Interim Results from a Phase 2 Pivotal Study (DALY II USA) of Tandem CD20-CD19-Directed Non-Cryopreserved CAR-T Cells – Zamtocabtagene Autoleucel (Zamto-Cel) in Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma

Nirav N. Shah, Richard T. Maziarz, Caron A. Jacobson, Patrick B. Johnston, Sunil Abhyankar, Iris Isufi, Miguel Angel Perales, Monalisa Ghosh, Matthew Ulrickson, Allison C. Rosenthal, Javier L. Munoz, Nancy M. Hardy, Aaron P. Rapoport, Reem Karmali, Farrukh T. Awan, Matthew S. McKinney, Mitchell Horwitz, Matthew Lunning, Nathan Denlinger, Marek Ancukiewicz, Madhavi Nallewar, Kimberly C. Coleman, Esther Eromosele, Remigiusz Kaleta, Johanna Theruvath, Anna Wijatyk, and David B. Miklos

TANDEM MEETINGS

ASTCT® CIBMTR®

Disclosure Slide

Speaker Name: Nirav Shah

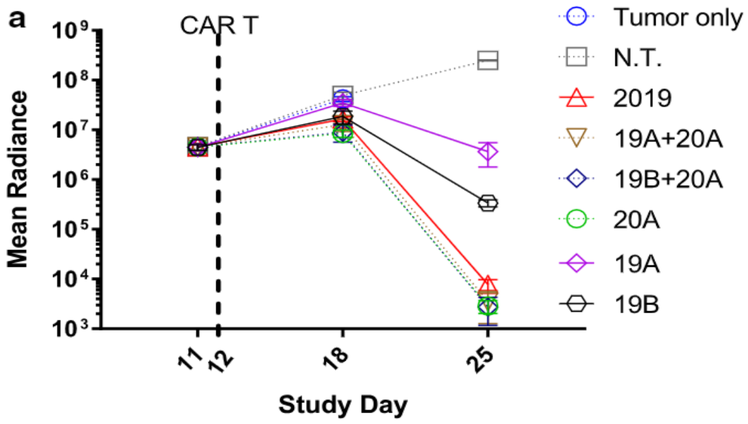
Disclosures

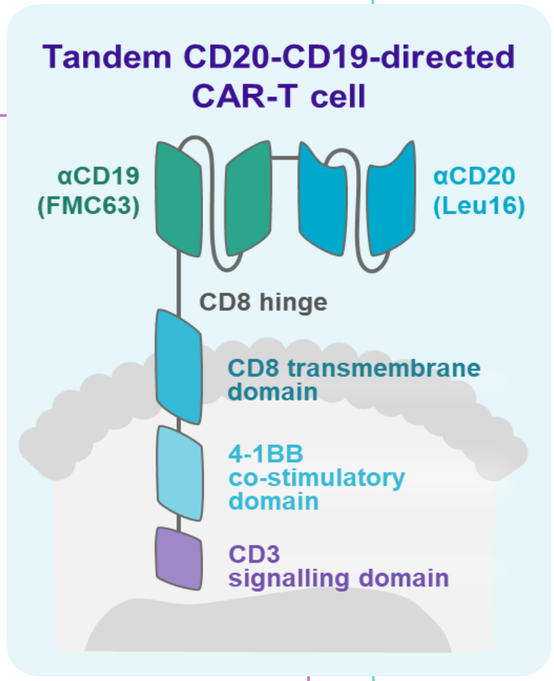
- N.S. reports participation on advisory boards and/or consultancy for Gilead-Kite, BMS-Juno, Miltenyi Biomedicine, Lilly Oncology, Incyte, Abbvie, Cargo, Beigene, Kite, Allogene, Astrazeneca, BMS, Ipsen, and Galapagos. He has research funding from Genentech, Miltenyi Biomedicine, and Lilly Oncology. In addition, N.S. is on a scientific advisory board for Tundra Therapeutics.

Dual targeting with CD20-CD19 CAR-T cell may limit antigen escape

Antigen loss observed in
~ 30% of pts after CD19 CAR-T therapy[1]

Pre-clinical studies[2]





First-in-human trials

Phase I (NCT03019055)[3]

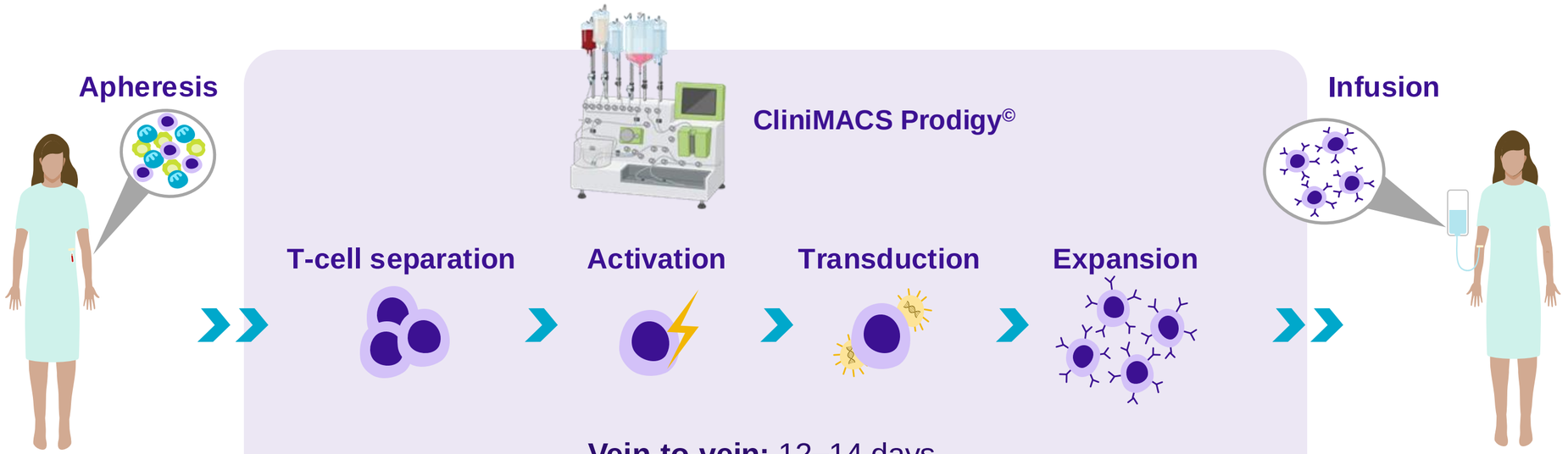
- Dose escalation and expansion trial
- Identified dose: 2.5x10e^6 cells/kg
- High Response Rate with durable remissions over >4 years post-treatment
- LTG 1497 CAR construct identical to MB2019.1 CAR construct

Phase I/II (DALY I, NCT03870495)[4]

- Multicenter, open-label
- Accessed feasibility, dosage, safety and toxicity
- Confirmed recommended dose of 2.5x10e^6 cells/kg
- Infused in 100% enrolled
- Well-tolerated, no CRS or neurotoxicity
- ORR at 75% with 5/12 achieving CR durable response

1. Majzner, R. and Mackall, C. Tumor Antigen Escape from CAR T–cell Therapy. Cancer Discov; 8(10); 1219–26;
2. Schneider D. et al. A tandem CD19/CD20 CAR lentiviral vector drives on-target and off-target antigen modulation in leukemia cell lines. J. ImmunoTherapy of (2017) 5:42;
3. Shah, N. N. et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. Nat Med 26, 1569-1575, doi:10.1038/s41591-020-1081-3 (2020)
4. Borchmann, P. et al. Phase I Trial of MB-CART2019.1 in patients with relapsed or refractory B cell non-hodgkin lymphoma: 2-year follow-up report. European Hematology Association Poster 1184 (2022).

Zamto-cel – an investigational autologous tandem CD20-CD19-directed non-cryopreserved CAR-T cell product with short vein-to-vein time



N=69

Inclusion criteria

- Adult patients with r/r DLBCL
- ≥2 prior lines of treatment
- Measurable disease (Lugano 2014 classification[1])

Interim analysis

- First 59 evaluable patients with min 3 months FU after treatment*
- LD regimen: Flu 30 mg/m^2 + Cy 300 mg/m^2, d(-5) to (-3) or Bendamustine 90 mg/m^2, d(-4) to (-3)

Lymphodepletion is initiated during manufacturing

Lymphodepletion chemotherapy

Zamto-cel | 2.5 x 10^6 | CAR-T cells/kg

Endpoints

Primary: ORR, defined as BOR of either CR or PR

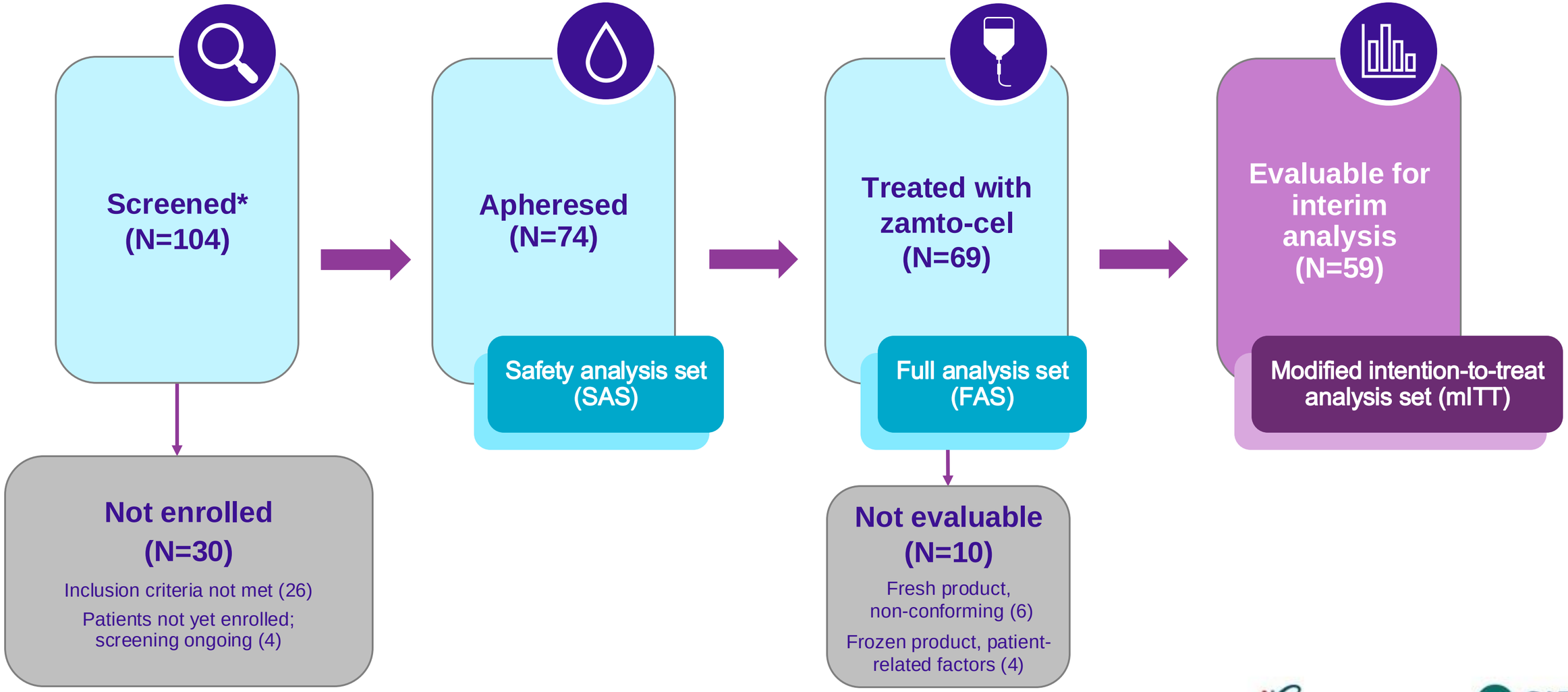
Secondary: CRR at 1 and 6 months; DOR; PFS; OS; safety; PK; CD19 and CD20 antigen expression at relapse

*Study start date: 25 May 2021.

BOR, best overall response; CAR-T cell, chimeric antigen receptor T cell; CR, complete response; CRR, complete response rate; Cy/Flu, Cyclophosphamide/Fludarabine; DOR, duration of response; FU, follow-up; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; r/r DLBCL, relapsed/refractory diffuse large B-cell lymphoma.

1. Cheson BD, et al. J Clin Oncol 2014;32(27):3059-68.

Patient disposition:
59 patients were evaluated in the planned interim analysis (mITT)



TANDEM MEETINGS

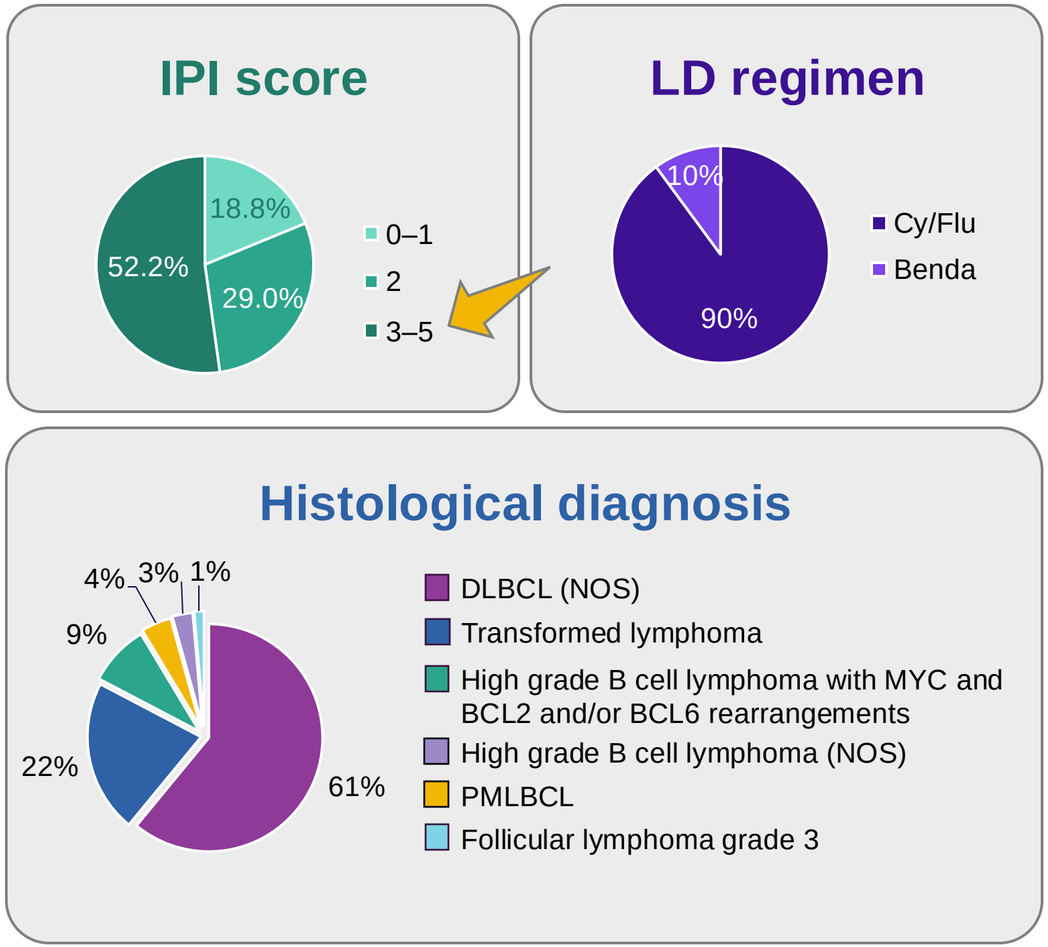
ASTCT

CIBMTR

*Data cut-off: 29 Mar 2024.

Patient baseline characteristics: Advanced, heavily pre-treated population with diverse histology

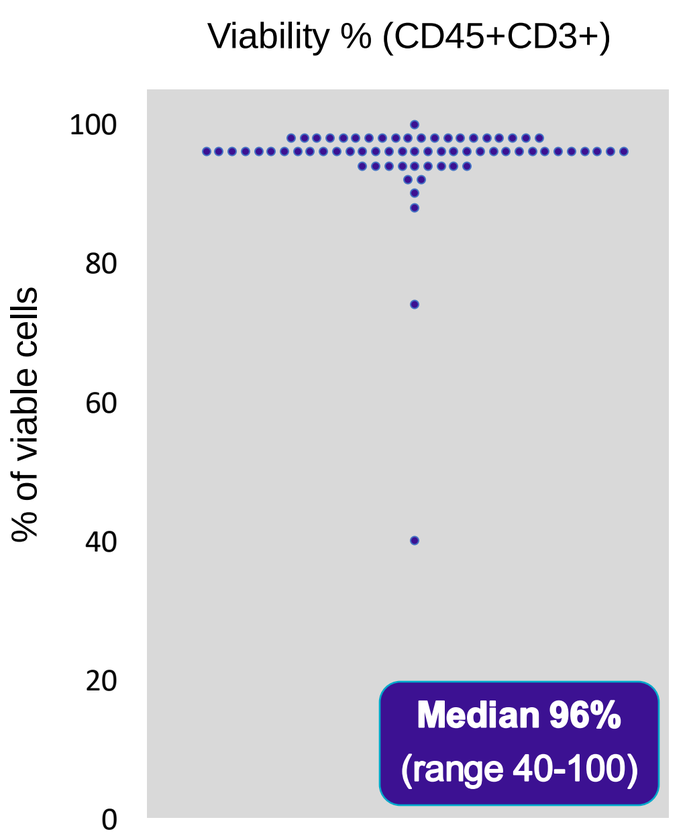
	FAS (N=69)
Median age, years (range)	65 (25–85)
Male sex, N (%)	47 (68.1)
Race, N (%)	
White	57 (82.6)
Asian	10 (14.5)
Black	1 (1.4)
Unknown	1 (1.4)
LDH elevated, N (%)	38 (55.1)
≥2 extranodal sites, N (%)	37 (53.6)*
Prior lines, N (%)	
2	52 (75.4)
3+	17 (24.6)
History of ASCT, N (%)	17 (24.6)
Bridging, N (%)	
Steroids	3 (4.3)
RT	1 (1.4)

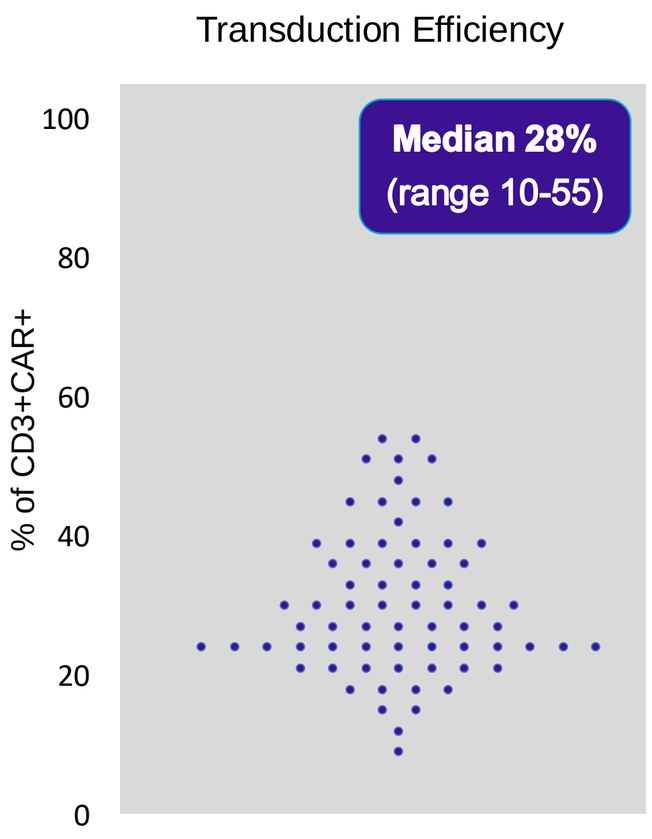


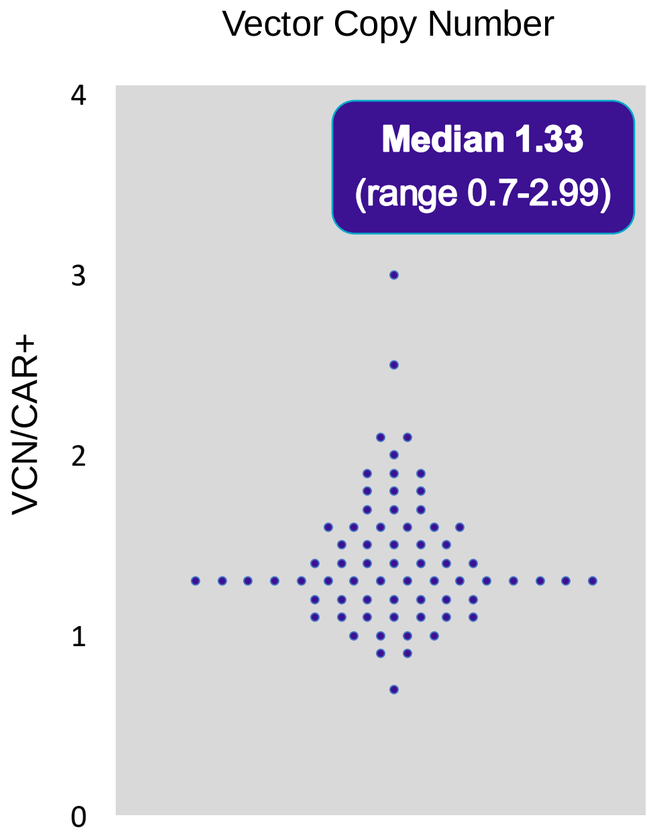
*As per IRC. ASCT, autologous stem cell transplant; BCL, B cell leukemia/lymphoma; Benda, Bendamustine; Cy/Flu, Cyclophosphamide/Fludarabine; DLBCL, diffuse large B cell lymphoma; FAS, full analysis set; IPI, International Prognostic Index; LD, lymphodepletion; LDH, lactate dehydrogenase; MYC, myelocytomatosis oncogene; NOS, not otherwise specified; PMLBCL, primary mediastinal (thymic) large B cell lymphoma; RT, radiotherapy.

Successful manufacturing of zamto-cel

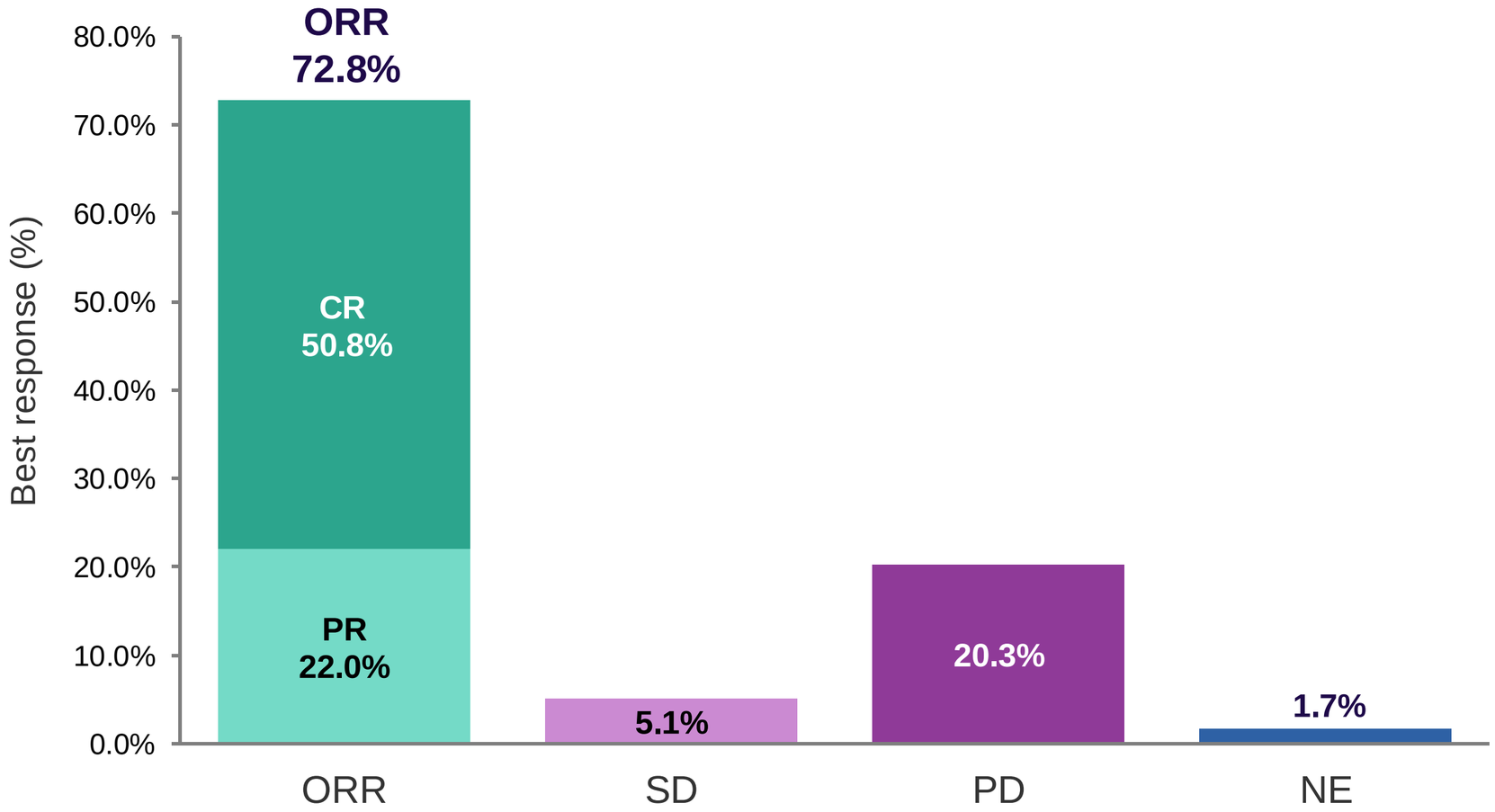
69 treated patients: 91.3% in-specification product manufacture







Response rates as Best Overall Response (BOR) showed high efficacy in the mITT (N=59) population



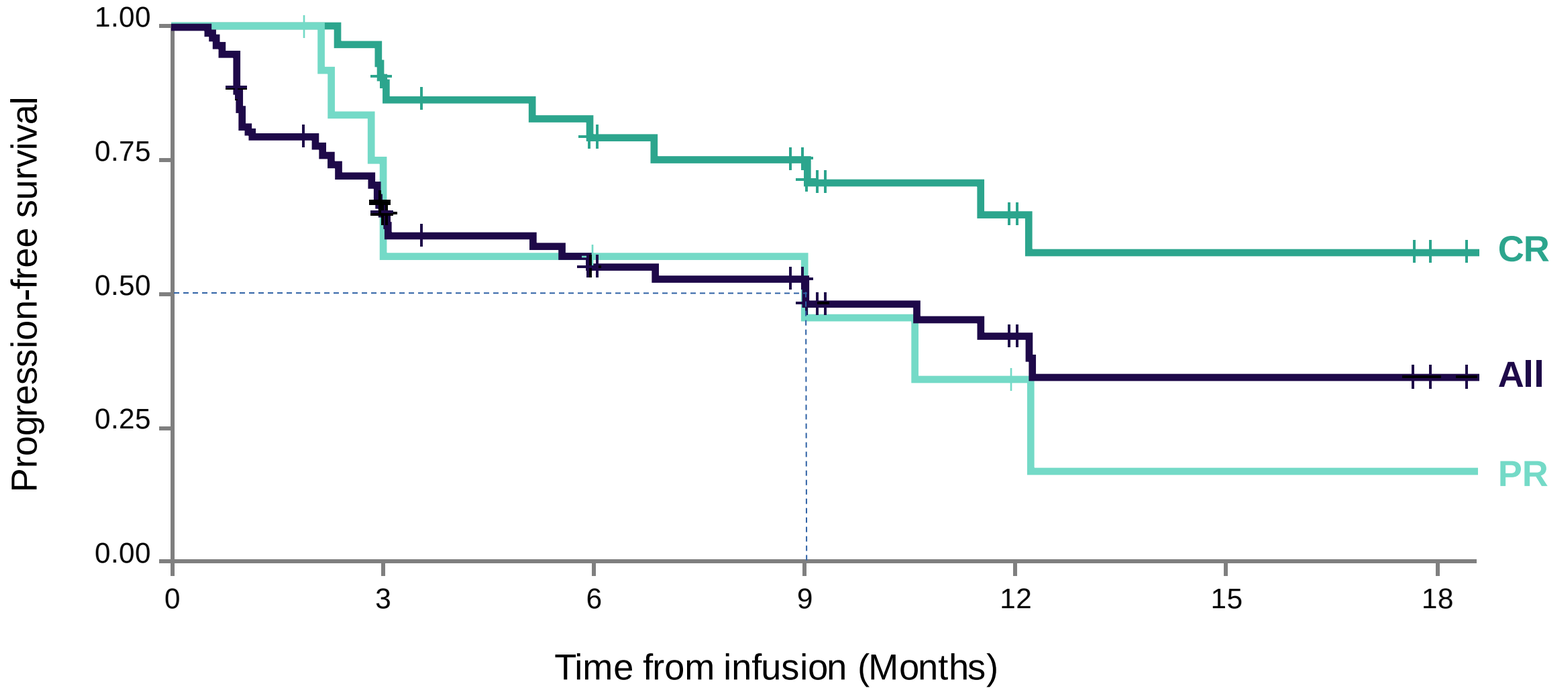
TANDEM MEETINGS

ASTCT

CIBMTR

CR, complete response; mITT, modified intention-to-treat; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Median Progression-free Survival (PFS) was 9 months



Number at risk

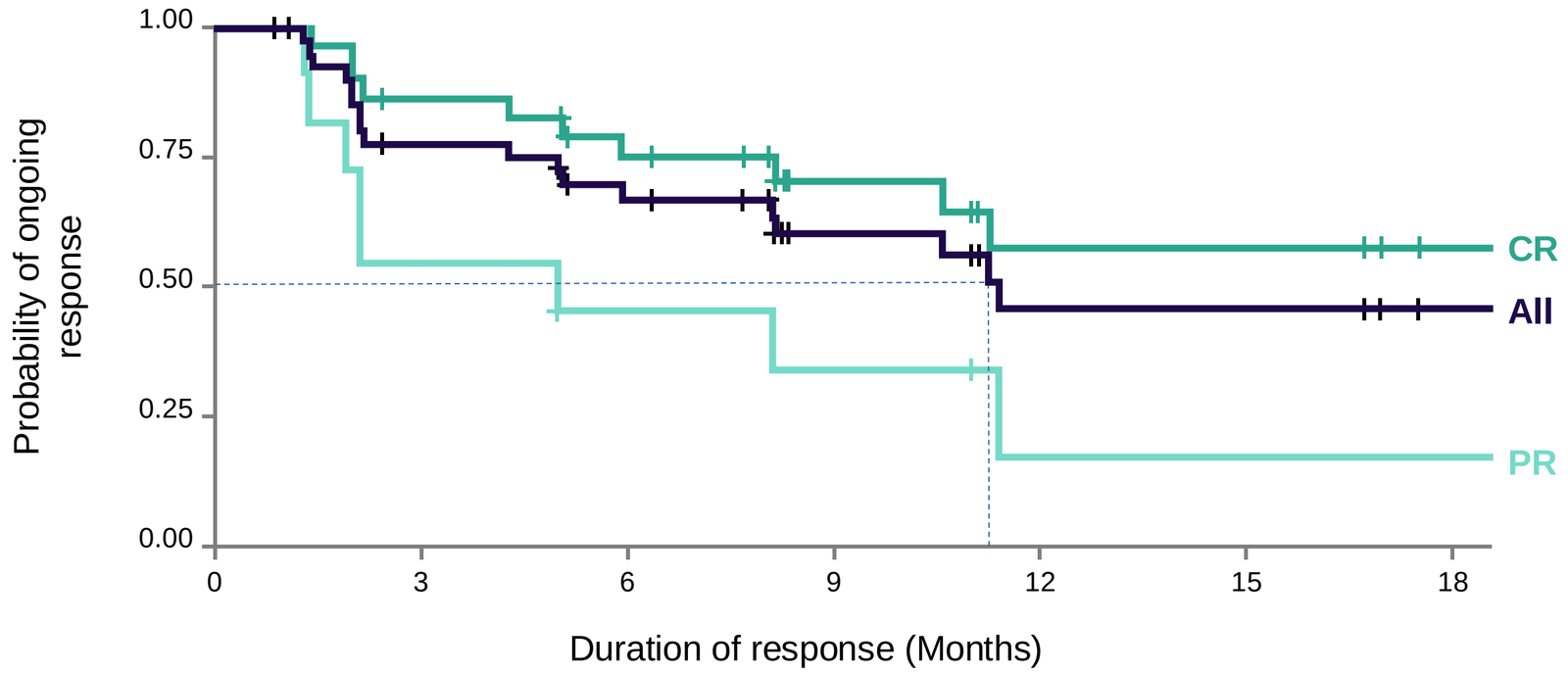
BOR							
CR	30	26	21	17	10	8	6
PR	13	7	5	5	2	1	1
All	59	34	26	22	12	9	7

Progression-free Survival

- 6-month PFS: 55%

BOR, best overall response; CR, complete response; mFU, median follow-up; PFS, progression-free survival; PR, partial response.

Median Duration of Response (DOR) was 11.4 months



Number at risk

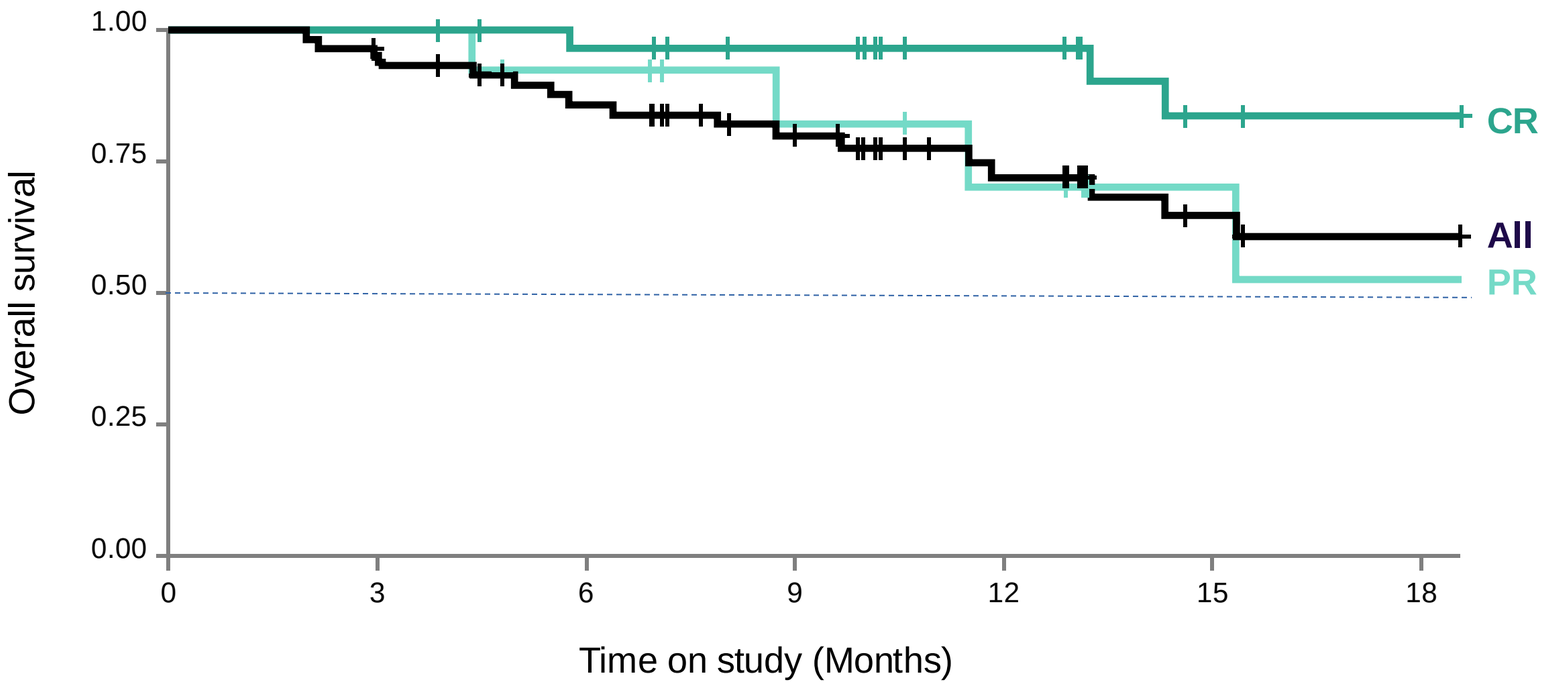
BOR								
	CR	30	24	19	12	8	8	5
	PR	13	6	4	3	1	1	1
	All	43	30	23	15	9	9	6

Duration of Response

- All mDOR: 11.4 months
- CR mDOR: not reached

BOR, best overall response; CR, complete response; mDOR, median duration of response; PR, partial response.

Median Overall Survival (OS) was not reached at the time of interim analysis

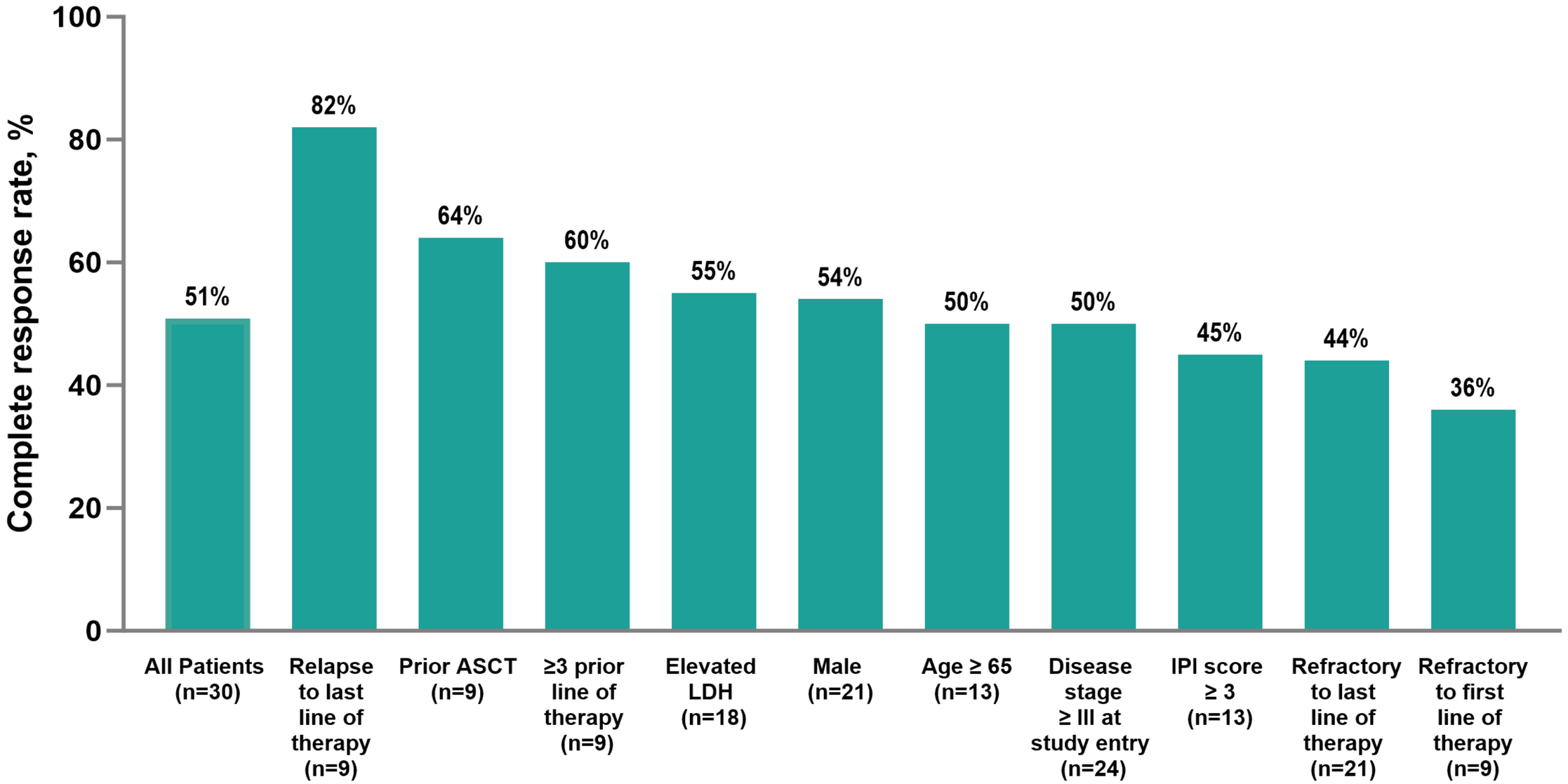


Number at risk

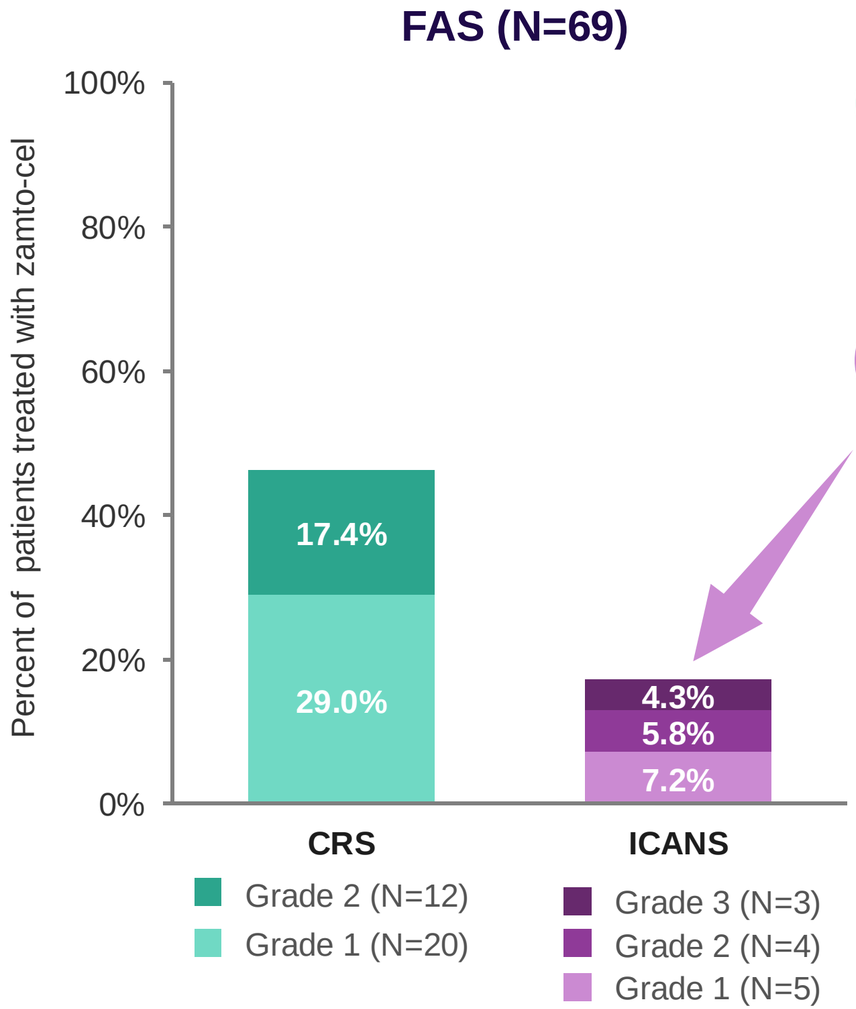
BOR							
CR	30	30	27	24	18	12	11
PR	13	13	11	8	6	4	3
All	59	55	47	38	25	17	15

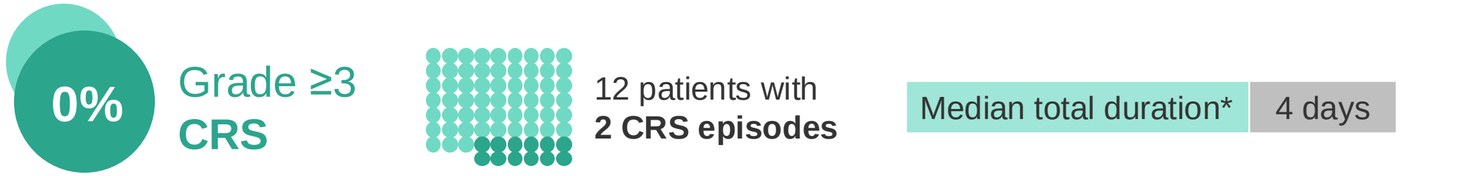
BOR, best overall response; CR, complete response; PR, partial response.

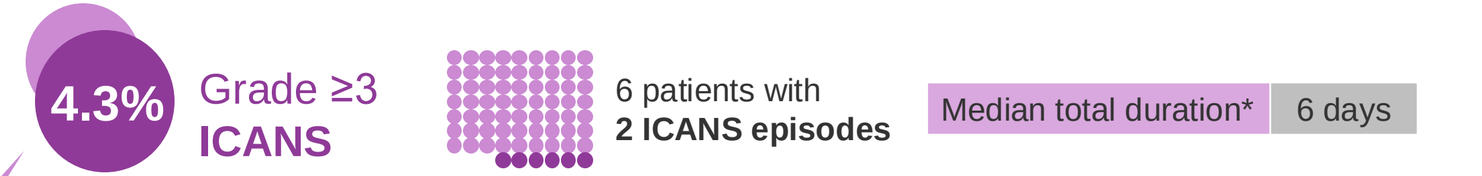
Zamto-cel: CRR as BOR by subgroups in mITT (N=59)

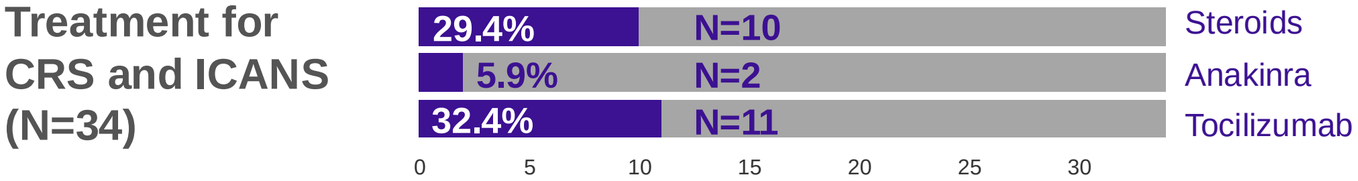


Low incidence of CRS and ICANS – mostly low grade









*Total duration includes gaps between episodes.
CRS, cytokine release syndrome; FAS, full analysis set; ICANS, immune effector cell-associated neurotoxicity syndrome.

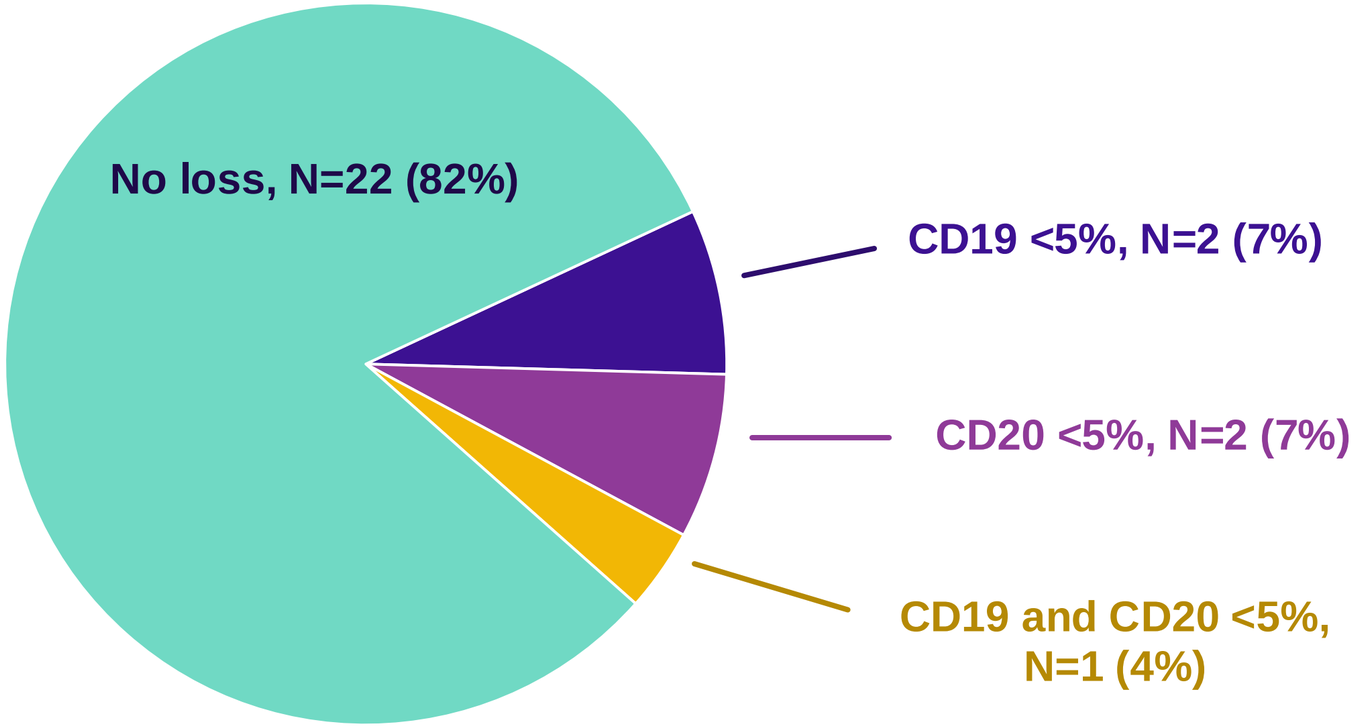
Adverse Events of Special Interest within 90 days

Toxicity*	Grade ≥3, N (%)**
Hematologic toxicities	43 (62.3)
Neutropenia/Neutrophil count decreased	33 (47.8)
Anemia/Hemoglobin decreased	14 (20.3)
Thrombocytopenia/Platelet count decreased	8 (11.6)
Infections	3 (4.3)
Deaths (due to any cause) * **	5 (7.2)
IEC-HS	1 (1.4)
Secondary malignancies	0

*Up to 90 days post-CAR T cell infusion. **FAS, N=69. ***Causes: 3 due to disease progression 1 bacterial sepsis/intestinal perforation. 1 COVID-19 pneumonia;
CAR-T cell, chimeric antigen receptor T cell; FAS, full analysis set; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome.

Antigen loss does not appear as a driver of progression

Number of tumors with CD19 and/or CD20 evaluation* at progression (N=27)

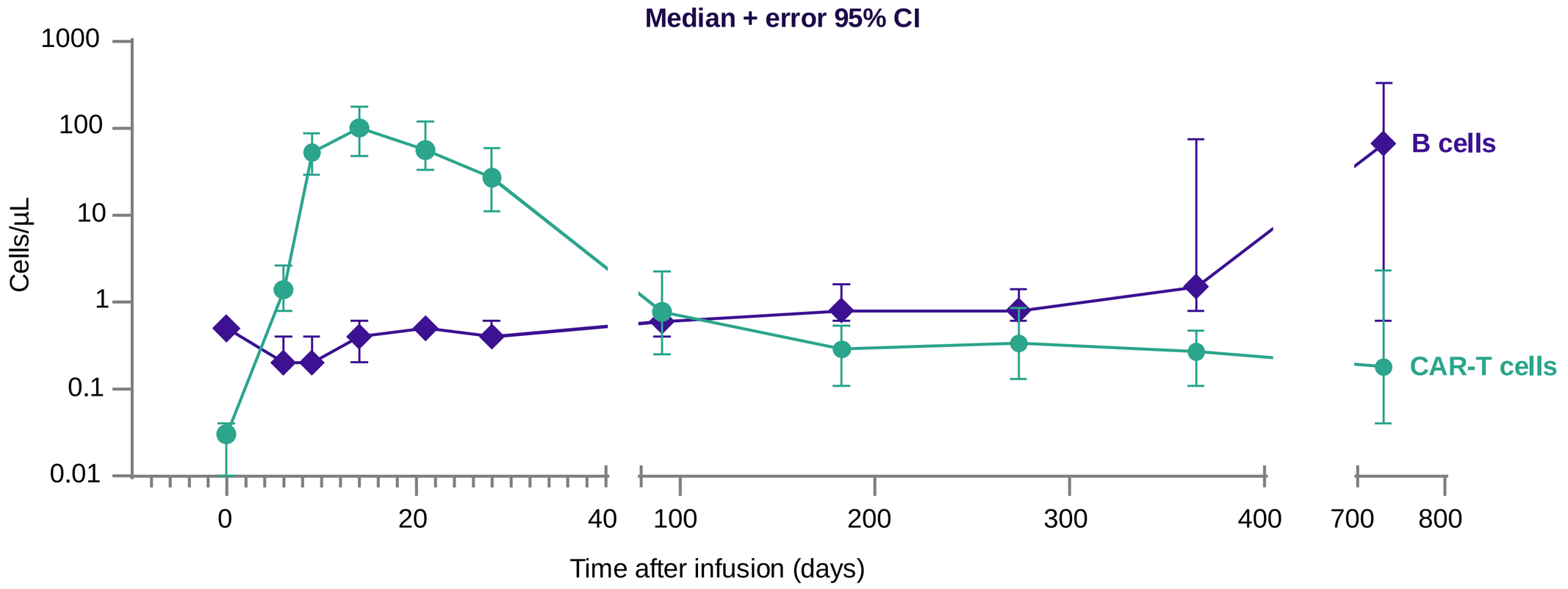


CD19/CD20

Only 1 patient experienced dual antigen loss

*Loss defined as <5% of positive cells.

CAR-T-positive cells persist and B cells recover over the time-period evaluated



CAR-T cell, chimeric antigen receptor T cell; CI, confidence interval.

Conclusions

Zamto-cel

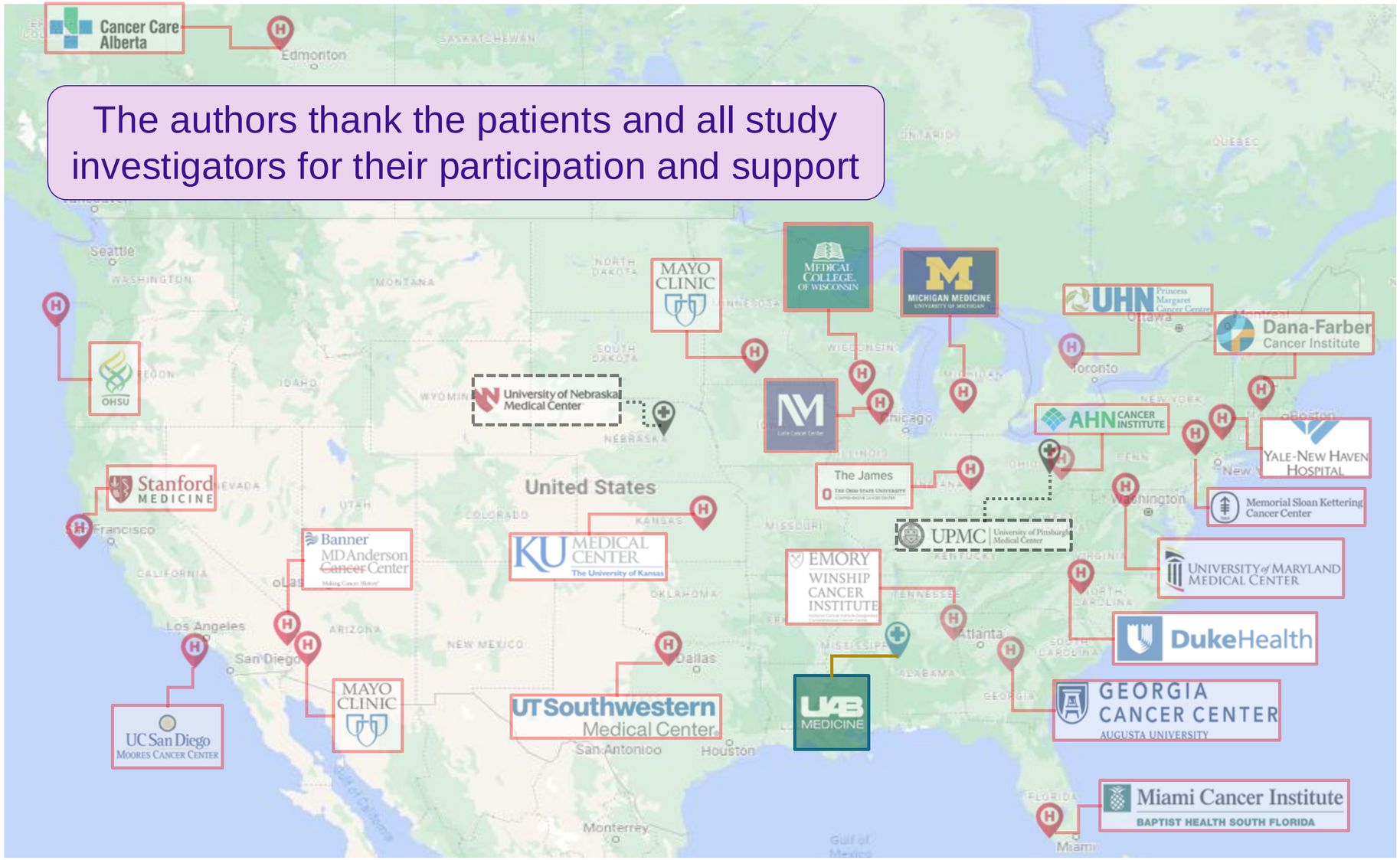
- The first tandem CD20-CD19-directed non-cryopreserved CAR-T cell product
- Administered as a fresh product with a short vein-to-vein time of 14 days
- Lymphodepletion is initiated during the manufacturing process

DALY II US

- Pre-planned interim analysis of 59 evaluable patients
- ORR 72.8%; CRR 50.8%
- 6-month PFS: 55% (95% CI: 41-67); median PFS: 9.0 months
- Well tolerated therapy:
  - No grade ≥3 CRS
  - Grade ≥3 ICANS in only 4.3% of patients
- Dual CD20-CD19 targeting appears to mitigate antigen loss as a mechanism of resistance
- No patient died while awaiting treatment with CAR-T

CAR-T cell, chimeric antigen receptor T cell; CRR, complete response rate; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; PFS, progression-free survival; r/r DLBCL, relapsed/refractory diffuse large B-cell lymphoma.

Thank you for your attention!



This study is sponsored by Miltenyi Biomedicine GmbH (Germany)