CAR-T in Lymphoma: Current and Future Landscape

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Disclosures

- Advisory: Bristol-Myers-Squibb, Abbvie, Ono Pharma, Seagen

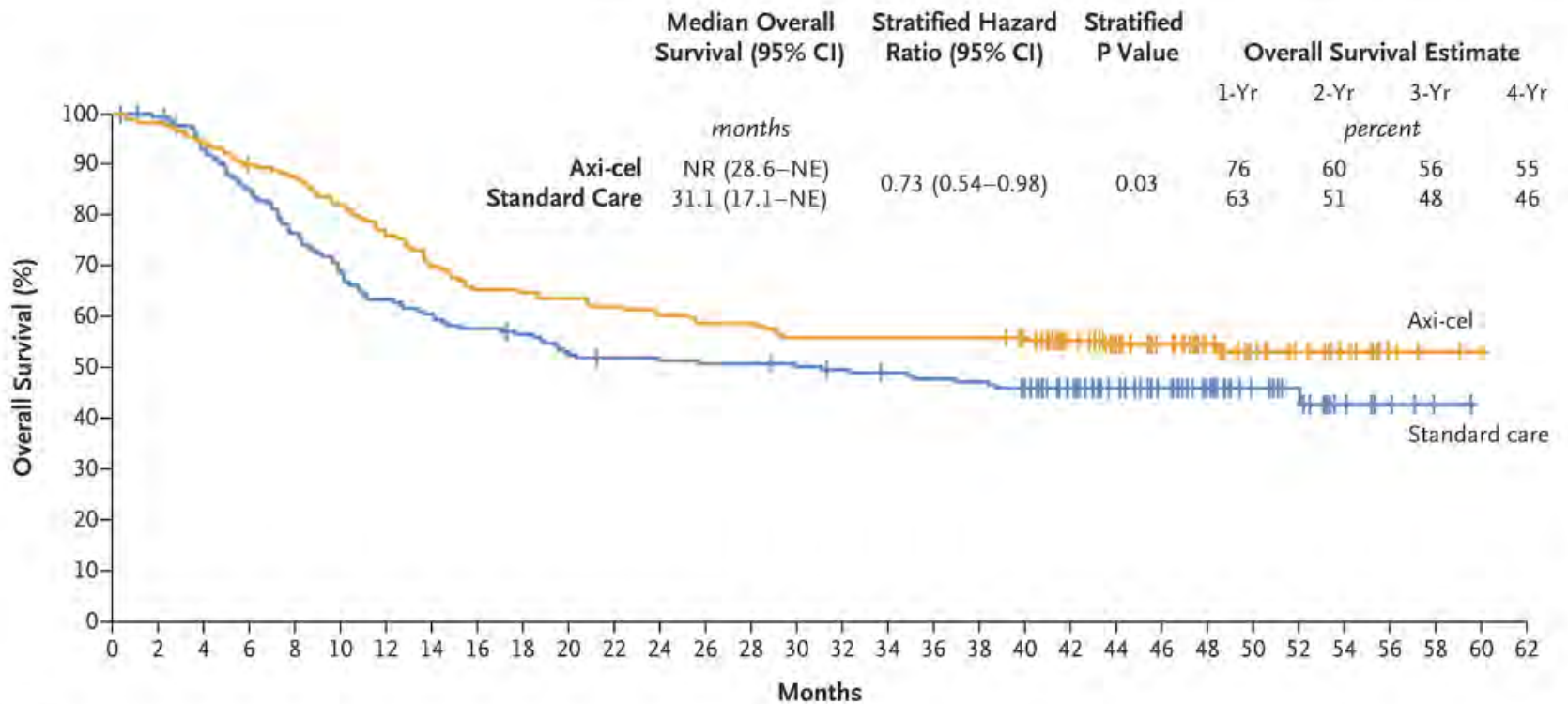- Research: Bristol-Myers-Squibb, Beigene, Fate Therapeutics

Outline

- Diseases
  - DLBCL
  - Mantle Cell Lymphoma
  - Follicular Lymphoma
  - Mantle Cell Lymphoma
  - CNS Lymphoma
- Sequencing
- Bridging/Pairing Therapy
- Novel Agents

Diffuse Large B-Cell Lymphoma

- Axi-cel Zuma-7 for 2L
- No bridging, no crossover

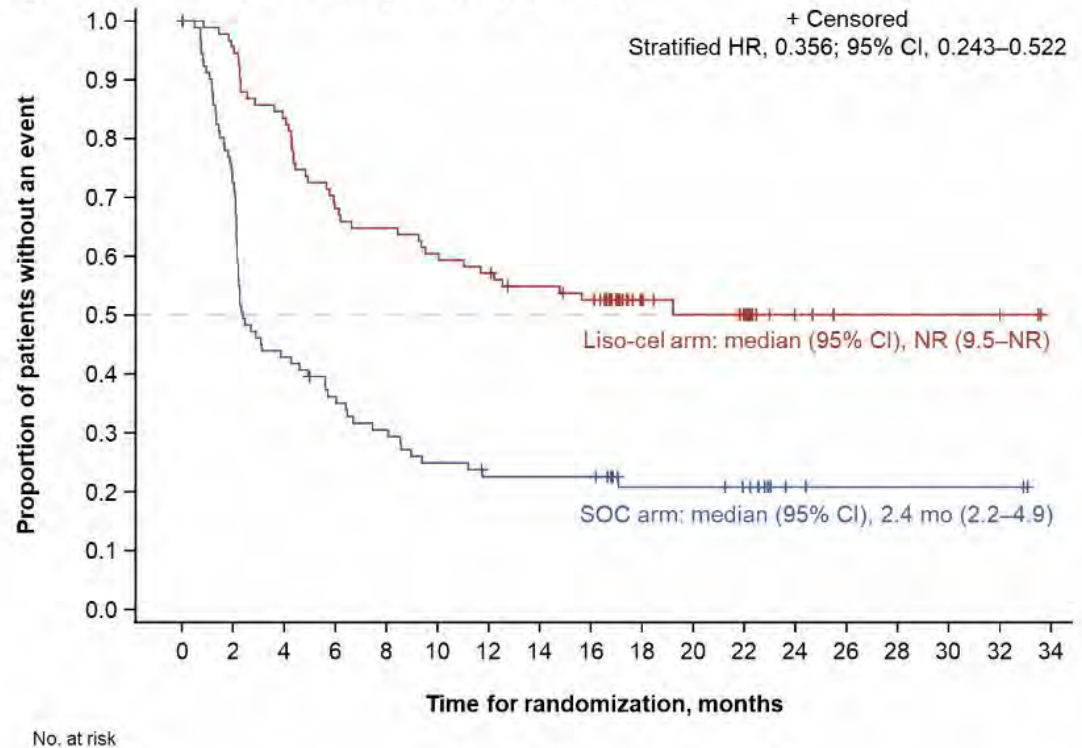|	Median Overall Survival (95% CI)	Stratified Hazard Ratio (95% CI)	Stratified P Value	Overall Survival Estimate			
				1-Yr	2-Yr	3-Yr	4-Yr
	months			percent			
Axi-cel	NR (28.6–NE)	0.73 (0.54–0.98)	0.03	76	60	56	55
Standard Care	31.1 (17.1–NE)			63	51	48	46

No. at Risk

Axi-cel: 180 177 170 161 157 147 136 125 117 116 114 111 108 105 105 100 100 100 100 100 96 80 67 54 41 29 20 14 4 2 1 0

Standard care: 179 176 163 149 134 121 111 106 101 98 91 89 88 87 87 85 83 81 79 78 73 63 51 41 31 19 14 7 4 1 0

Liso-cel 2L Updated Analysis

- ORR 87%, CR 74%
- Duration of CR
  - 12mo – 73%
  - 18 mo- 65%
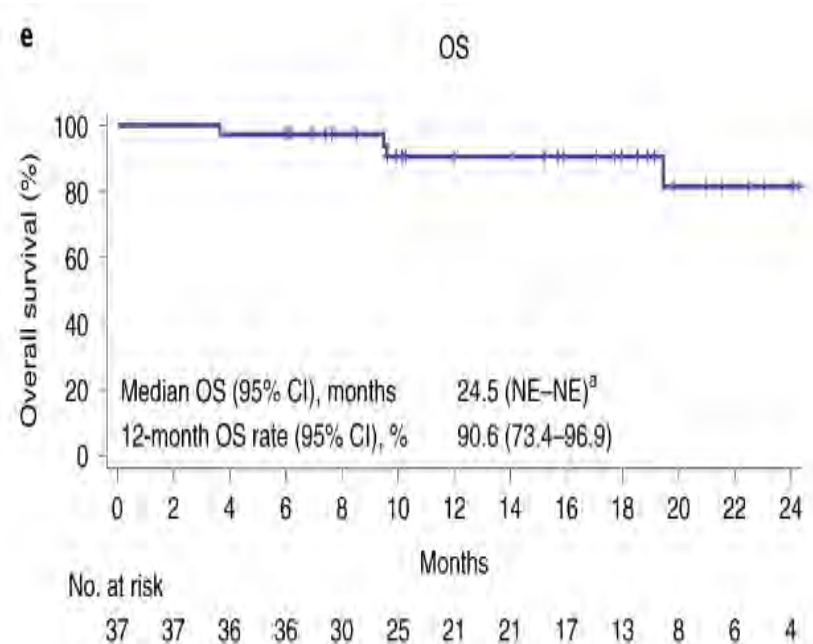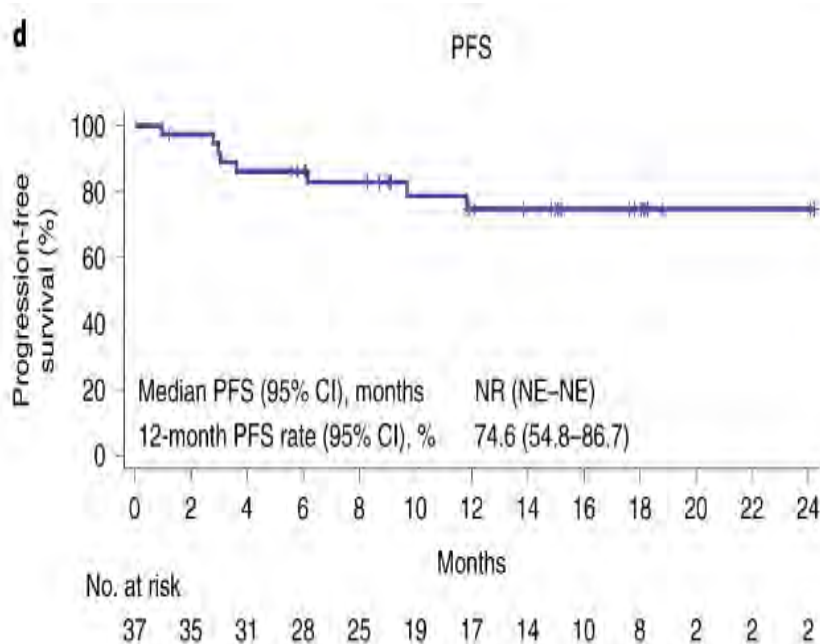
Figure. Kaplan-Meier plot of EFS by IRC (ITT population)

+ Censored
Stratified HR, 0.356; 95% CI, 0.243–0.522

Liso-cel arm: median (95% CI), NR (9.5–NR)

SOC arm: median (95% CI), 2.4 mo (2.2–4.9)

Proportion of patients without an event

Time for randomization, months

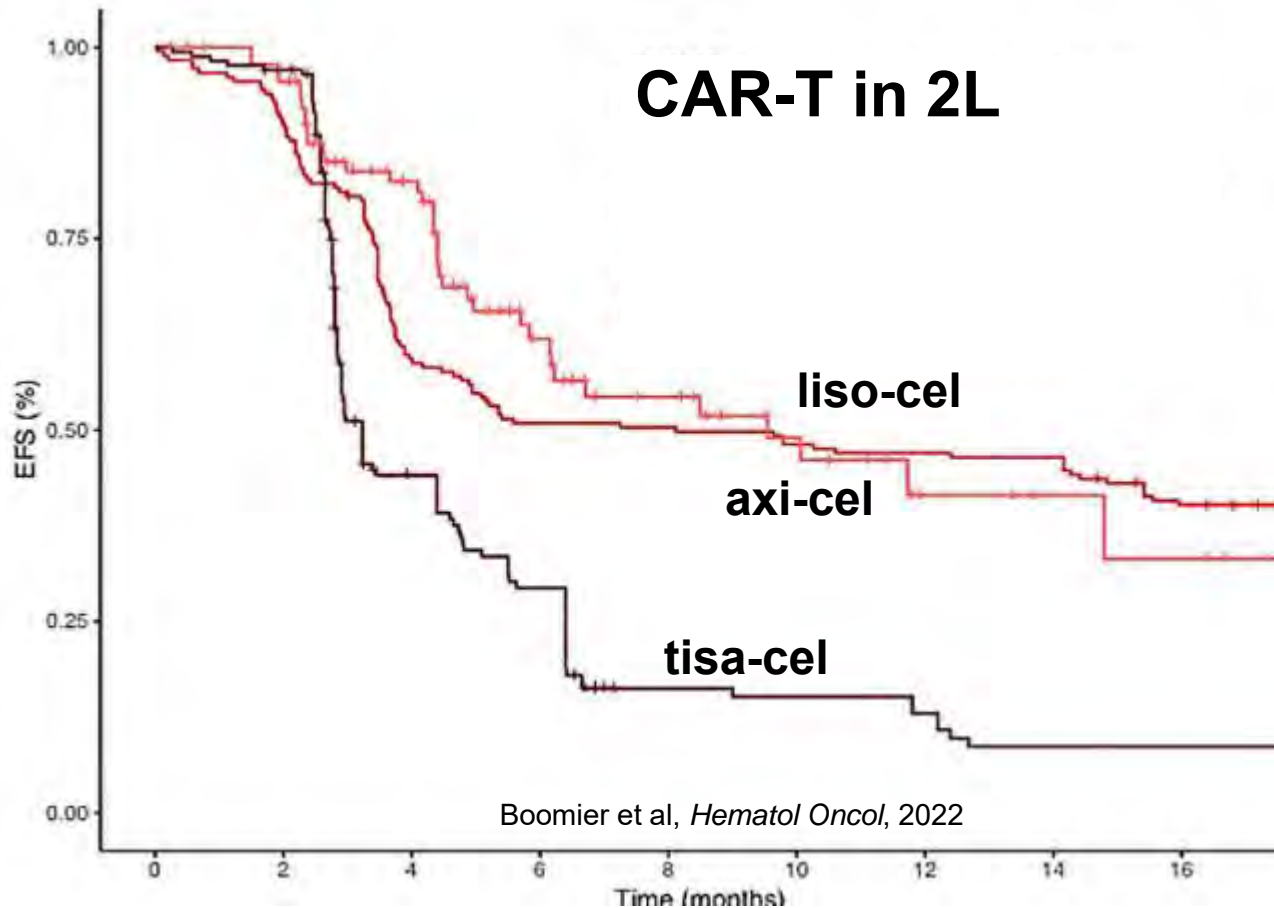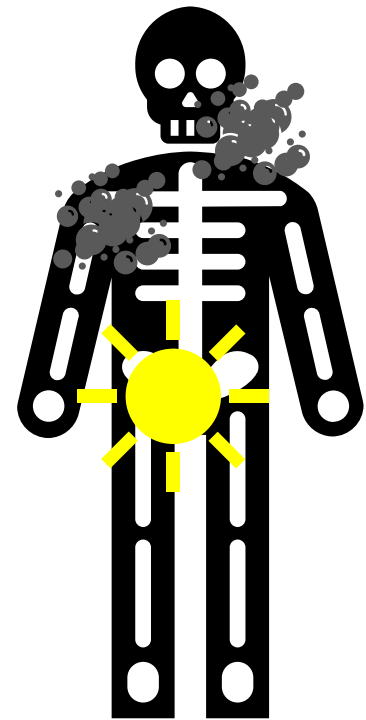No. at risk

Abramson et al, abstract
655, 12/11/22

Frontline CAR-T DLBCL

- Zuma-12: axi-cel following poor response to 1L
- High risk population:
    - double/triple-hit or IPI ≥3
    - PET2+ (D4 or D5) (50/50)

Neelapu, S.S., Dickinson, M., Munoz, J. *et al.* Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. *Nat Med* **28,** 735–742 (2022). https://doi.org/10.1038/s41591-022-01731-4

Problem: the majority of DLBCL pts receiving CAR-T will relapse/progress

CAR-T in 2L

Why?

liso-cel

axi-cel

tisa-cel

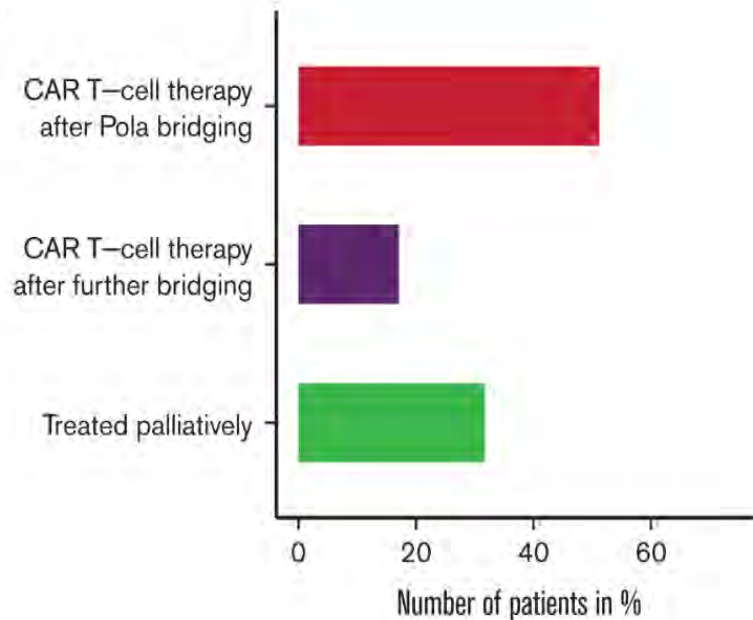Boomier et al, *Hematol Oncol*, 2022

Solution: A better bridge to CAR

- **Historically a poor prognostic sign- aggressive disease, ineffective agents**
- **Goal of bridging**
  - **Control disease**
  - **Limit toxicity/lymphotoxicity**
  - **Enhance CAR-T?**
- **Options?**
  - **ADCs -> polatuzumab, loncastuximb**
  - **Bi-specific antibodies**
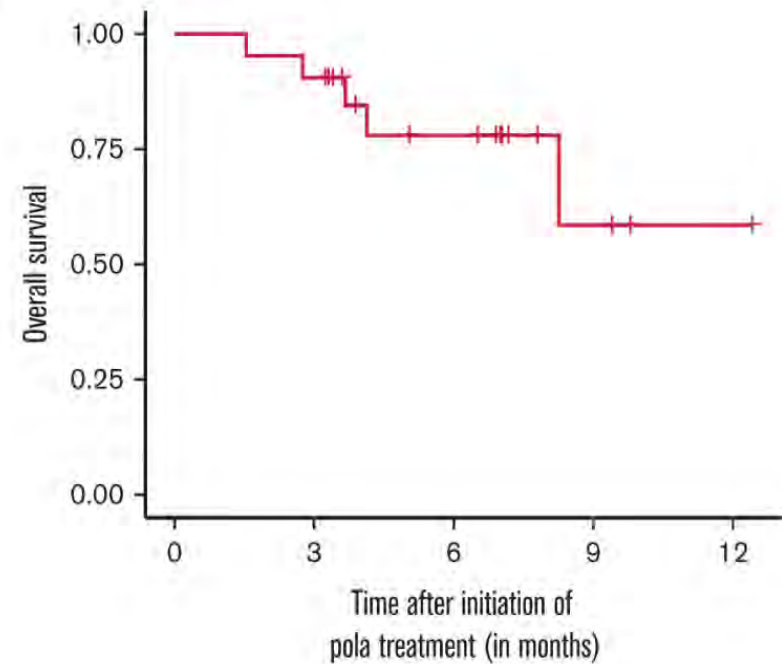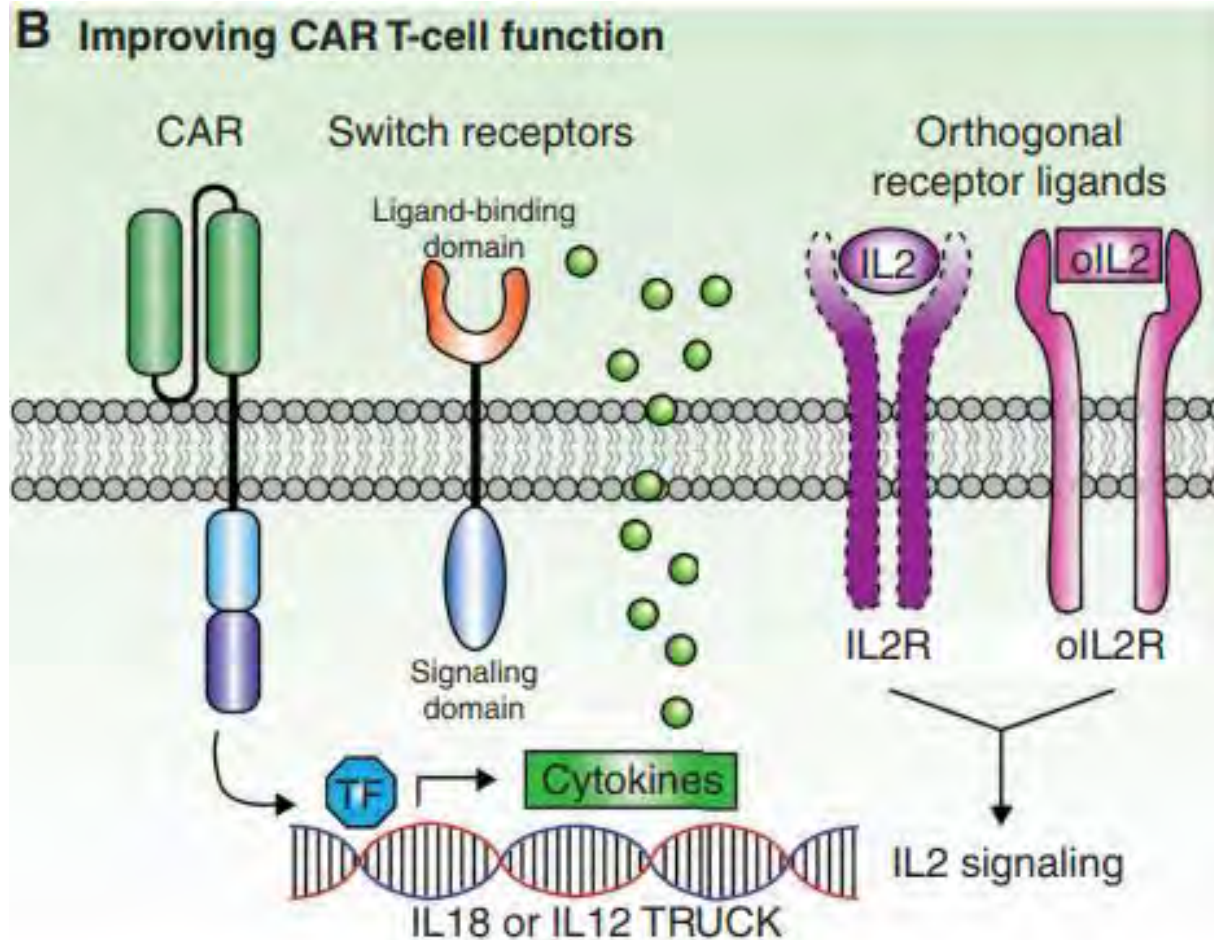 - **Radiation Therapy!!**

Polatuzumab bridging

Future CAR-T Therapy: Trucks

B Improving CAR T-cell function
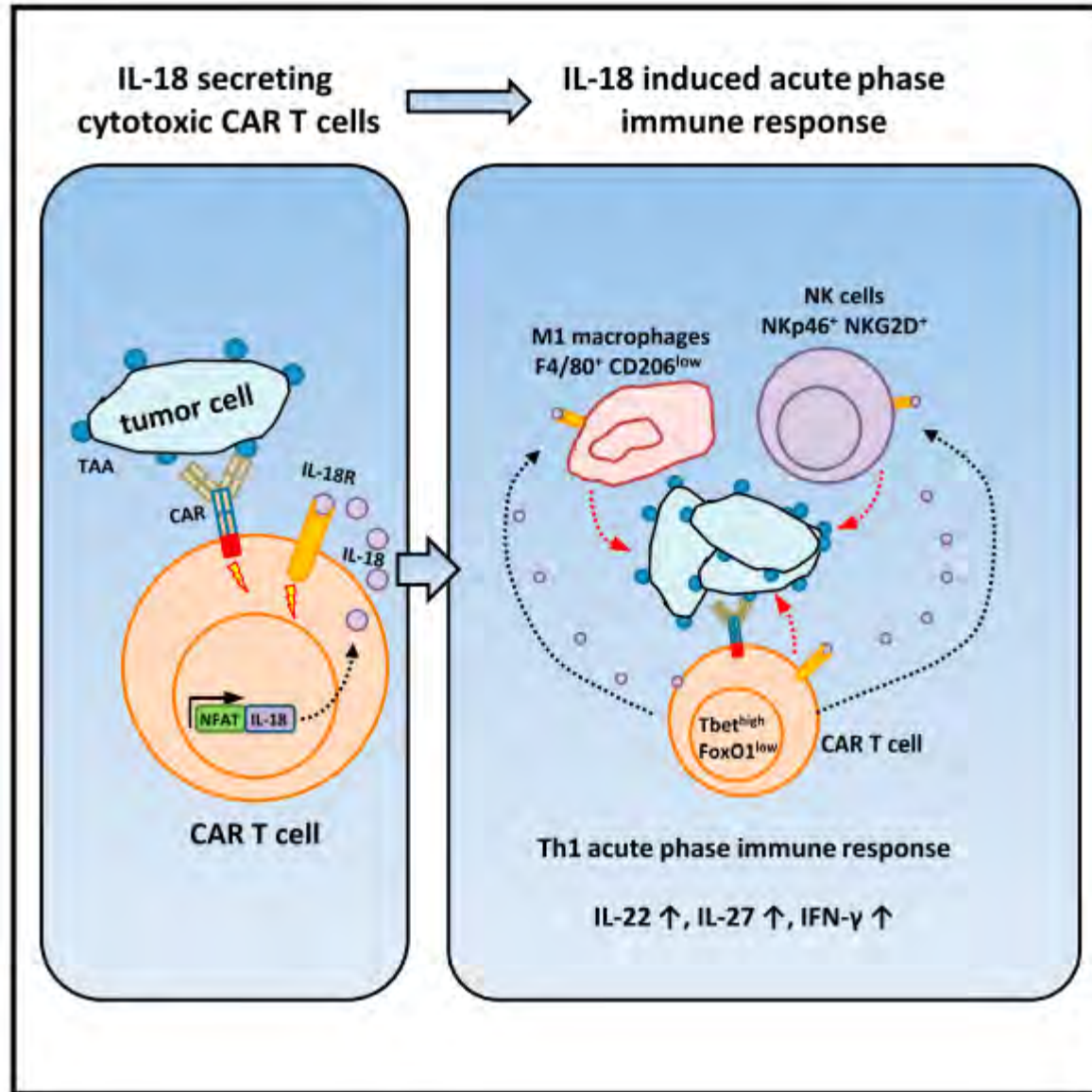
Trucks

Chmielewski M, Abken H. CAR T Cells Releasing IL-18 Convert to T-Bet[high] FoxO1^{low} Effectors that Exhibit Augmented Activity against Advanced Solid Tumors. Cell Rep. 2017 Dec 12;21(11):3205-3219. doi: 10.1016/j.celrep.2017.11.063. PMID: 29241547.

CD19-IL18

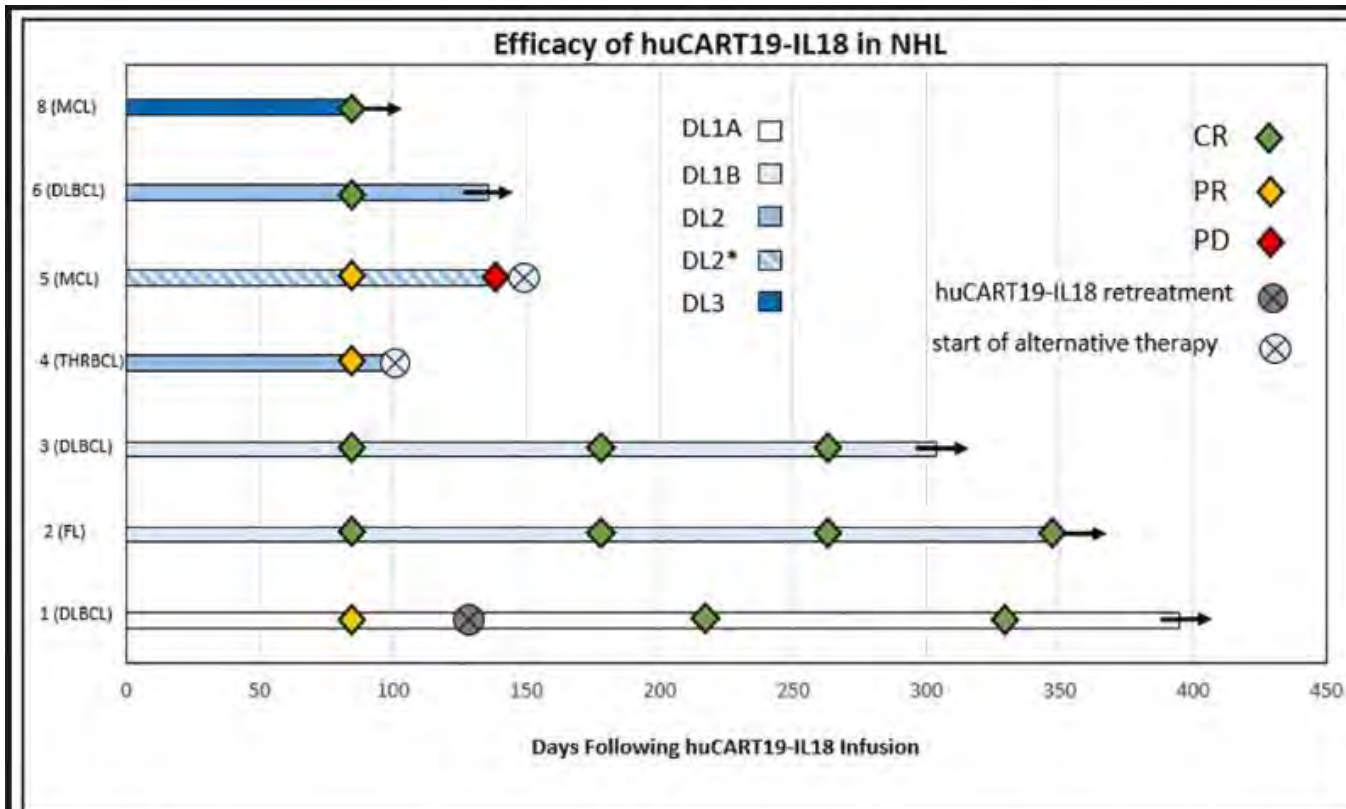Figure 1A. Swimmer plot of responses to huCART19-IL18 in NHL. Disease subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), T-cell histiocyte-rich large B-cell lymphoma (THRBCL), mantle cell lymphoma (MCL). Dose level (DL): DL1A (no lymphodepletion; 3x10^6), DL1B (lymphodepletion; 3x10^6), DL2 (7x10^6), DL2* (2.8x10^7), DL3 (3x10^7).

Svoda et al, ASH 2022, https://doi.org/10.1182/blood-2022-162393

Allogeneic CAR-T in Development

- ## Alpha2: allogeneic CAR-T and CD52 Ab
  - 11 enrolled, 10 received CAR-T
  - Heavily pre-treated population with aggressive dz
  - 2 CR
  - FDA hold placed for chromosomal abnormality observed in CAR-T cells in bone marrow

Locke FL, Malik S, Tees MT, et al. First-in-human data of ALLO-501A, an allogeneic chimeric antigen receptor (CAR) T-cell therapy and ALLO-647 in relapsed/refractory large B-cell lymphoma (R/R LBCL): ALPHA2 study. *J Clin Oncol.* 2021; 39 (suppl 15): 2529-2529. doi: 10.1200/JCO.2021.39.15_suppl.2529

Allogeneic CAR-T

- ## Antler-1: CB-010 in rr NHL
  - NCTNCT04637763 Caribou Biosciences
  - N=6 100% CR rate, 2/5 in CR at 6mo
  - No GVHD, 1 G3 ICANS 2 G2 CRS
  - Cont dose escalation

ANTLER Phase 1 trial in r/r B-NHL

Patient	Subtype	Prior lines therapy	Best response
1	FL[1]	8	CR
2	MCL	4	CR
3	FL[1]	2	CR
4	DLBCL	4	CR
5[2]	PMBCL	2	CR
6	DLBCL	2	CR

Response:
- CR: Complete Response
- PR: Partial Response
- PD: Progressive Disease
- Continuing on ANTLER

Months from CB-010 infusion

FL: follicular lymphoma. MCL: mantle cell lymphoma. DLBCL: diffuse large B cell lymphoma. PMBCL: primary mediastinal large B cell lymphoma
[1] Aggressively behaving, with POD24 (high risk)
[2] Patient 5's 3-month scan conducted on day 63 post CB-010 as per investigator's discretion
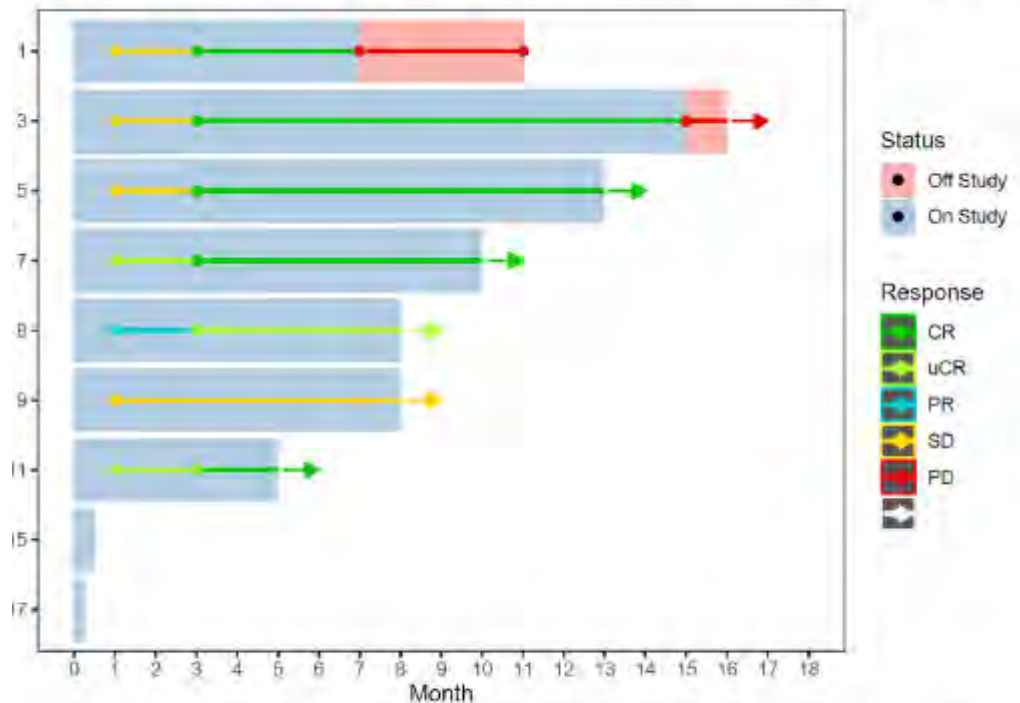As of May 13, 2022 data cutoff date, data collection ongoing, efficacy based on Lugano criteria

Nastoupil et al, EHA congress 2022, 6/10/22, Abstract P1455

CAR-T CNS Lymphoma

- Proof of concept n=9
- CR 86%
- No increased signal for ICANS/CRS

Jacobsen et al,
abstract
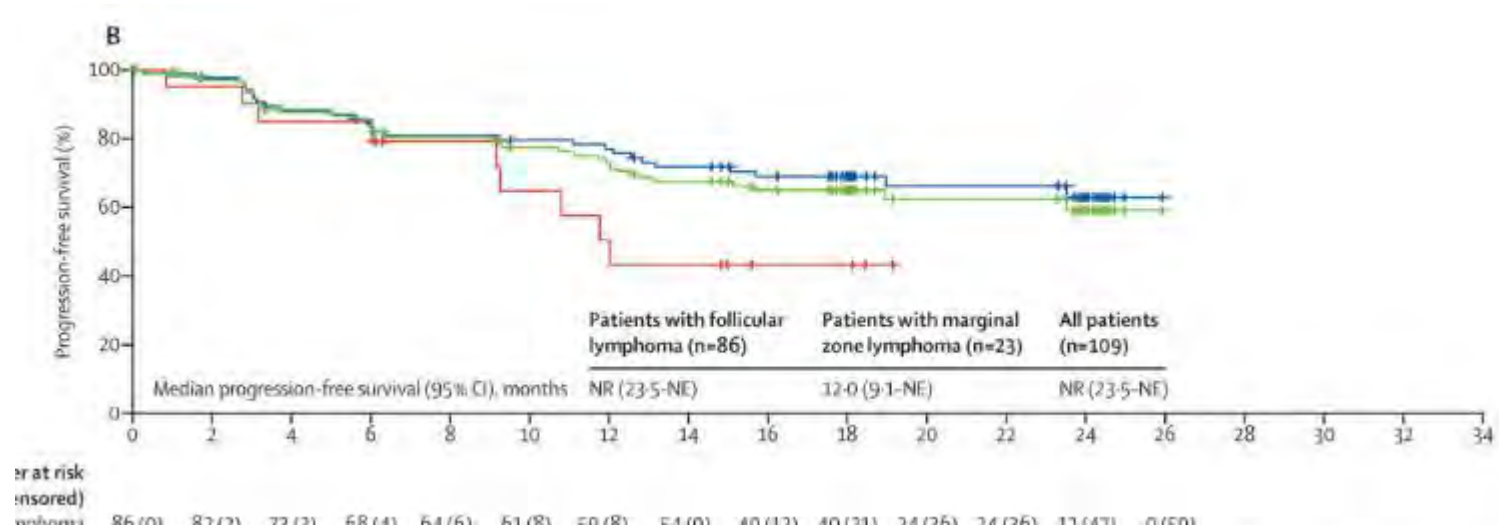440,12/11/22

Figure 1. Swimmer Plot of Response to Axi-cel Over Time

CR: complete response; uCR: unconfirmed complete response; PR: partial response;
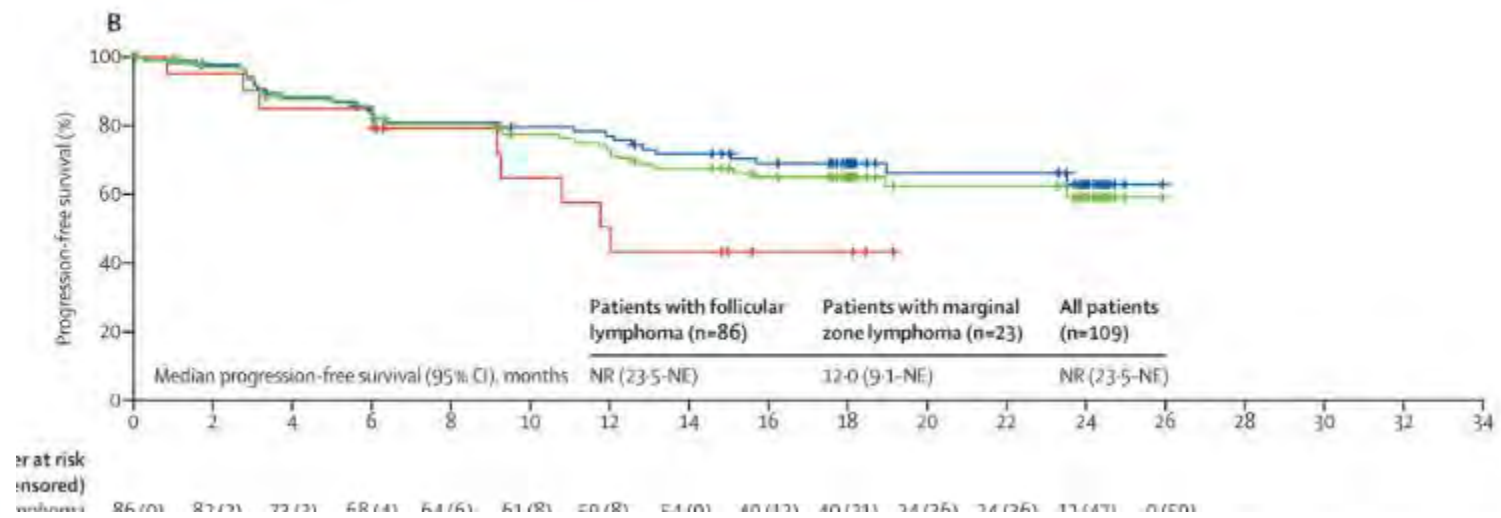SD: stable disease (SD); PD: progressive disease

Lymphoma where CAR-T Is Less Effective

- Burkitt lymphoma (Samples et al, ASCO 2023
  - 1/21 in multi-center with durable CR

- Marginal Zone lymphoma
  - Zuma 5

CAR-T For Follicular Lymphoma
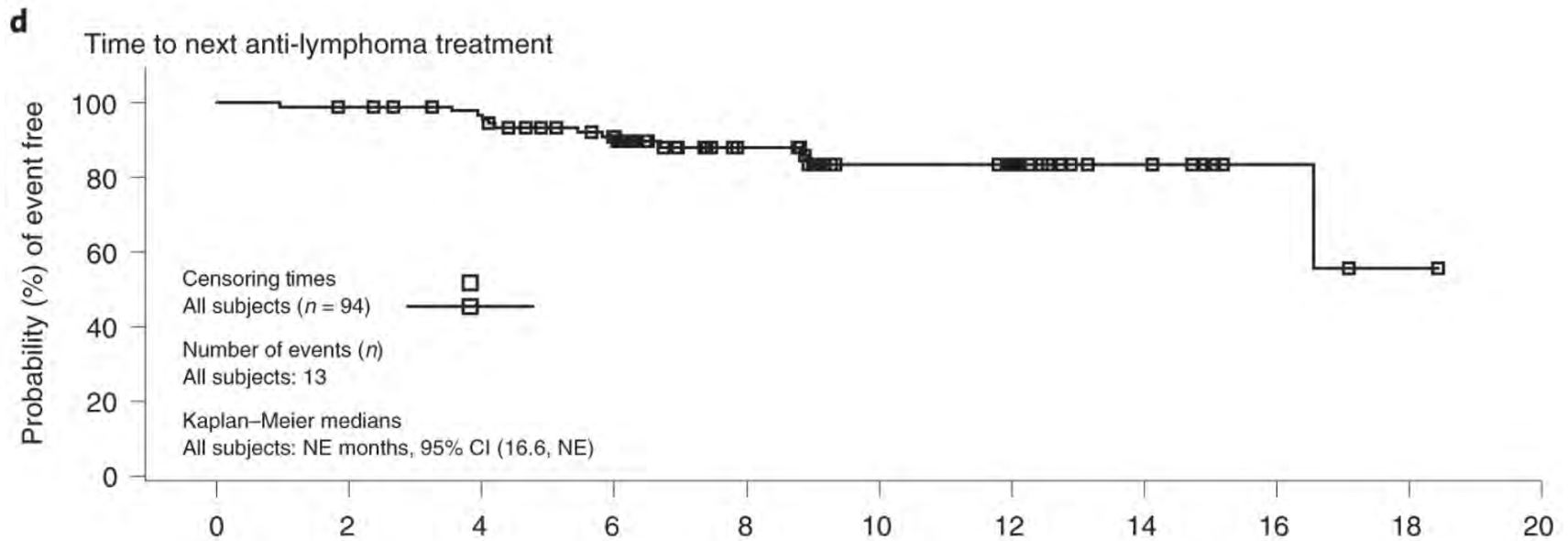
CAR-T for Follicular lymphoma
Liso-cel
Phase 2 Transcend FL

Table. Summary of efficacy and safety

Efficacy endpoints	3L+ FL EE pts (n = 101)
ORR, n (%)	98 (97.0)
(95% CI; one-sided *P* value)	(91.6–99.4; <0.0001)
CR rate, n (%)	95 (94.1)
(95% CI, one-sided *P* value)	(87.5–97.8; <0.0001)
PR, n (%)	3 (3.0)
Stable disease, n (%)	1 (1.0)
Progressive disease, n (%)	1 (1.0)
Not evaluable, n (%)	1 (1.0)
DOR, median (95% CI)	NR (18.0–NR)
Continued response at 12 mo, % (SE)	81.9 (3.986)
PFS, median (95% CI)	NR (18.96–NR)
PFS rate at 12 mo, % (SE)	80.7 (3.989)
Safety	Liso-cel–treated pts (2L+ FL; safety set) (n = 130)
AEs of special interest, n (%)	

Tisa-cel FL

d

Time to next anti-lymphoma treatment

Probability (%) of event free vs. time (0–20)

Censoring times
All subjects (n = 94)

Number of events (n)
All subjects: 13

Kaplan–Meier medians
All subjects: NE months, 95% CI (16.6, NE)

Mantle Cell Lymphoma

Brexucabtagene autoleucel

3 year followup

Toxicity concern- ICANS

Mantle Cell lymphoma
Liso-cel

Table . Summary of time to event efficacy and safety endpoints

Efficacy	Efficacy set[a] (n = 83)	COVID-19 sensitivity analysis set[b] (n = 83)
DOR, median (95% CI), mo	15.7 (6.2–24.0)	17.5 (7.6–24.0)
Continued response at 18 mo, % (95% CI)	42.7 (29.9–54.9)	48.8 (34.8–61.4)
DOR follow-up, median (95% CI), mo	22.8 (16.7–23.0)	22.6 (16.2–22.8)
PFS, median (95% CI), mo	15.3 (6.6–24.9)	17.8 (7.6–24.9)
PFS rate at 18 mo, % (95% CI)	43.9 (31.8–55.4)	49.9 (36.9–61.7)
PFS follow-up, median (95% CI), mo	23.5 (17.7–23.8)	18.2 (12.4–23.7)
OS, median (95% CI), mo	18.2 (12.9–36.3)	24.8 (15.7–NR)
OS rate at 18 mo, % (95% CI)	50.8 (39.2–61.2)	56.0 (43.9–66.6)
OS follow-up, median (95% CI), mo	24.0 (23.7–24.2)	23.8 (23.6–24.2)
Safety	Safety set[c] (n = 88)	
Grade ≥ 3 TEAEs,[d] n (%)	76 (86.4)	
Grade ≥ 3 TEAEs in ≥ 10% of patients, n (%)		
Neutropenia	49 (55.7)	
Anemia	33 (37.5)	
Thrombocytopenia	22 (25.0)	
Grade 5 TEAEs,[d] n (%)	4 (4.5)	
Cryptococcal meningoencephalitis[e]	1 (1.1)	
Cardiopulmonary arrest[f]	1 (1.1)	
Lung infection (COVID-19 pneumonia)[e]	1 (1.1)	
Tumor lysis syndrome[g]	1 (1.1)	
TEAEs of special interest, n (%)		
Any-grade CRS	54 (61.4)	
Grade ≥ 3 CRS	1 (1.1)	
Any-grade NEs	27 (30.7)	
Grade ≥ 3 NEs	8 (9.1)	
Prolonged cytopenias[h]	35 (39.8)	
Grade ≥ 3 infections	13 (14.8)	

Summary

- CAR-T established in
    - 2L DLBCL (axi-cel, liso-cel)
    - 3L FL (axi-cel, tisa-cel, now lisa-cel)
    - Post BTKI MCL (brexu-cel, now lisa-cel)
- Emerging for CNS Lymphoma
- Bridging therapy important for LBCL
    - Optimal regimen undefined
- Future CAR-T therapies
    - Allogeneic "off-the shelf" CAR-T
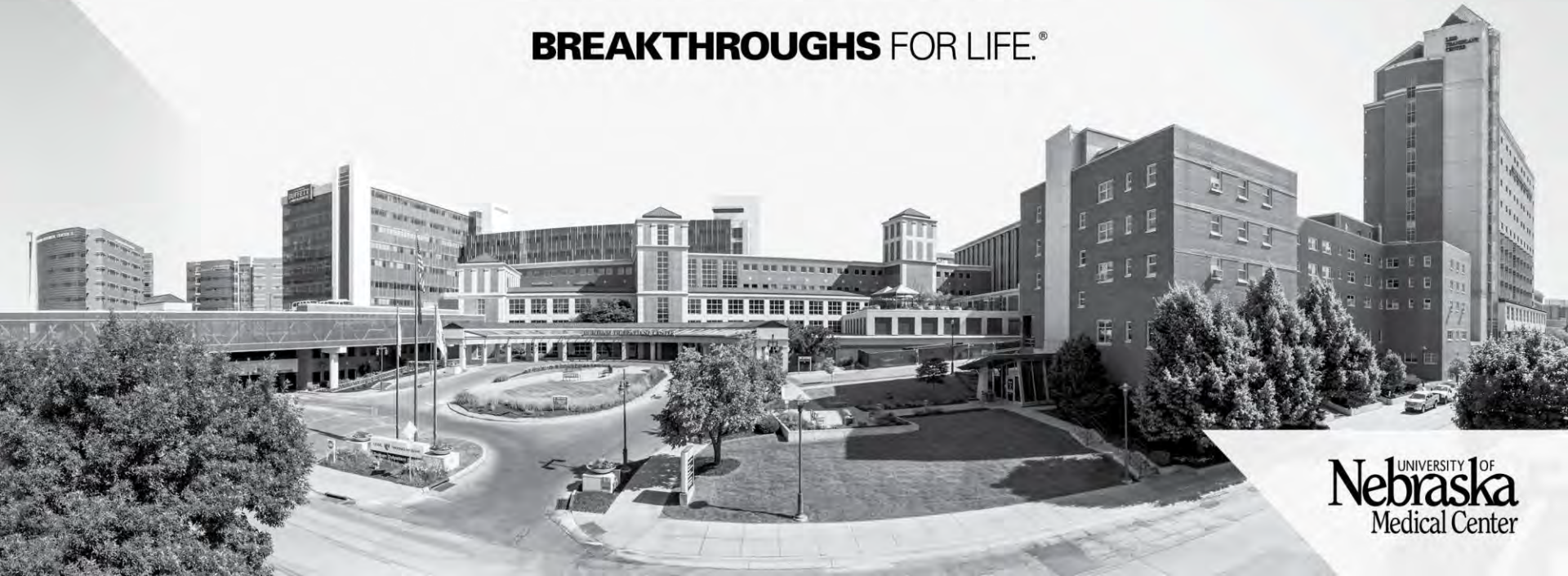   - CAR-T + cytokine (TRUCKS)

Thank you!!!!
Questions?
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