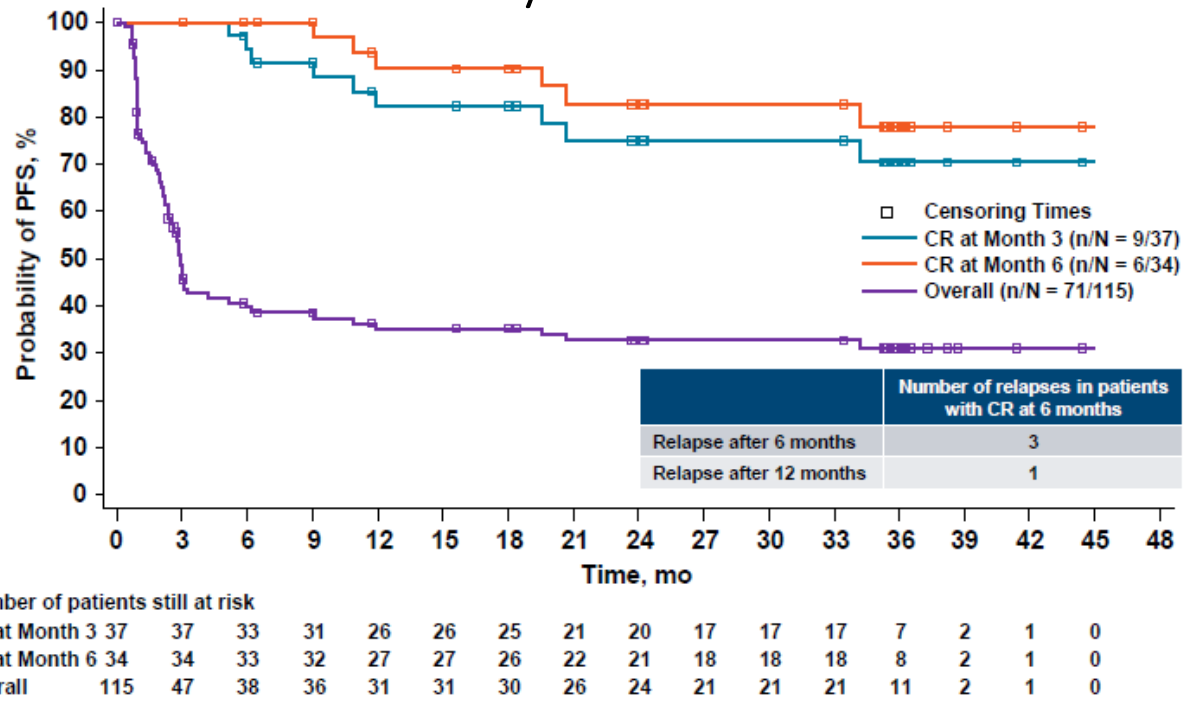
JULIET
Tisa-Cel in Patients With R/R DLBCL

Patient Characteristic	Phase 1 and 2 (N = 111)
Median age (range), y	56 (22-76)
Double- /triple-hit lymphoma, %	27
No. of prior lines of therapy, %	
2	44
3	31
4-6	21
Refractory to last therapy, %	55
Prior ASCT, %	49

- ORR, %: 52
- CR, %: 40
- CRS (%): Any (58); Grade ≥ 3 (22)
- Neurotoxicity (%): Any (21); Grade ≥ 3 (12)*

- *Penn scale.
- Schuster SJ, et al. *N Engl J Med*. 2019;380:45-56. Jaeguer ASH 2020#1194

3 year PFS and OS



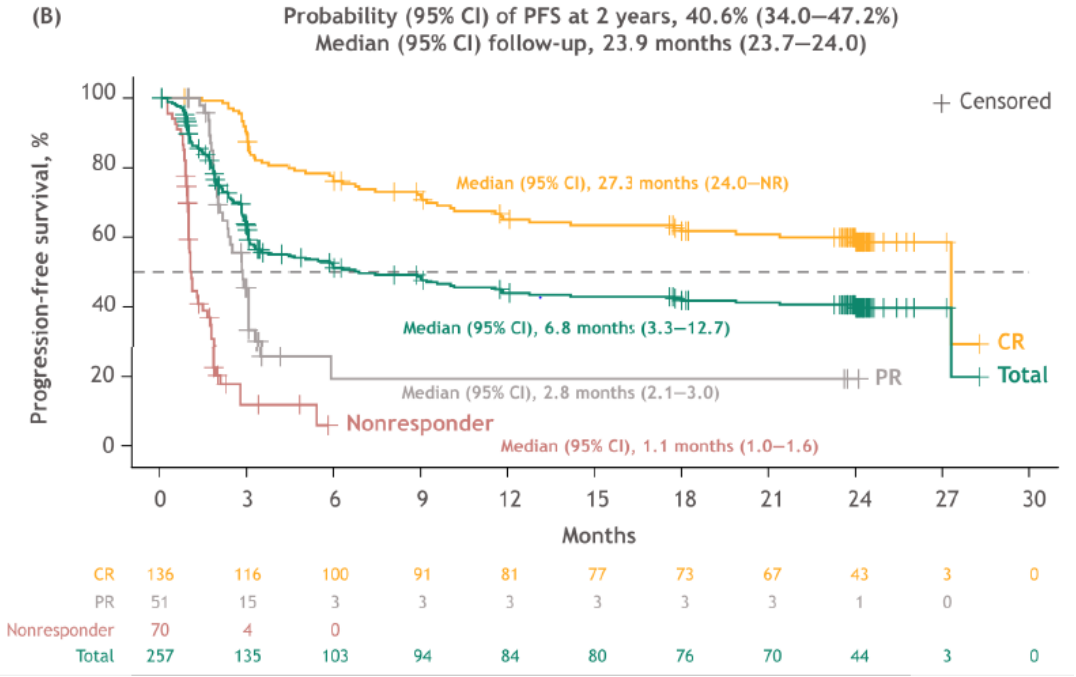
- Median follow-up of 40.3 months
  - Relapse-free probability was 60.4% at 24 and 30 months
  - Median OS was 11.1 months (95% CI, 6.6-23.9)
  - Survival probability at 12, 24, and 36 months was 48.2%, 40.4%, and 36.2%

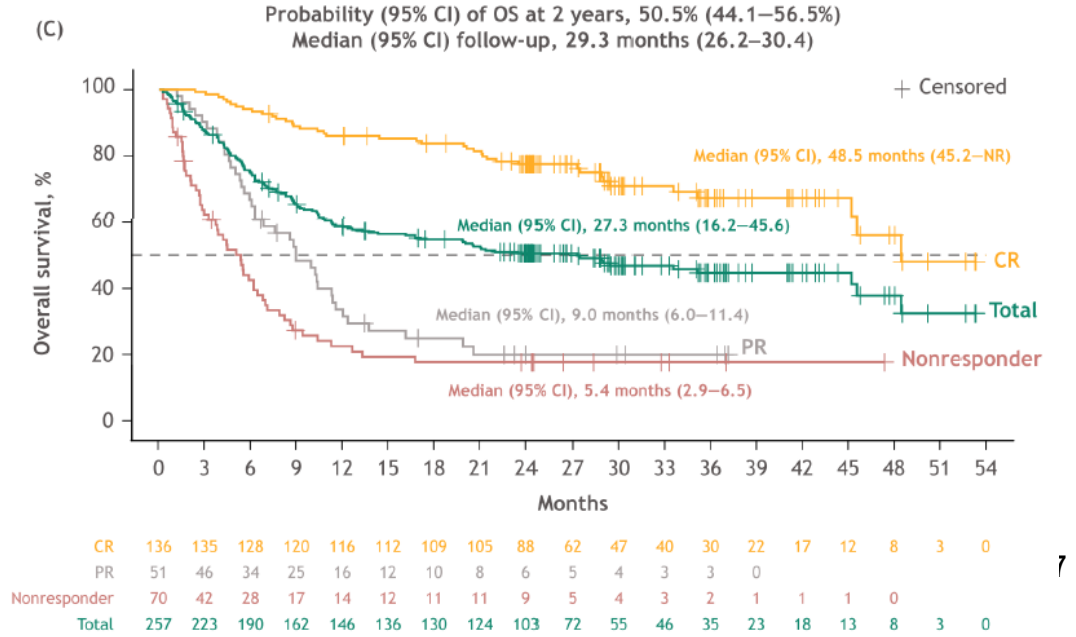
TRANSCEND-NHL-001
Liso-Cel in Patients With R/R LBCL

Patient Characteristic	Patients (N = 269)
Median age (range), y	63 (54-70)
Double- /triple-hit lymphoma, No. (%)	36 (13)
CNS involvement, No. (%)	7 (3)
Median prior lines, No. (range)	3 (2-4)
Chemo-refractory, No. (%)	181 (67)
Prior HSCT, No. (%)	94 (35)

Best Response	Patients (N = 256)
Best ORR, %	73
Best CR, %	53
12-month DOR, %	55

- CRS (%): Any (42); Grade ≥ 3 (2)
- Neurotoxicity (%): Any (30); Grade ≥ 3 (10)

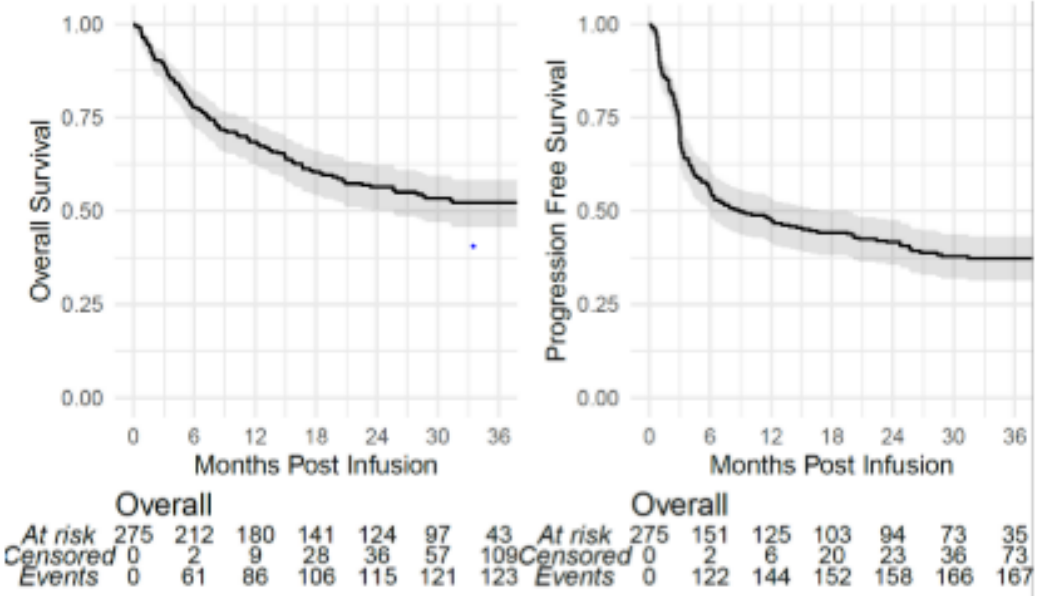


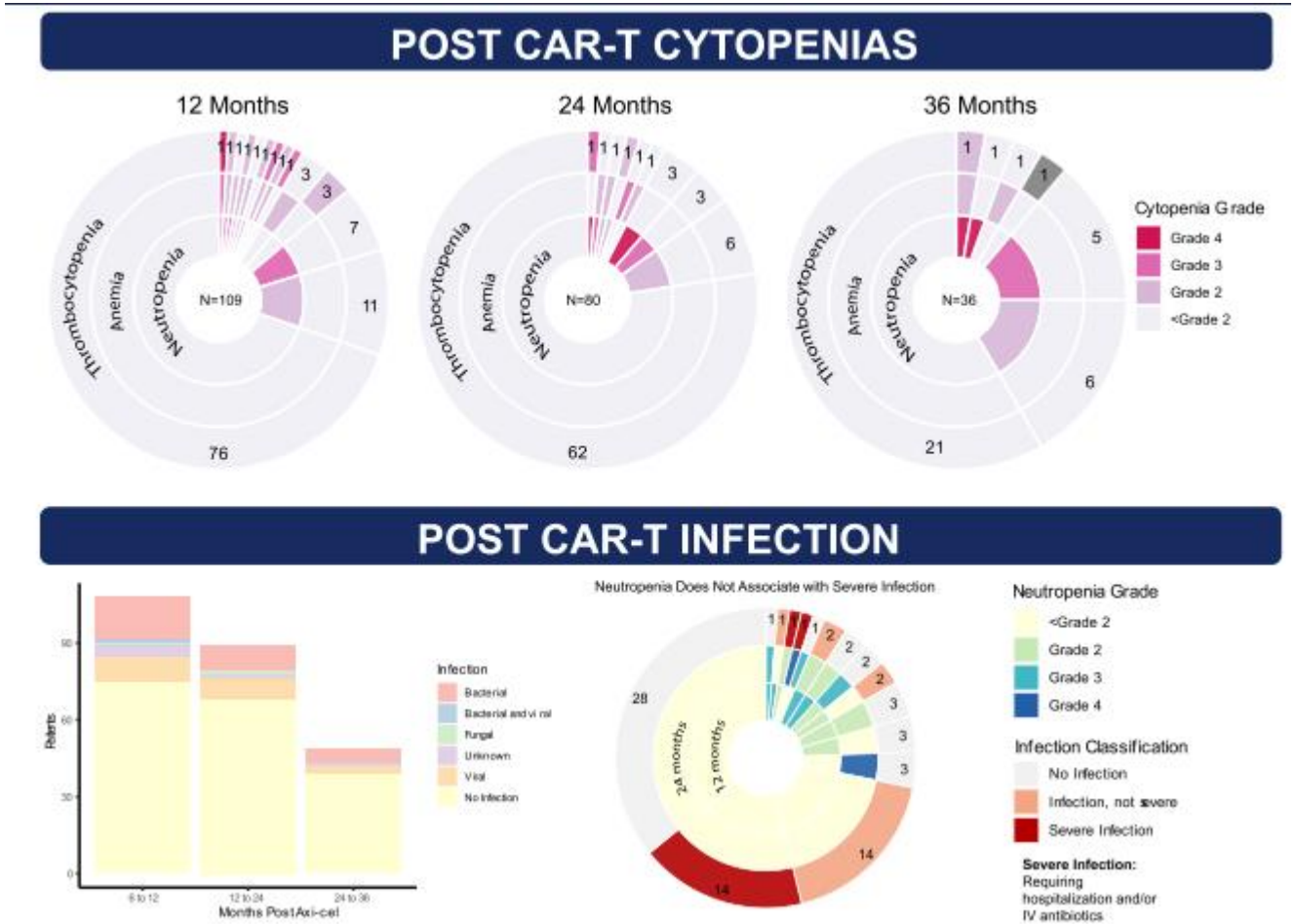


Abramson JS, et al. *Lancet*. 2020;396:839-852; Abramson ASH 2021 #2840

Outcomes with SOC Axi-Cel

275 pts were infused – after median follow-up of 32.3 months median OS was not reached (95% CI 25.6 – not evaluable [NE]) (**Figure 1A**) with 1-, 2- and 3-year OS of 68.5% (95% 62.6-73.7), 56.4% (95% 50.1-62.2)
Median PFS was 9 months (95% CI 5.9-19.6) (**Figure 1B**); 1-, 2- and 3-year PFS was 47.4% (95%CI 41.4-53.2), 41.6% (95%CI 35.6-47.5) and 37.3% (31.3-43.2)
Nineteen late (1 year +/- 1 month) progression events (range 11 – 28 months) were seen

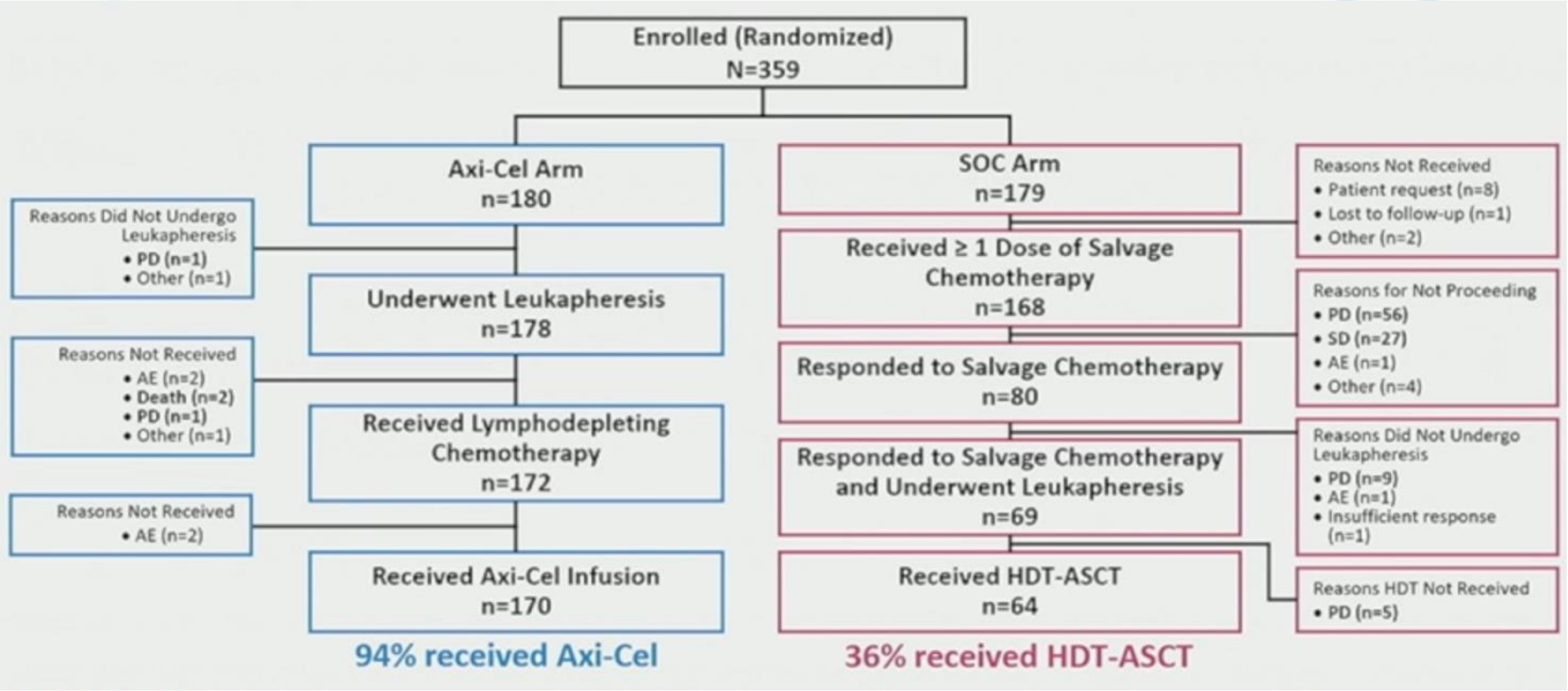




#LearnACI

Spiegel ASH 2021 #3826

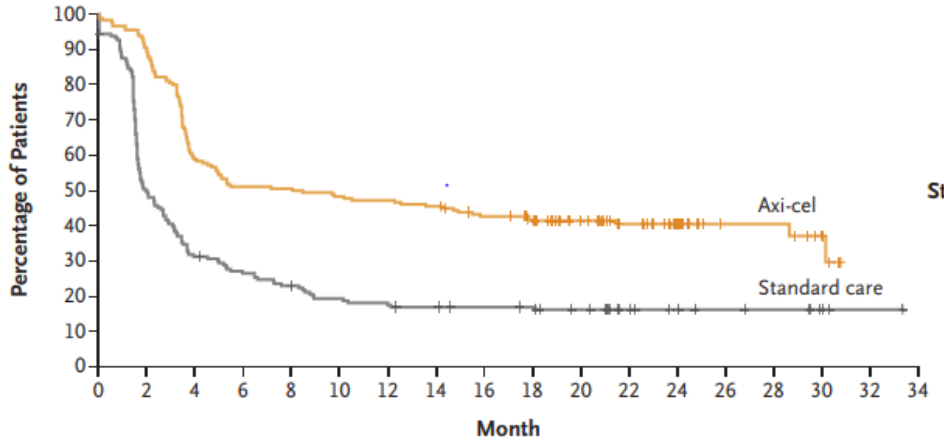
ZUMA-7- Axi-Cel in Second-line LBCL



Locke, ASH 2021 plenary abstract 2

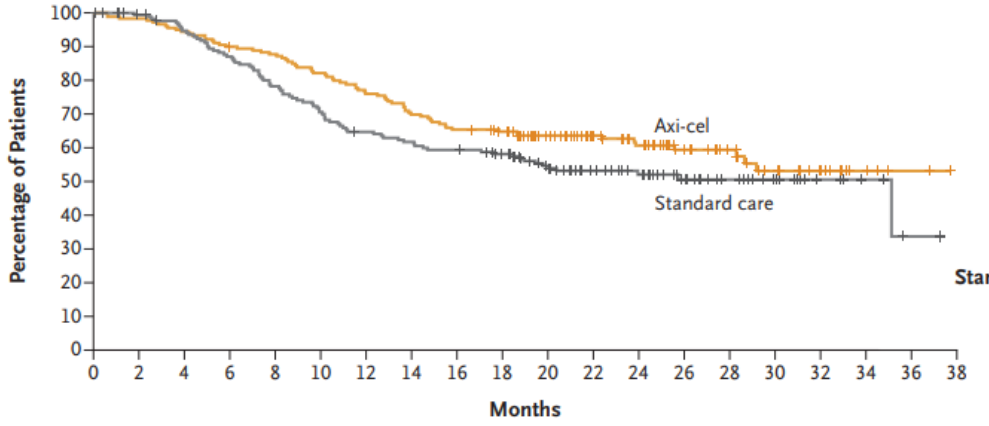
Axi-Cel in Second-line LBCL

A Event-free Survival



No. at Risk																	
Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6	
Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

A Overall Survival

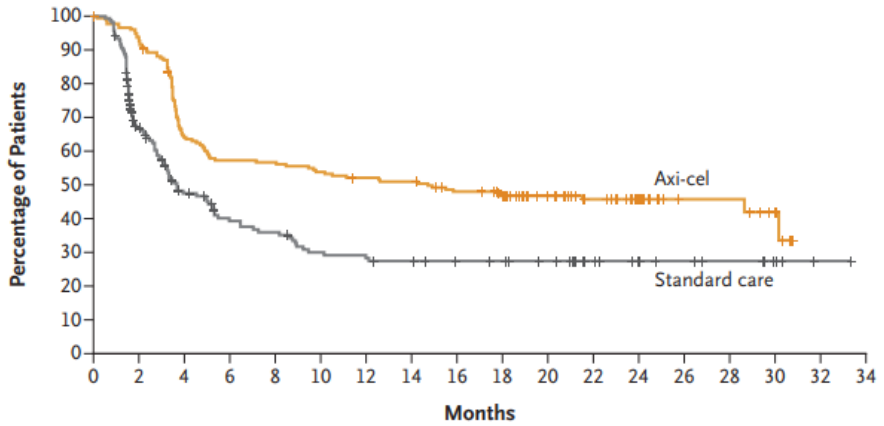


No. at Risk																				
Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2	0
Standard care	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1	0

	No. of Patients	Median Overall Survival (95% CI)
		mo
Axi-cel	180	NR (28.3–NE)
Standard Care	179	35.1 (18.5–NE)

Stratified hazard ratio for death, 0.73 (95% CI, 0.53–1.01)

B Progression-free Survival



No. at Risk																				
Axi-cel	180	166	112	100	99	94	90	88	80	73	56	43	28	12	12	6				
Standard care	179	94	61	47	43	35	33	31	28	27	24	15	11	9	7	4	1	0		

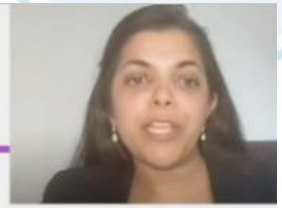
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Axi-cel	180	14.7 (5.4–NE)
Standard Care	179	3.7 (2.9–5.3)

Stratified hazard ratio for disease progression or death, 0.49 (95% CI, 0.37–0.65)

#LearnACI

Locke et al, NEJM 2021

TRANSFORM: Liso-cel in 2nd-line



TRANSFORM study design

Key eligibility
- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count

Screening + leukapheresis → 1:1 Randomization

Bridging therapy allowed[a]

PET[b] LDC[c]

Liso-cel arm (100 × 10⁶ CAR⁺ T cells)

Stratification
- Refractory vs relapsed
- sAAIPI: 0/1 vs 2/3

SOC arm[d] 3 cycles of salvage CT, followed by HDCT + ASCT

Response assessments
- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Primary endpoint
- EFS (per IRC)

Key secondary endpoints
- CR rate, PFS, OS

Other secondary endpoints
- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints
- Cellular kinetics
- B-cell aplasia

Crossover to liso-cel allowed
- Failure to respond by 9 weeks post-randomization
- PD at any time
- Start of new antineoplastic therapy after ASCT

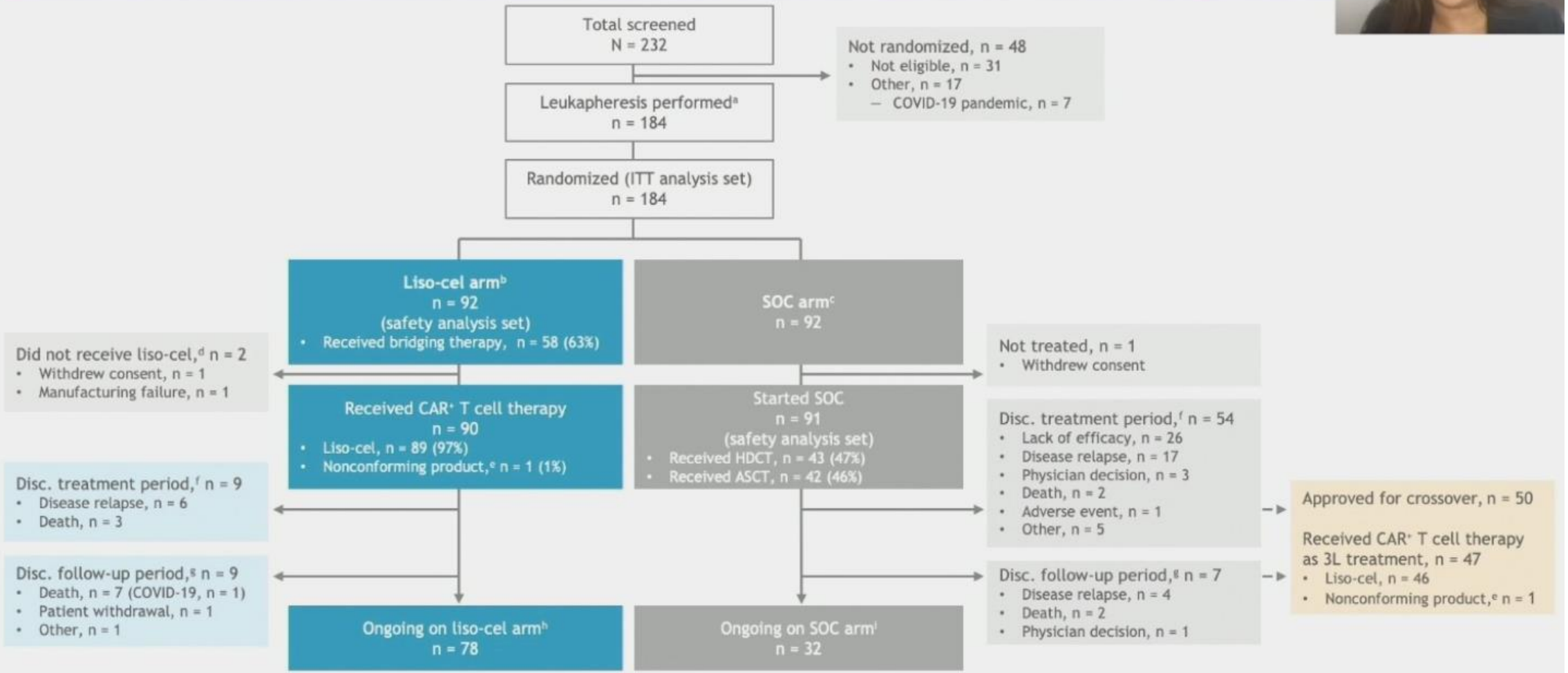
TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

- **EFS is defined as 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, whichever occurs first**

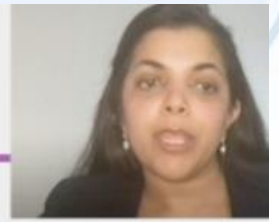
[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

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

TRANSFORM: CONSORT diagram

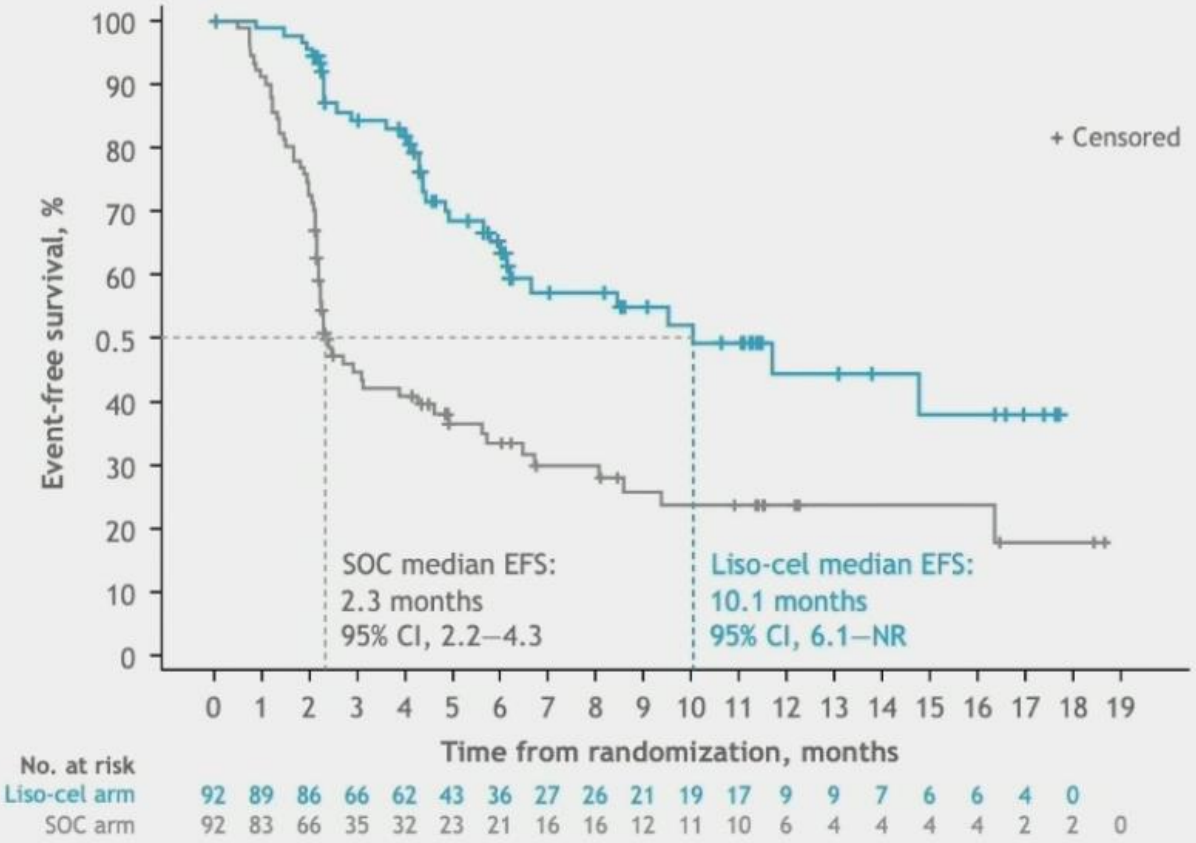


[a]During screening, patients were assessed for eligibility, underwent unstimulated leukapheresis, and subsequent randomization; [b]Patients received LDC followed by liso-cel infusion; bridging therapy was allowed per protocol; [c]Patients received 3 cycles of SOC salvage CT (see Methods for details) 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.



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

Median follow-up in both arms: 6.2 months



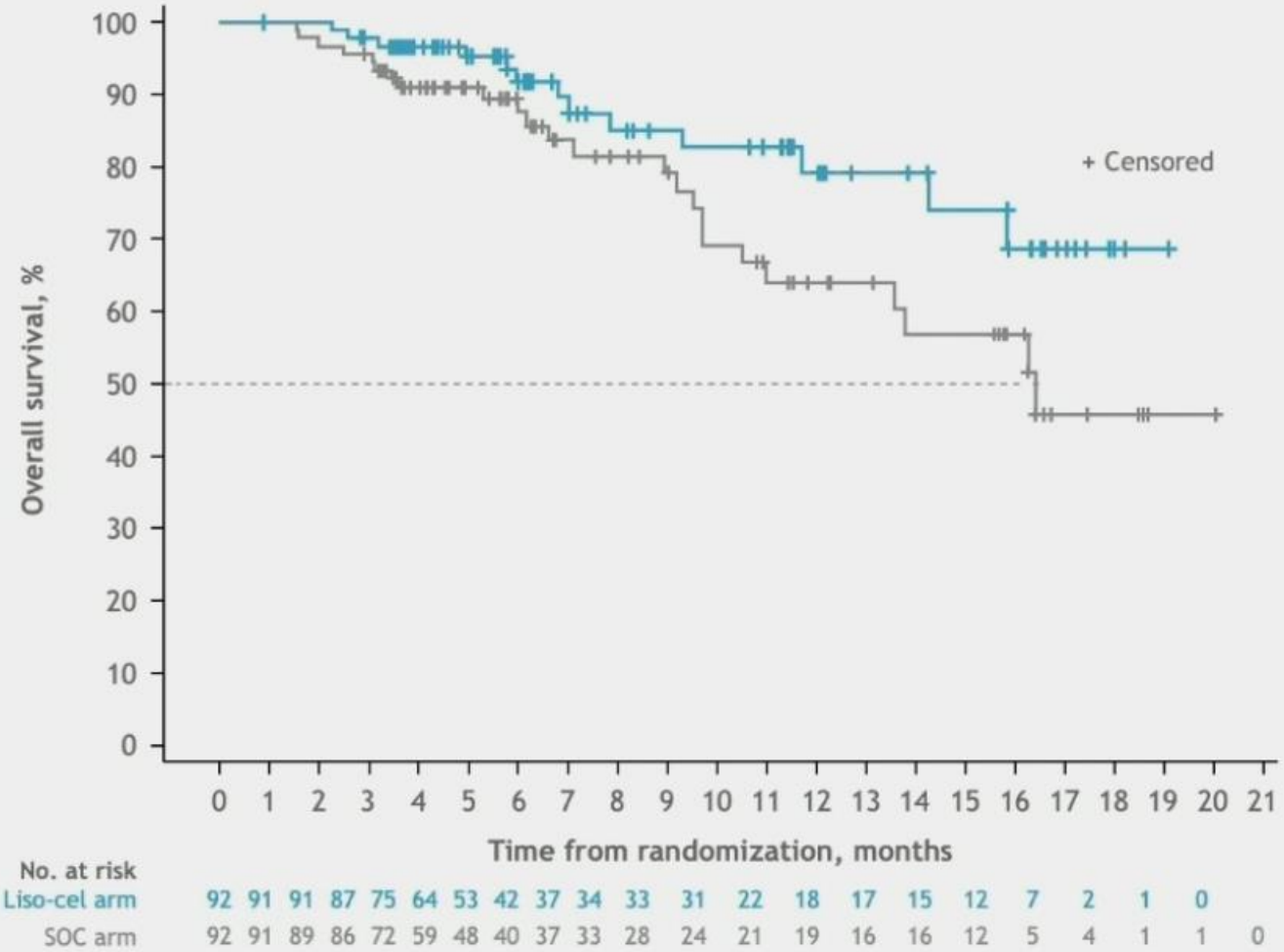
No. at risk																			
Liso-cel arm	92	89	86	66	62	43	36	27	26	21	19	17	9	9	7	6	6	4	0
SOC arm	92	83	66	35	32	23	21	16	16	12	11	10	6	4	4	4	4	2	2	0

	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.

TRANSFORM: Overall survival (ITT set)



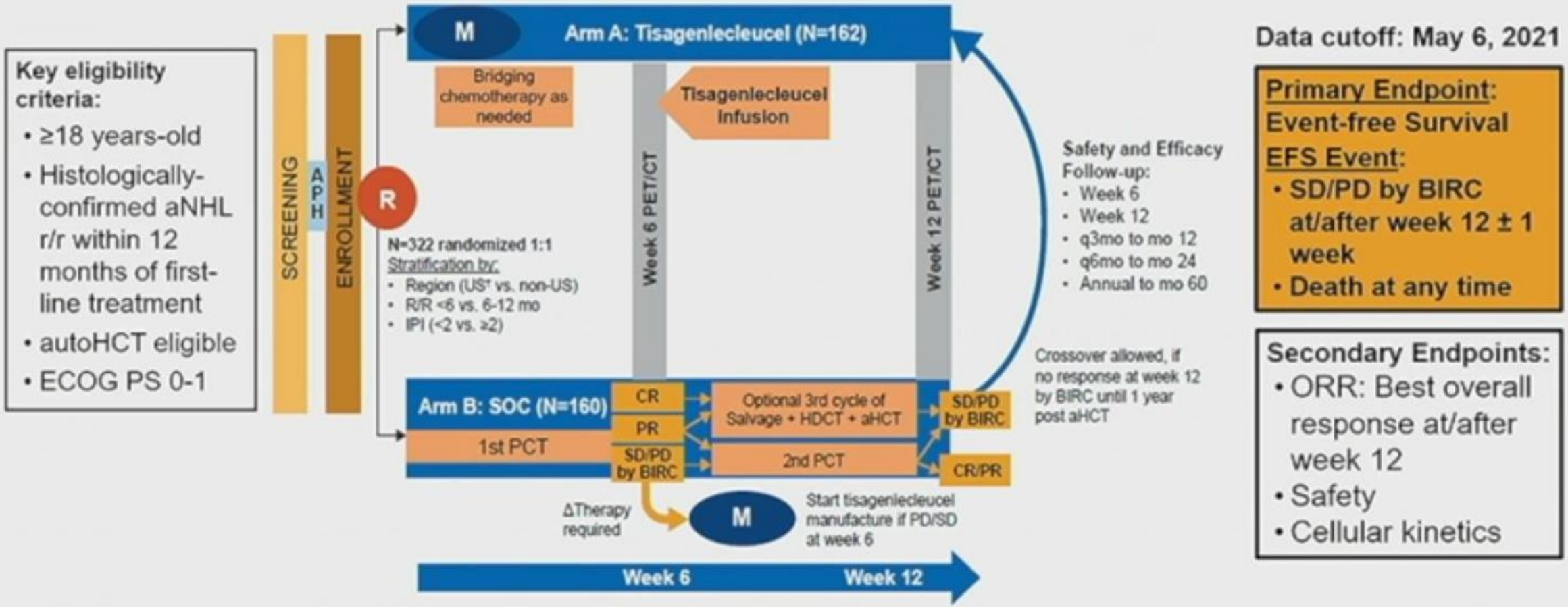
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004) *P* = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

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

#L

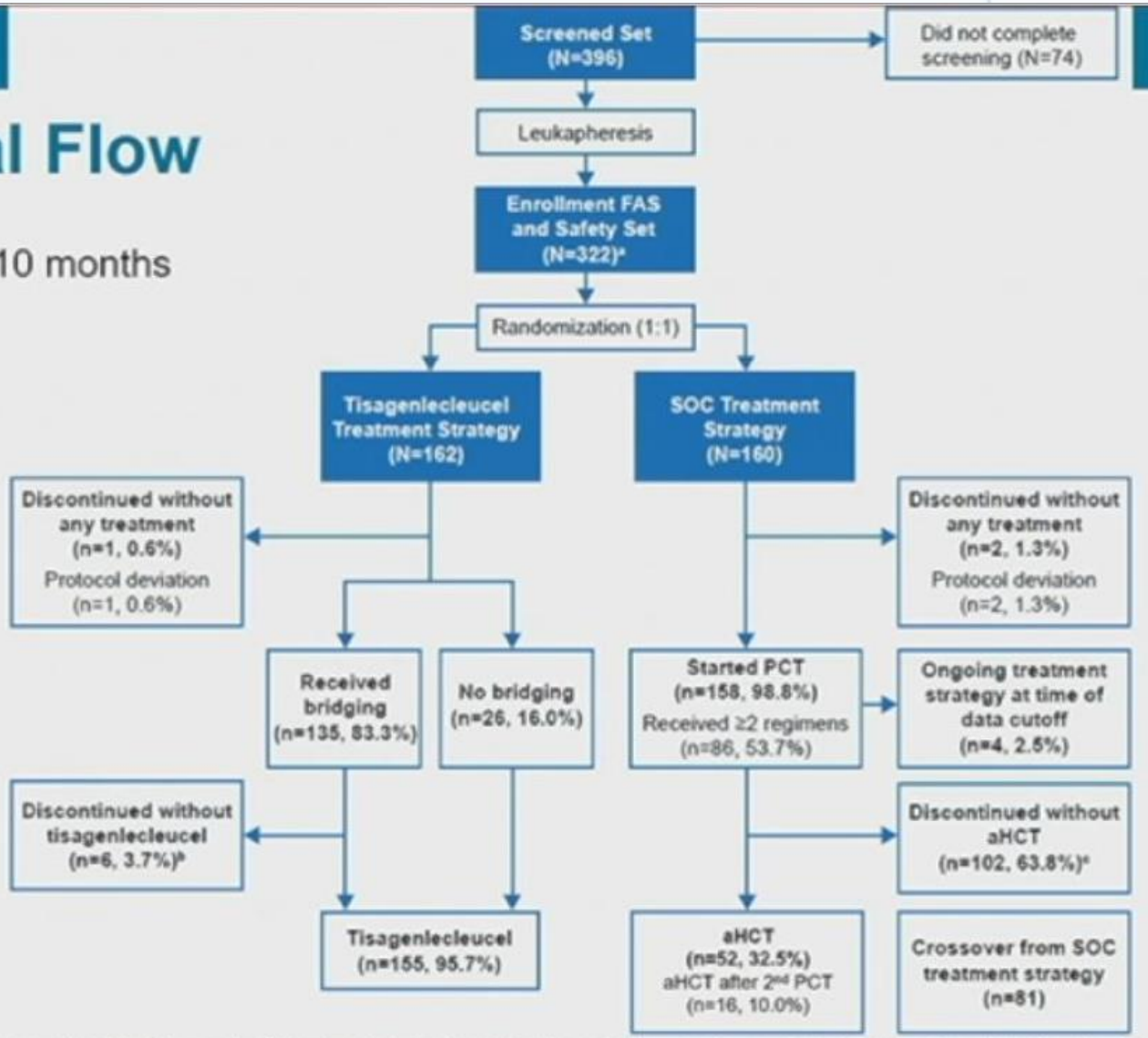
BELINDA Study Design



aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

Patient Trial Flow

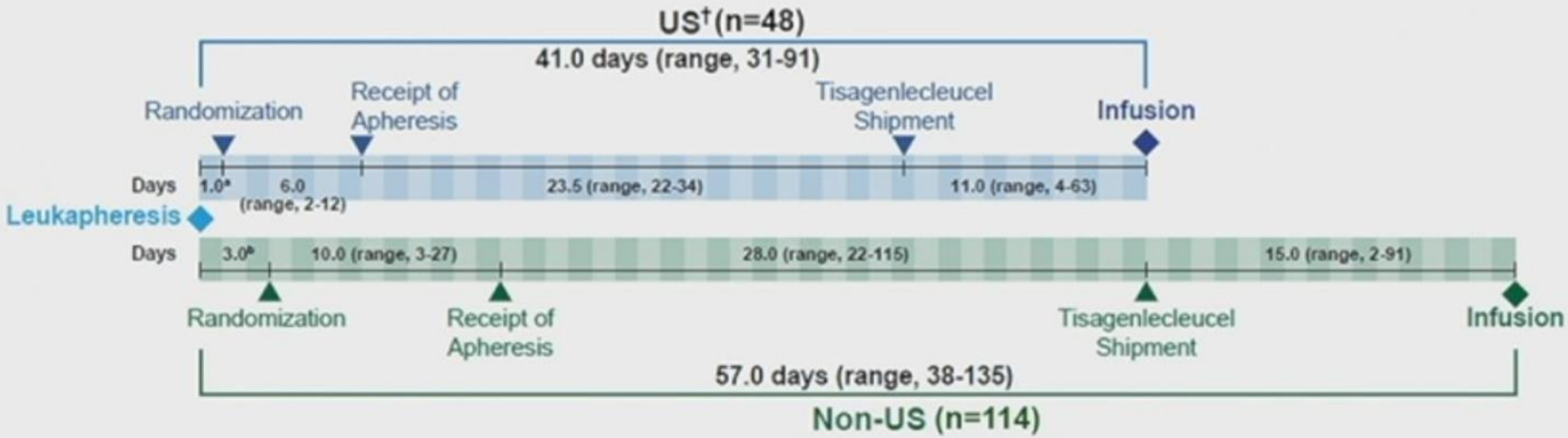
- Median follow-up: 10 months (range, 2.9-23.2)



[a]FAS and safety sets used to compare efficacy and safety between the 2 treatment strategies during the safety comparison period, defined as from day of randomization to the earlier of 56 days after last dose of study treatment or start date of new anticancer therapy. [b]Reasons for discontinuation without tisagenlecleucel infusion include physician decision (n=2, 1.2%), PD (n=2, 1.2%), Manufacturing issue (n=1, 0.6%), and patient decision (n=1, 0.6%). [c]Reasons for discontinuation without aHCT include PD (n=76, 47.5%), physician decision (n=14, 8.8%), death (n=7, 4.4%), patient decision (n=2, 1.3%), technical problems (n=2, 1.3%), and protocol deviation (n=1, 0.6%). aHCT, autologous hematopoietic cell transplantation; FAS, full analysis set; PCT, platinum-based immunochemotherapy; SOC, standard of care.

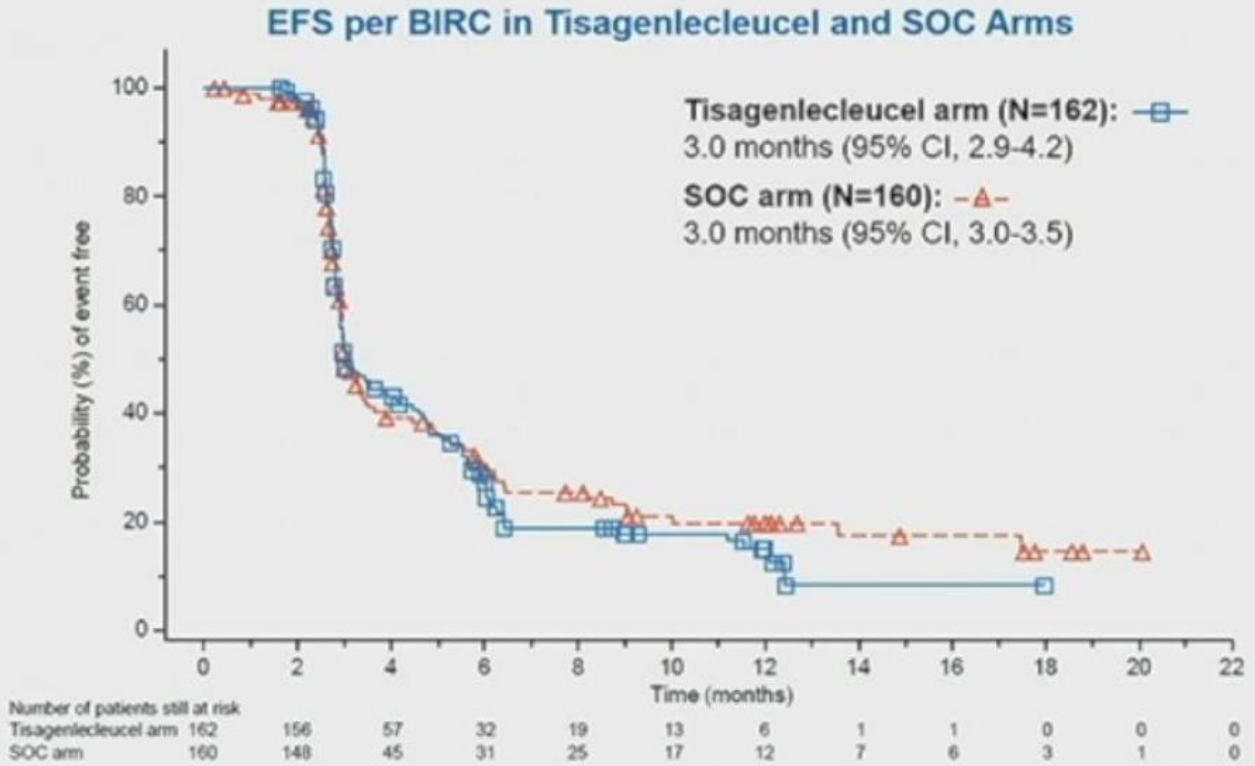
Time to Tisagenlecleucel Infusion

- Median time to infusion for all patients on the Tisagenlecleucel arm was 52 days (range, 31-135)



†North America was a stratification factor, and all enrolled patients in this group were from the United States (US).
ªrange, 1-6 days. ᵇrange, 1-17 days

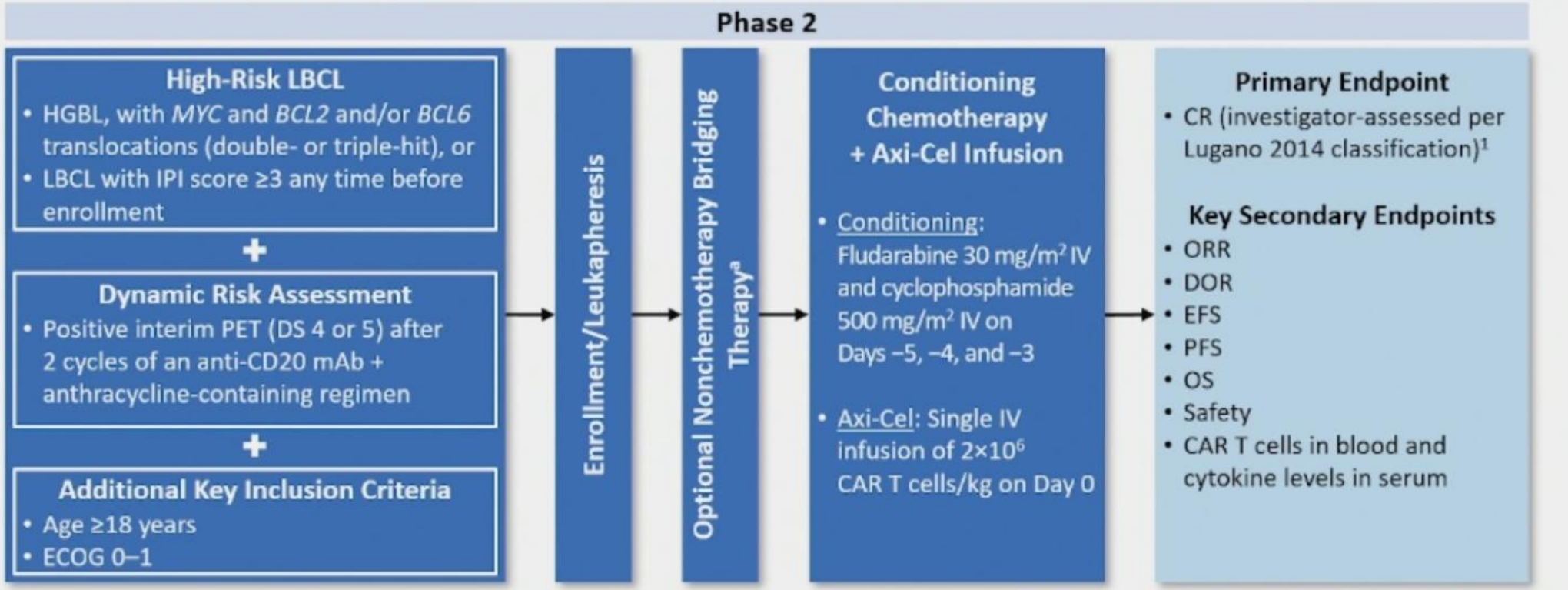
No Difference in EFS Between Treatment Arms



- EFS[a] was not significantly different between treatment arms
  - Primary analysis: Stratified unadjusted HR: 1.07 (95% CI, 0.82-1.40, p[b]=0.69)
  - Supportive analysis: Stratified adjusted[c] HR: 0.95 (95% CI, 0.72-1.25)
  - 6 patients responded to tisagenlecleucel infusion, but were captured as an EFS event due to SD/PD before or soon after infusion[d]

[a]EFS events defined as PD/SD after day 71 or death at any time. [b]p-value derived from 1-sided stratified log-rank test. [c]Adjusted for for potential imbalances in patient characteristics with pre-specified covariates of age, sex, race, ECOG performance status, histological subgroup, disease stage, and disease subtype. [d]Stratified adjusted HR accounting for delayed responses in both arms yield HR of 0.84 (95% CI: 0.63, 1.12).
BIRC, blinded independent review committee; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PD, progressive disease; SD, stable disease; SOC, standard of

ZUMA-12 Study Design

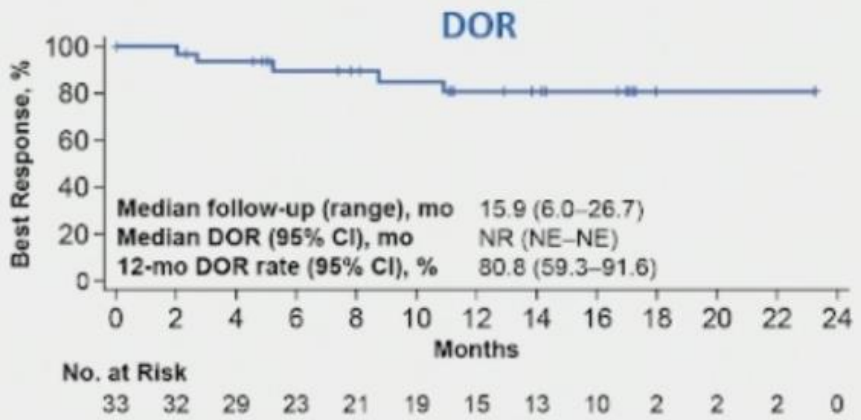


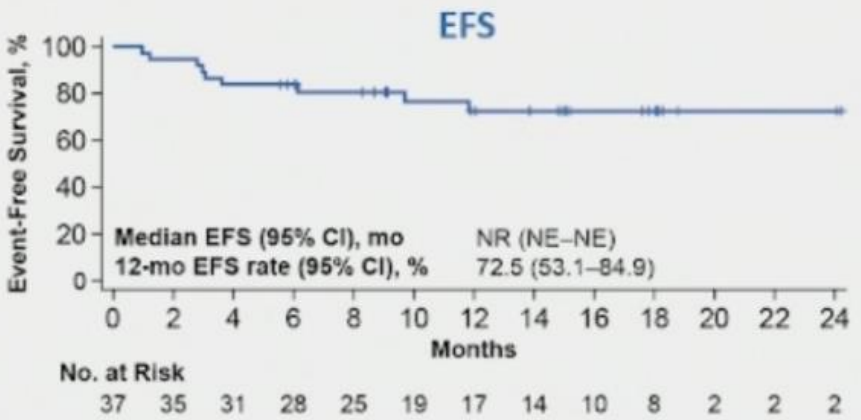
[a] Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

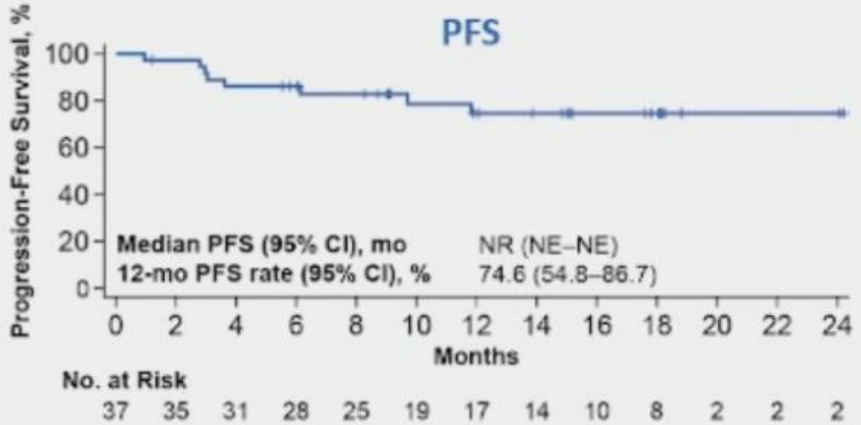
1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

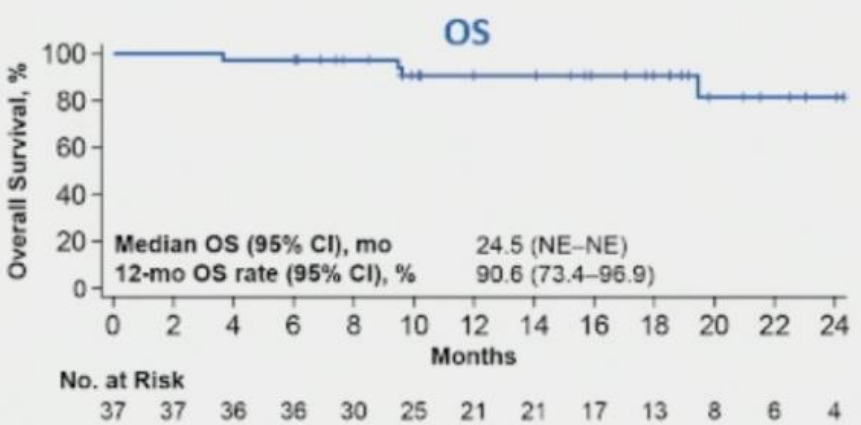
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

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





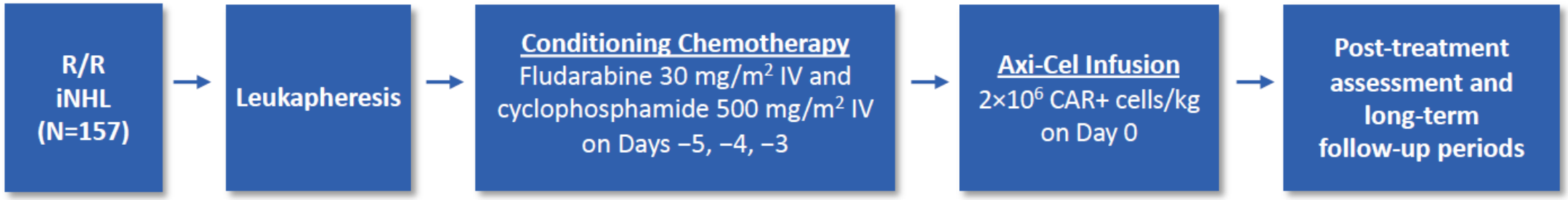




#Lear

[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.

ZUMA-5 Study Design



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

[a] Patients with stable disease (without relapse) >1 year from completion of last therapy were not eligible. [b] Single-agent anti-CD20 antibody did not count as line of therapy for eligibility.

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

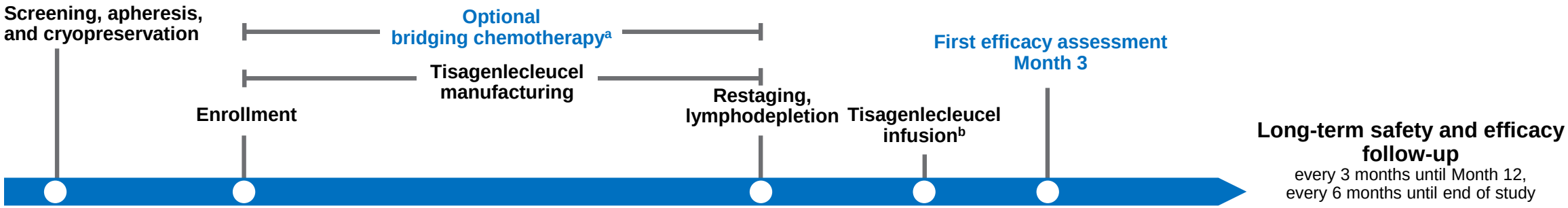
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IRRC, Independent Radiology Review Committee; IV, intravenous; mAb, monoclonal antibody; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Axi-Cel in R/R FL

Safety Results

- Consistent with prior reports, the most common Grade ≥3 AEs were neutropenia (33%), decreased neutrophil count (28%), and anemia (25%)
- Grade ≥3 CRS and NEs occurred in 7% of patients (6% FL; 8% MZL) and 19% of patients (15% FL; 36% MZL), respectively
  - Most CRS cases (120 of 121) and NEs (82 of 87) of any grade resolved by data cutoff[a]
  - Nearly half of NEs (49%) resolved ≤2 weeks after onset; most NEs (76%) resolved ≤8 weeks after onset
- Grade ≥3 cytopenias present ≥30 days post-infusion were reported in 34% of patients (33% FL; 36% MZL), most commonly neutropenia in 29% of patients (27% FL; 36% MZL)

ELARA Study Design



Key eligibility criteria	Study treatment	End points

• ≥18 years of age
• FL grade 1, 2, or 3A
• Relapsed/refractory disease[c]
• No evidence of histological transformation/FL3B
• No prior anti-CD19 therapy or allogeneic HSCT
	• Lymphodepleting chemotherapy options:
	  • Fludarabine (25 mg/m^2 IV daily for 3 days) + cyclophosphamide (250 mg/m^2 IV daily for 3 days)
	  • Bendamustine 90 mg/m^2 IV daily for 2 days
	• Tisagenlecleucel dose range (single IV infusion) was 0.6-6×10^8 CAR-positive viable T cells
		Primary: CRR by IRC
		
		Secondary: ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed and was followed by disease re-evaluation before tisagenlecleucel infusion
- Timing of planned analyses

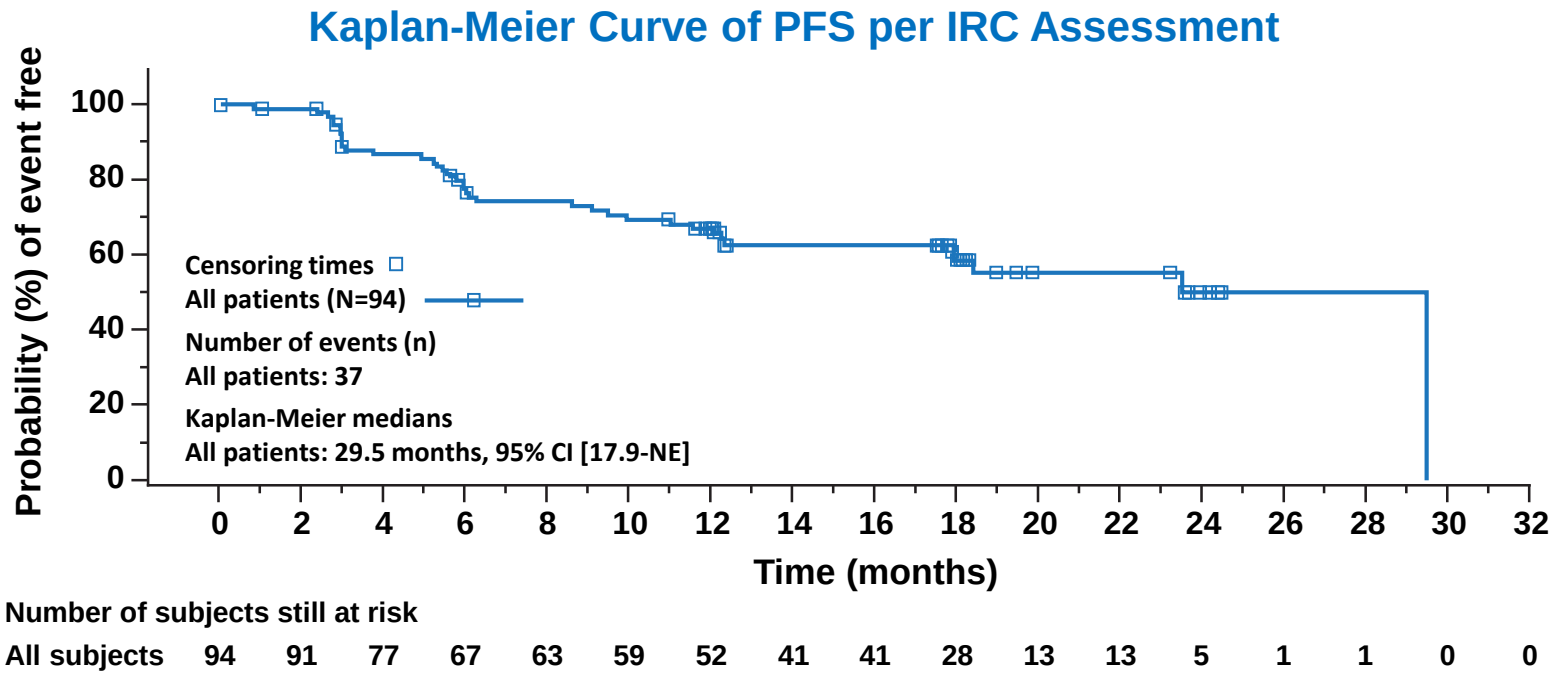
Planned analyses	Minimum follow-up from infusion	Median follow-up
Interim analysis	≈50 patients with ≥6 months follow-up	10 months
Primary analysis	90 patients with ≥6 months follow-up	11 months
Extended follow-up analysis	**90 patients with ≥12 months follow-up**	**17 months**

[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Refractory to ≥2nd line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after ≥2nd line of therapy or after an autologous HSCT.
CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; EAS, efficacy analysis set; FL, follicular lymphoma; HSCT, hematopoietic stem cell transplant; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Thieblemont, ASH 2021 #131

ELARA: Durable Response and Promising 12-mo PFS Confirmed with Longer Follow-up

- With a longer median follow-up of 21 months (August 3, 2021 data cutoff)
  - Median PFS was 29.5 months (95% CI, 17.9-NE)[a]



[a]Median PFS should be interpreted with caution due to the low number of patients at risk after Month 24.
CI, confidence interval; IRC, independent review committee; NE, not estimable; PFS, progression-free survival.

Thieblemont, ASH 2021 #131

ZUMA-2: Phase 2 study of KTE-X19 in r/r MCL

Phase 2

Enrollment/ Leukapheresis

R/R MCL (1 – 5 prior lines of therapy)

→

Optional Bridging Therapy

Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg/day or acalabrutinib 100 mg PO twice daily

→

Conditioning Chemotherapy

Fludarabine 30 mg/m^2 IV+ cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

→

CAR T Cell Dose

2 × 10^6 KTE-X19 cells/kg single IV infusion on Day 0

→

Follow-up Period

First tumor assessment on Day 28

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification2)

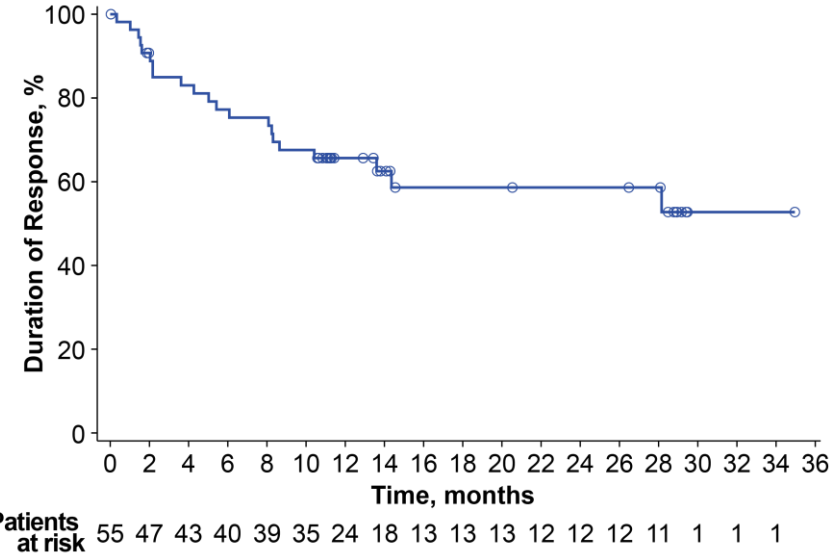
Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- Levels of CAR T cells in blood and cytokines in serum

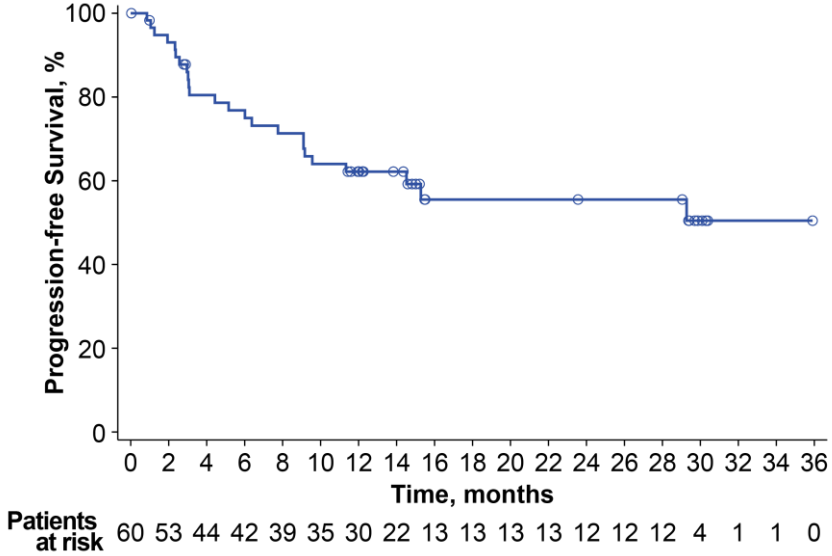
Wang et al, *N Eng J Med*, 2020
Wang et al. ASH 2020; Abstract 1120

ZUMA-2: DOR, PFS, and OS

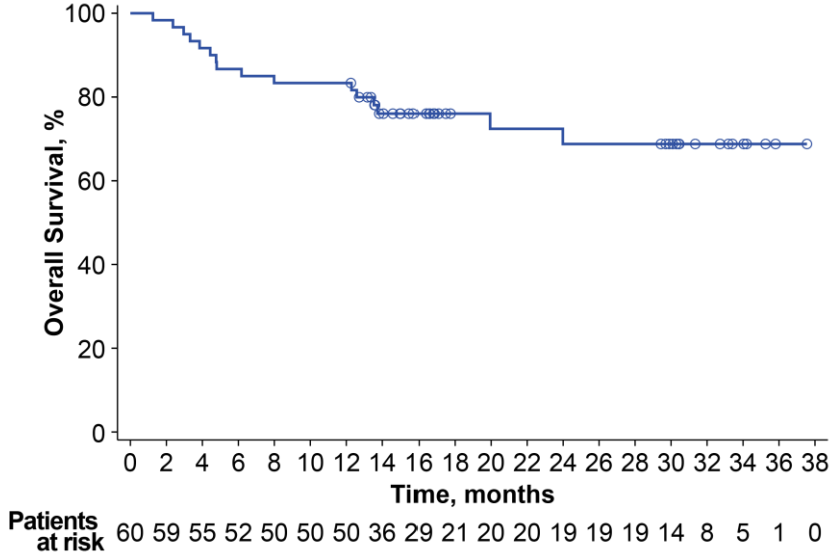
DOR



PFS



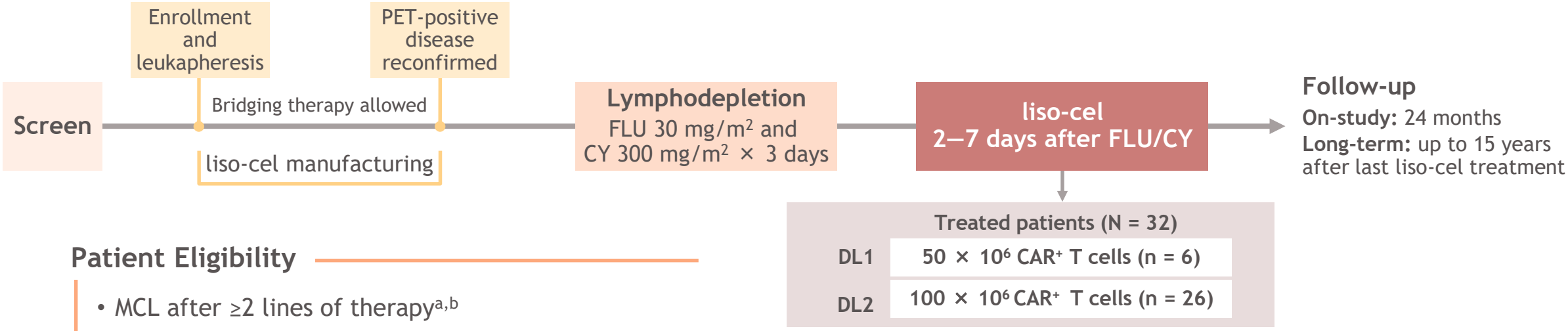
OS



- Median DOR, PFS, and OS were not reached after a median f/u of 17.5 mos
- 48% of all efficacy-evaluable patients at the data cutoff date
- 70% of patients who achieved CR remain in response

Wang et al, *N Eng J Med*, 2020
Wang et al. ASH 2020; Abstract 1120

TRANSCEND NHL 001: Preliminary results with liso-cel in r/r MCL



Patient Eligibility

- MCL after ≥2 lines of therapy[a,b]
- Prior BTKi, alkylating agent, and an anti-CD20 agent[c]
- Prior HSCT allowed (autologous/allogeneic)
- Secondary CNS lymphoma allowed
- ECOG PS of 0–2[d]
- CrCl >30 mL/min/1.73 m²
- LVEF ≥40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

End Points

Primary

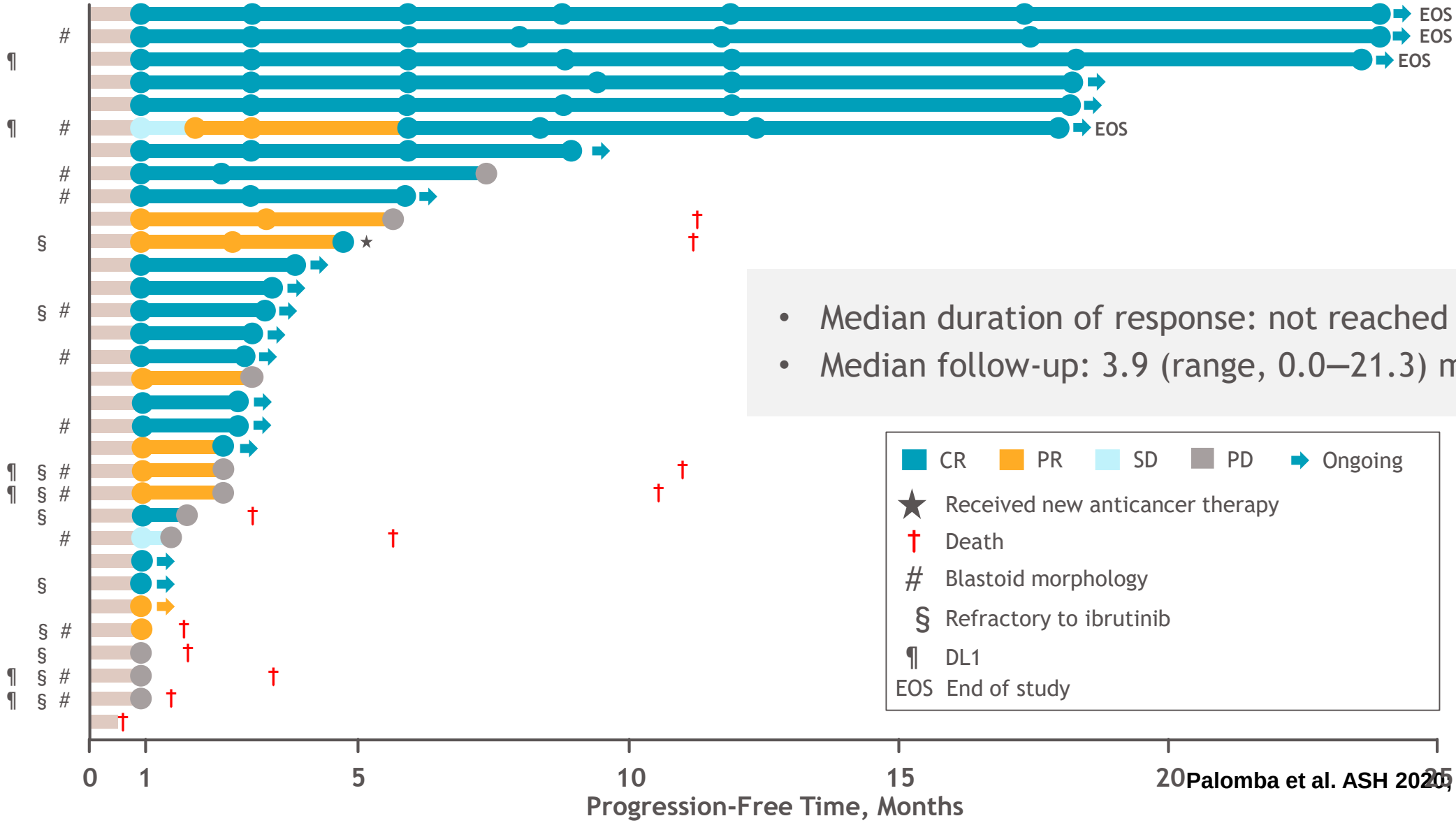
- AEs, DLTs, ORR by IRC per Lugano classification

Secondary

- CR rate by IRC, duration of response, PFS, OS, cellular kinetics, HRQoL, number of ICU days

Palomba et al. ASH 2020; Abstract 118

TRANSCEND MCL: Patient responses over time



- Median duration of response: not reached
- Median follow-up: 3.9 (range, 0.0—21.3) months

Palomba et al. ASH 2020, Abstract 118

Conclusions

- CAR T cell therapy has transformed the management of chemo-refractory large B-cell lymphoma
- Commercial CAR T has resulted in similar efficacy and comparable safety despite application in sicker/frailer patients
- CAR T is superior to salvage chemo/ASCT in high risk patients in 2nd-line
  - How do we approach those that relapse > 12 months
  - Will we bridge to CAR T at relapse?
- How do we balance safety with efficacy in indolent NHL in the ever expand treatment landscape?
- CAR T post BTKi is effective in R/R MCL,
  - will bispecifics be disruptive?