Interim analysis of a Phase II study of administered fresh bispecific anti-CD20/anti-CD19 CAR T cell therapy - zamtocabtagene autoleucel (zamto-cel) for relapsed/refractory (R/R) DLBCL

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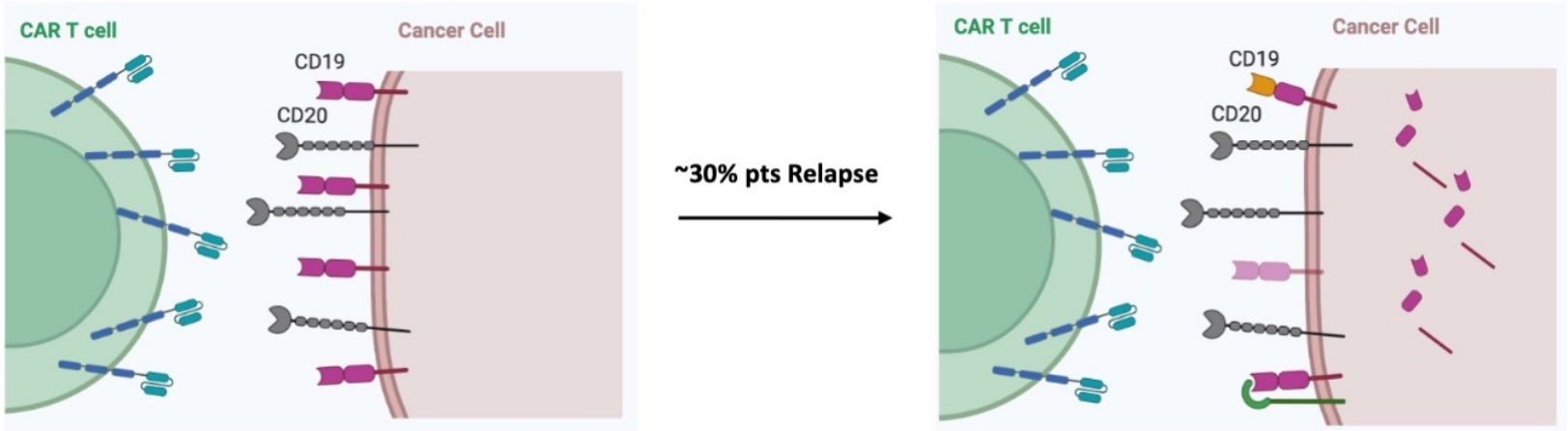
Disclosures

Roles	Relationship	Company/ies
Advisory Board	Advisor	Legend, Epizyme, TG therapeutics, Kite Pharma, Novartis, LOXO-Lilly, Janssen, BMS-Juno, Seattle Genetics
Research Funding	Researcher	Miltenyi Biotec, LOXO-Lilly Oncology
Consulting	Consultant	Miltenyi Biotec, Lilly Oncology, Incyte
Scientific Advisor Board	Member/Founder	Tundra Therapeutics

Limitations of mono CD19 CAR T cell therapy



- **CD19 CAR T cell therapy is an established treatment for pts with R/R DLBCL**
  - Relapse remains a clinical challenge
- **One proposed mechanism of resistance**
  - Loss of epitope recognition or downregulation of the CD19 receptor
- **Dual targeting may be effective in overcoming resistance and improving outcomes**

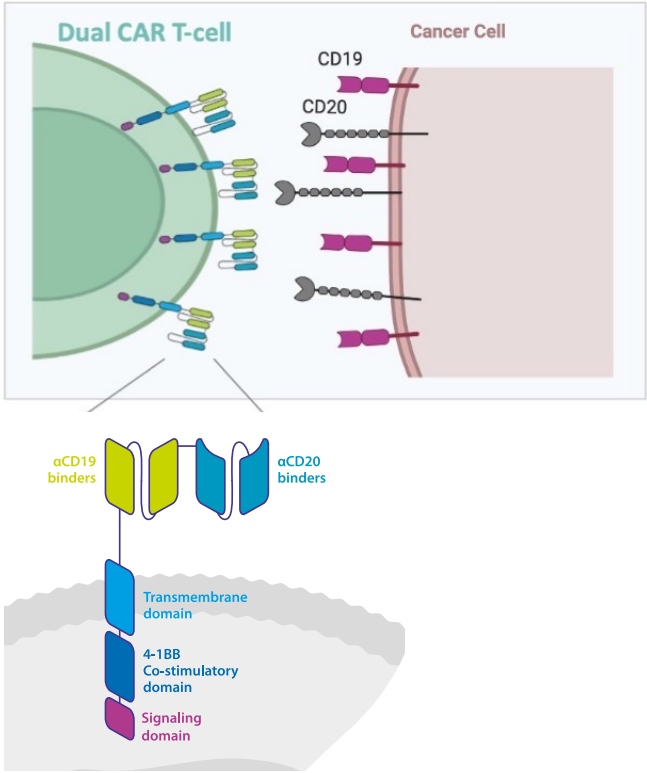
1. Plaks, V. *et al.* CD19 target evasion as a mechanism of relapse in large B-cell lymphoma treated with axicabtagene ciloleucel. *Blood* **138**, 1081-1085, doi:10.1182/blood.2021010930 (2021).
2. Locke, F. L. *et al.* Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol* **20**, 31-42, doi:10.1016/S1470-2045(18)30864-7 (2019).

Background

- **First-in-human trial** of bispecific **anti-CD20, anti-CD19** (LV20.19) Phase I dose escalation and expansion trial (NCT03019055)[1]
  - Fresh cells administered – Identified does 2.5x10e6 cells/kg
  - High Response Rate reported with durable remissions over >4 years post-treatment
  - LTG 1497 CAR construct identical to MB2019.1 CAR construct

- Prospective first-in-human, **multicenter**, open-label, Phase I/II trial assessing feasibility, dosage, safety and toxicity of anti-CD20/19 (MB CART2019.1 Lymphoma / DALY I, NCT03870495)[2]
  - Confirmed recommended dose of 2.5x10e6 cells/kg for future investigations
  - Infused in 100% enrolled
  - Well tolerated, no CRS or neurotoxicity
  - ORR at 75% with 5/12 achieving CR durable response

- **DALY II USA trial**: First multicenter, prospective, single-arm Phase II trial of **dual target** CD19/CD20 CAR T (zamtocabtagene autoleucel) **administered fresh** for patients (pts) with R/R diffuse large B-cell lymphoma (DLBCL). (**DALY II USA, NCT04792489**)

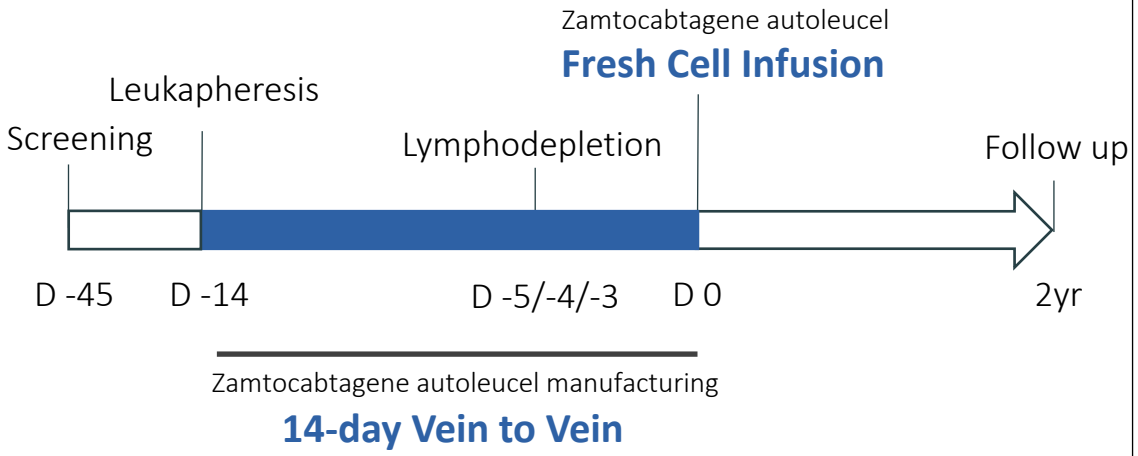


IL7/15 expansion

1. 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)
2. 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).

DALY II USA Study Design

Open label, single arm, Phase II study to determine the efficacy, safety, and PK (persistence) of zamtocabtagene autoleucel in adults with R/R DLBCL after receiving at least two lines of therapy



Key Eligibility Criteria

- Age ≥18 years
- ECOG 0 or 1
- LBCL confirmed by histology
- Measurable disease confirmed by PET/CT
  - per Lugano 2014 Criteria
- Relapsed/Refractory to at least 2 prior lines of treatment including rituximab + anthracycline-based chemotherapy

Study Treatment

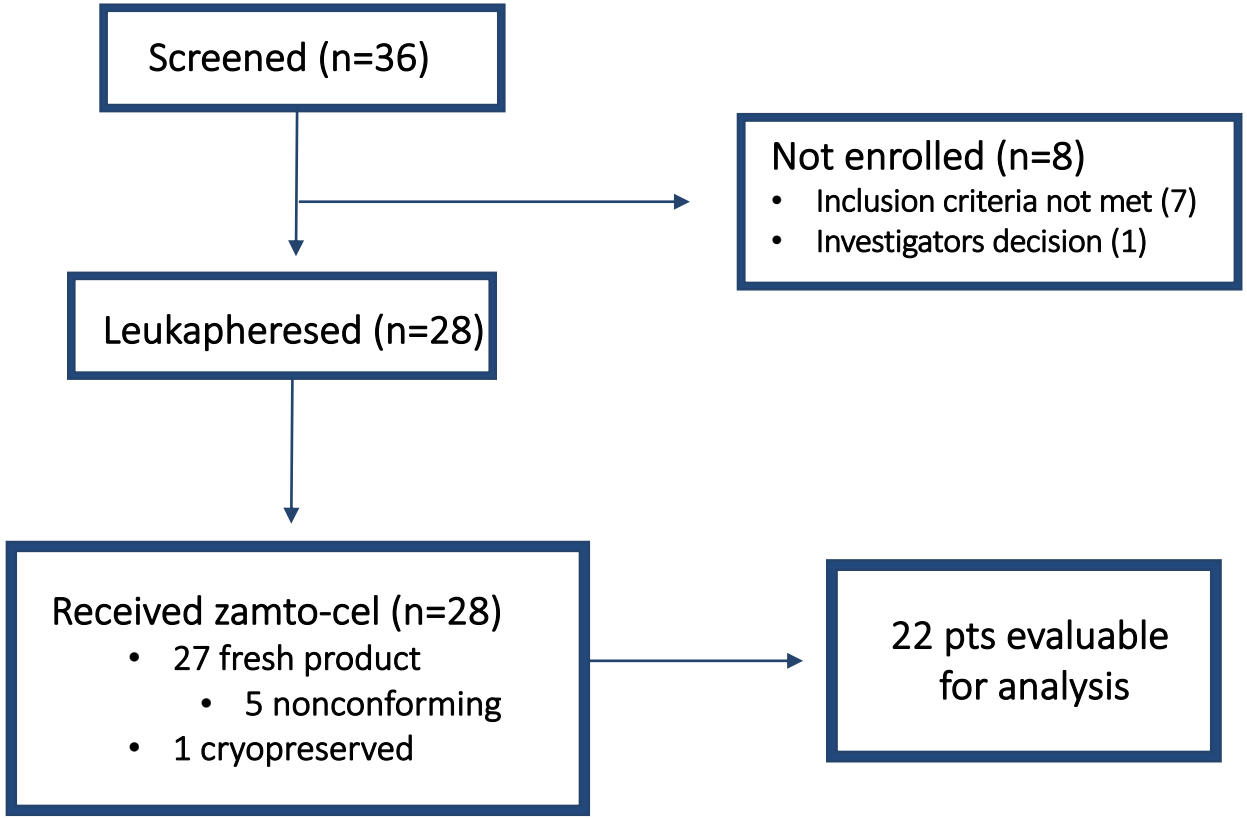
- Lymphodepleting chemotherapy
  - Flu 30mg/m^2 +Cy 300mg/m^2, d(-5) to (-3)
    OR
  - Bendamustine 90mg/m^2, d(-4) to (-3)
- Zamtocabtagene autoleucel 2.5x10^6 CAR T cells/kg

Key Endpoints

- Primary: D28 ORR (Independent Radiology Review)
- Secondary: CRR, DOR, BOR, PFS, OS, Safety, Cellular kinetics, Cytokine levels

ORR – Overall Response Rate; CRR – Complete Response Rate; DOR – Duration of Response; BOR – Best Overall Response; PFS – Progression Free Survival; OS – Overall Response

Patient disposition



Patient and disease baseline characteristics

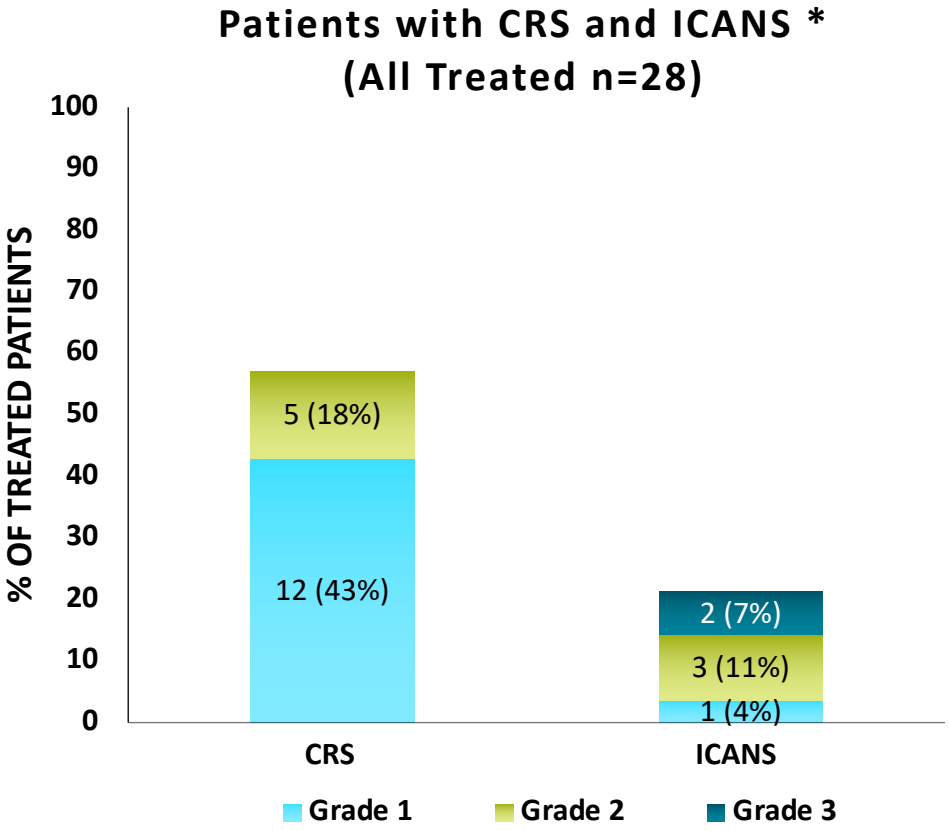
	Evaluable Set (N=22)	All Treated (N=28)
Median Age, years (range)	59 (37-75)	60 (38-77)
Male, n (%)	13 (60%)	17 (61%)
ECOG PS at baseline, n (%)		
0	5 (23%)	6 (21%)
1	17 (77%)	22 (79%)
2 - 5	0	0
IPI score, n (%)		
0-1	2 (9%)	2 (7%)
2	5 (23%)	5 (19%)
3-5	15 (68%)	21 (75%)
LDH elevated*, n (%)	15 (68%)	22 (79%)
≥2 extranodal sites, n (%)	12 (55%)	14 (50%)
Prior Lines, n (%)		
2	16 (72%)	22 (79%)
3+	6 (23%)	6 (21%)
Prior anti-CD-19 antibody, n (%)	3 (13%)	4 (14%)
Prior polatuzuamb, n (%)	2 (9%)	4 (14%)

Histology, n (%)	All Treated (N=28)
DLBCL	13 (46%)
GCB	10 (35%)
HGBL	3 (11%)
PMBCL	1 (4%)
Transformed Lymphoma	1 (4%)

- **Advanced Disease Population (Advanced disease population with high proportion of IPI score 3-5 and elevated LDH)**
- **Prior treatment included contemporary treatment algorithms (CD19 and CD79 targeting agents)**
- **Patient characteristics consistent between population sets**

*above the institutional normal

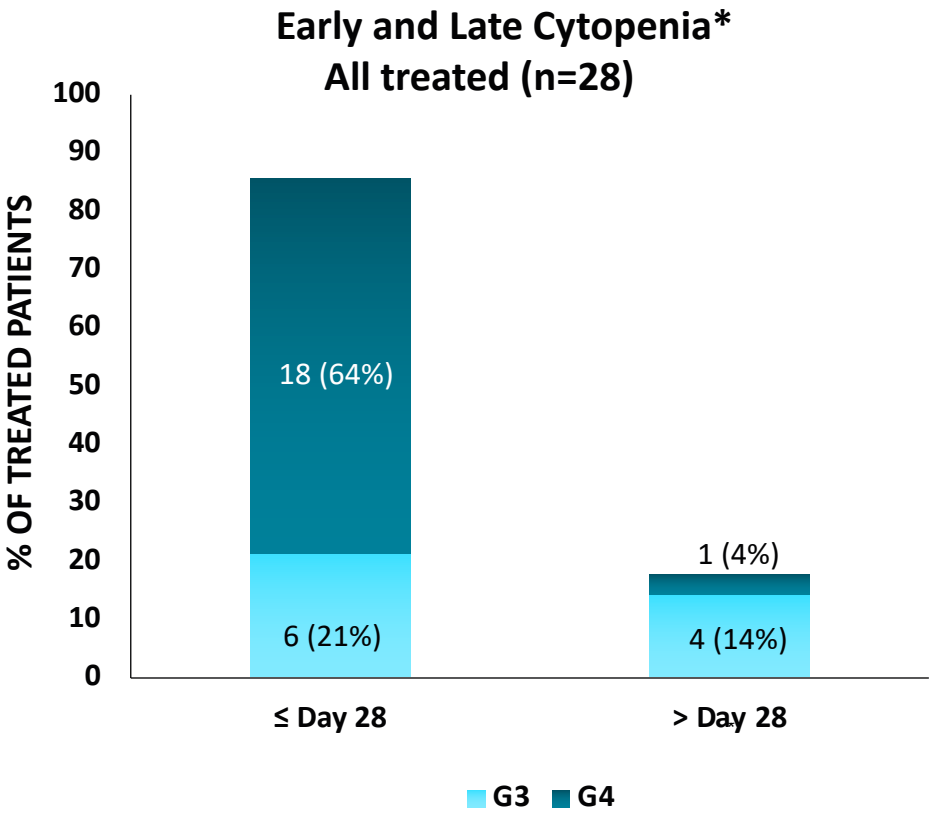
Safety: CRS and ICANS



All Treated Patients (n=28)	
Management	
Steroids**	6 (21%)
Tocilizumab	5 (18%)
Anakinra	2 (7%)

*AE of highest grade per patient
** 1 pts for CRS,3 pts ICANS and 2 pts for CRS and ICANS

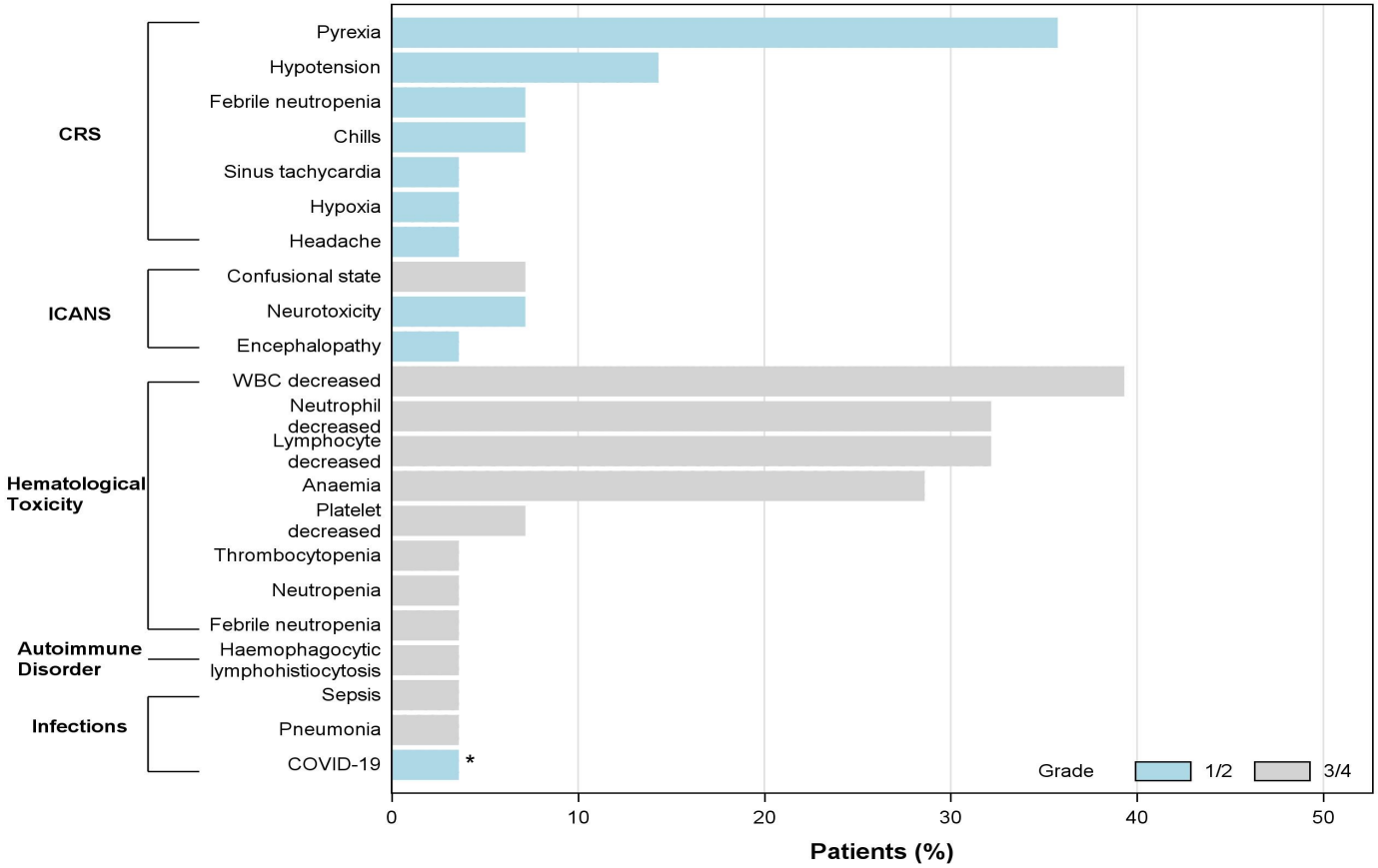
Safety: hematological events



All Treated Patients (n=28)		
Grade ≥ 3,	**≤ Day 28**	**> Day 28**
Neutropenia	23 (82%)	4(14%)
Thrombocytopenia	7(25%)	2(7%)

*AE of highest grade per patient

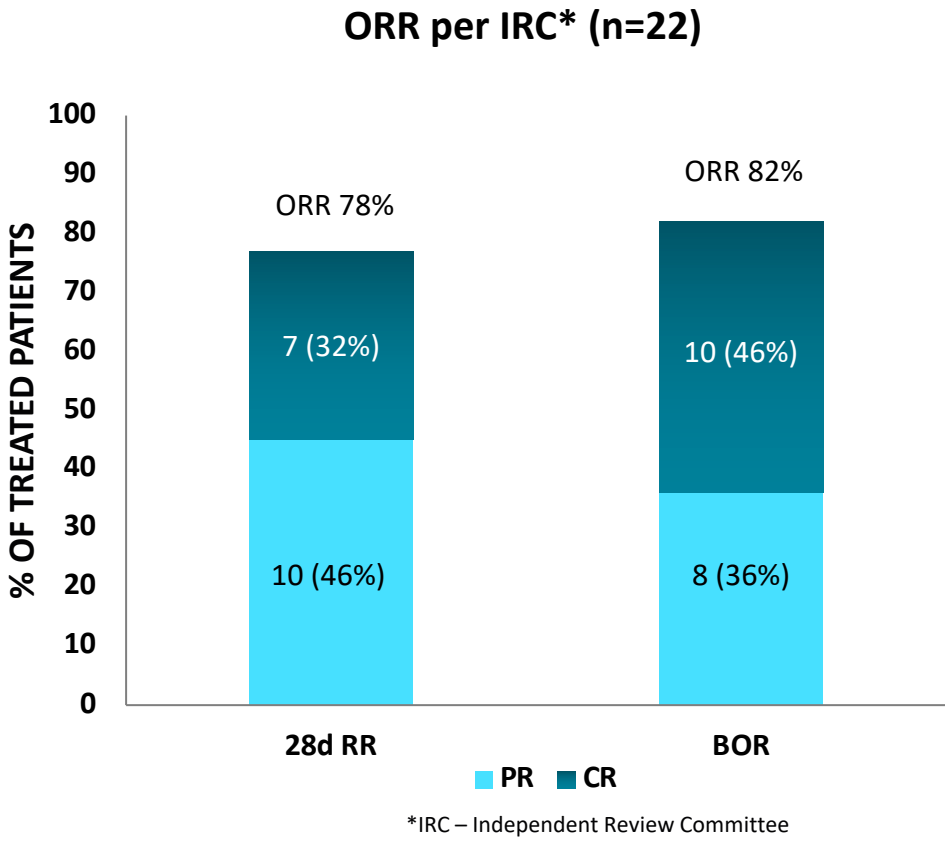
Safety: related adverse events (n=28)



*Per investigator relatedness incorrectly recorded

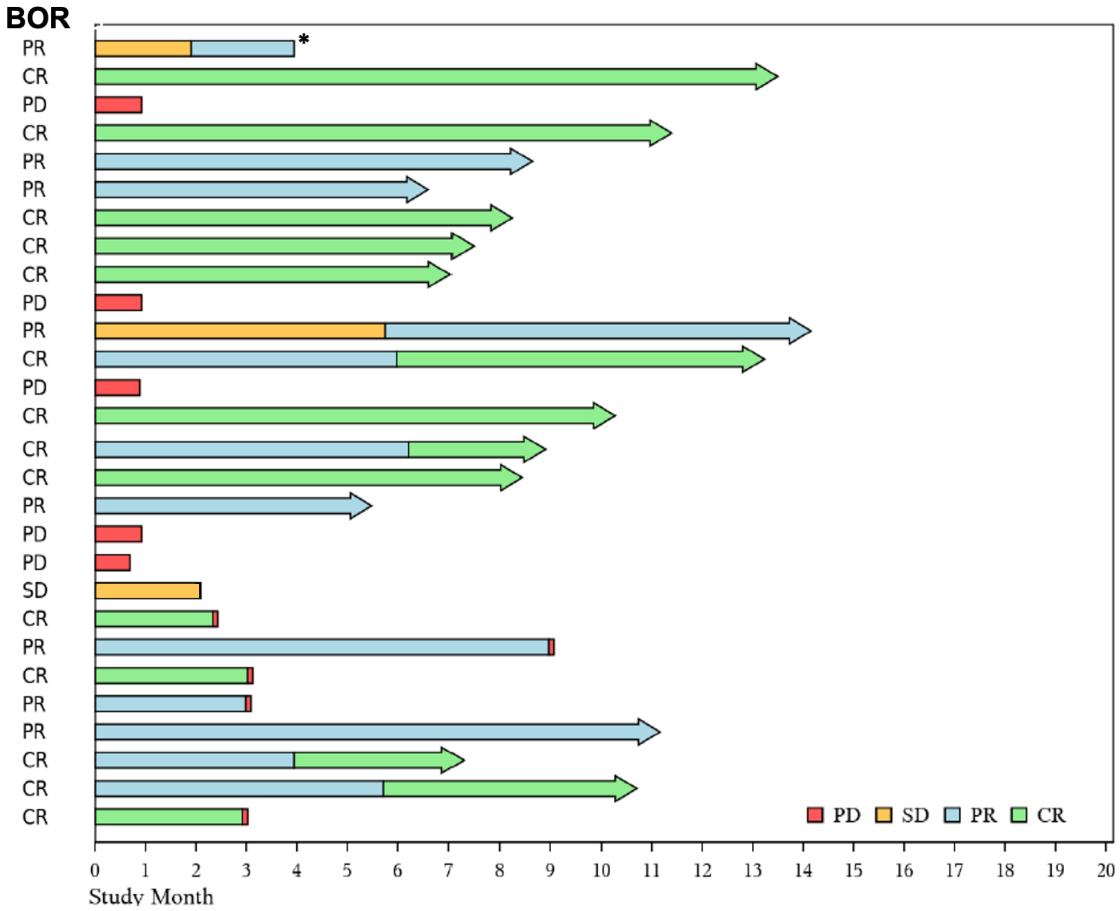
Efficacy: response evaluation*

	Evaluable Set		All Treated	
	IRC	Per Site	IRC	Per Site
BOR, n(%)	18 (82%)	17 (77%)	22 (79%)	20 (71%)
CR	10 (46%)	11 (50%)	14 (50%)	13 (46%)
PR	8 (36%)	6 (27%)	8 (29%)	7 (25%)
SD	1 (4%)	2 (9%)	1 (4%)	2 (7%)
PD	3 (14%)	3 (14%)	5 (17%)	5 (18%)



*IRC – Independent Review Committee

Efficacy: duration of response** (all treated, n=28)



Durable responses observed in the majority of treated patients

Per IRC:

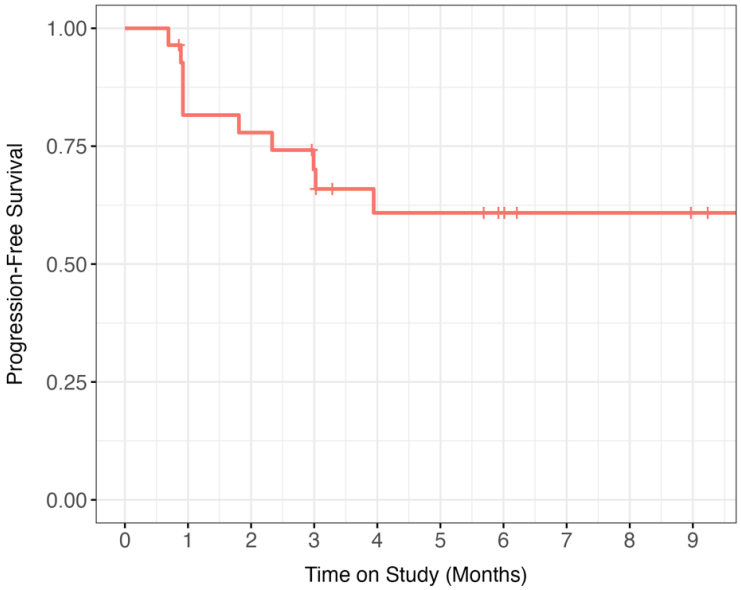
- PR converted to CR (3 pts)
- SD converted to PR (2 pts)

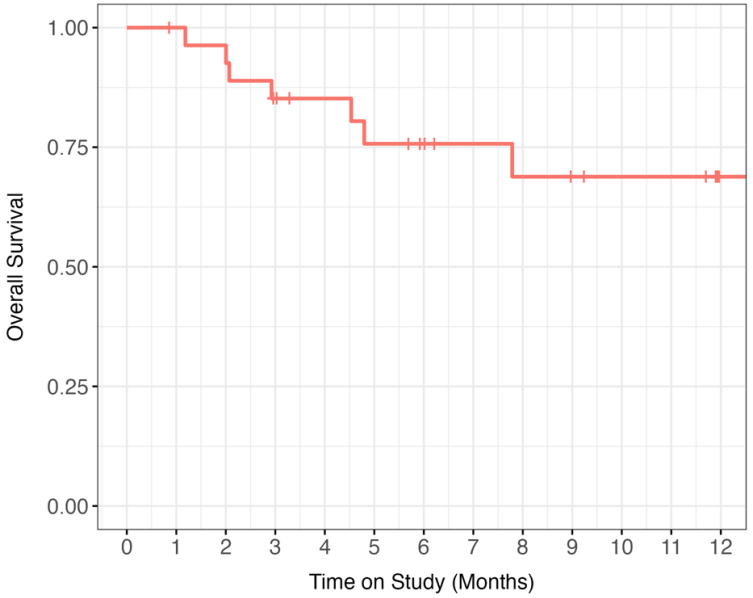
At the time of PD

- CD20 loss (2 pts)
- Both CD19 and CD20 loss (1 pt)

**IRC – Independent Review Committee
* Treatment stopped due to PD per investigator. PR per IRC

Efficacy: progression-free and overall survival* (n=28)



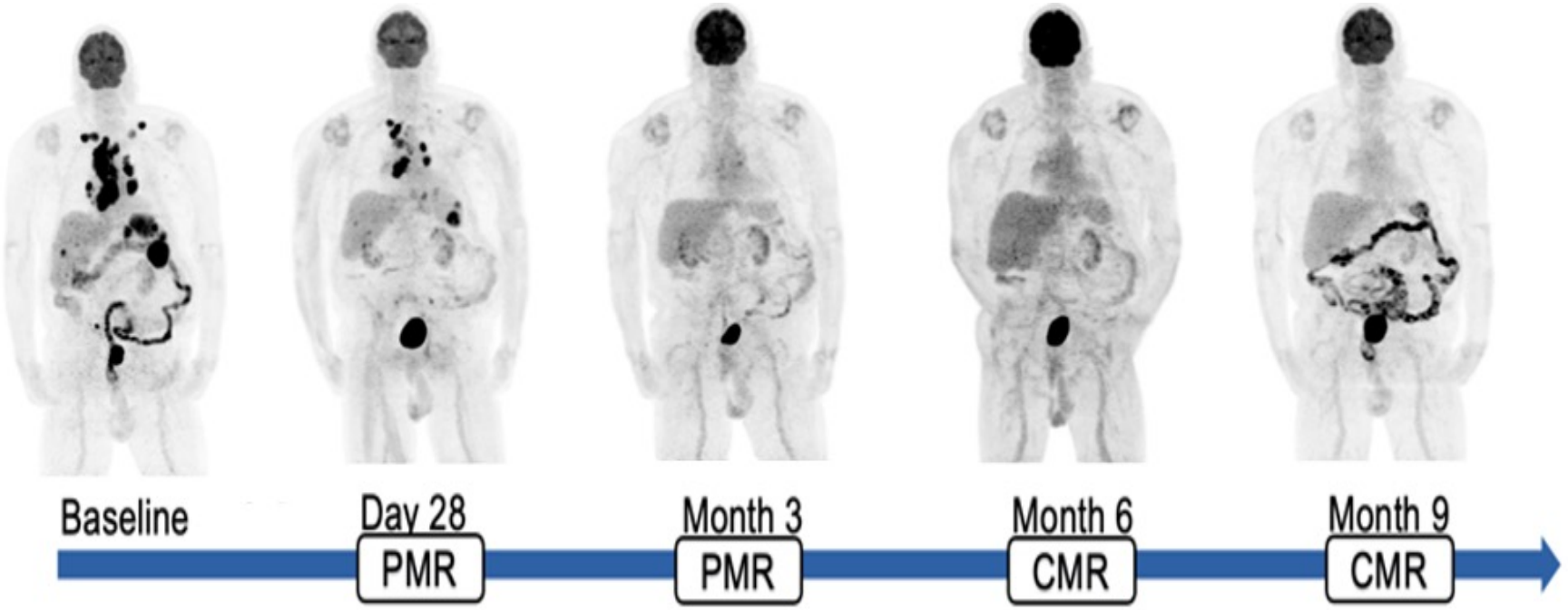


- **Median FU 10.3 months**
- **Total deaths 8: 6 DLBCL** and 2 COVID-19**
- **PFS rate at 6-months was similar between All treated (n=28) and Evaluable set (n=22) at 61% and 64%, respectively**

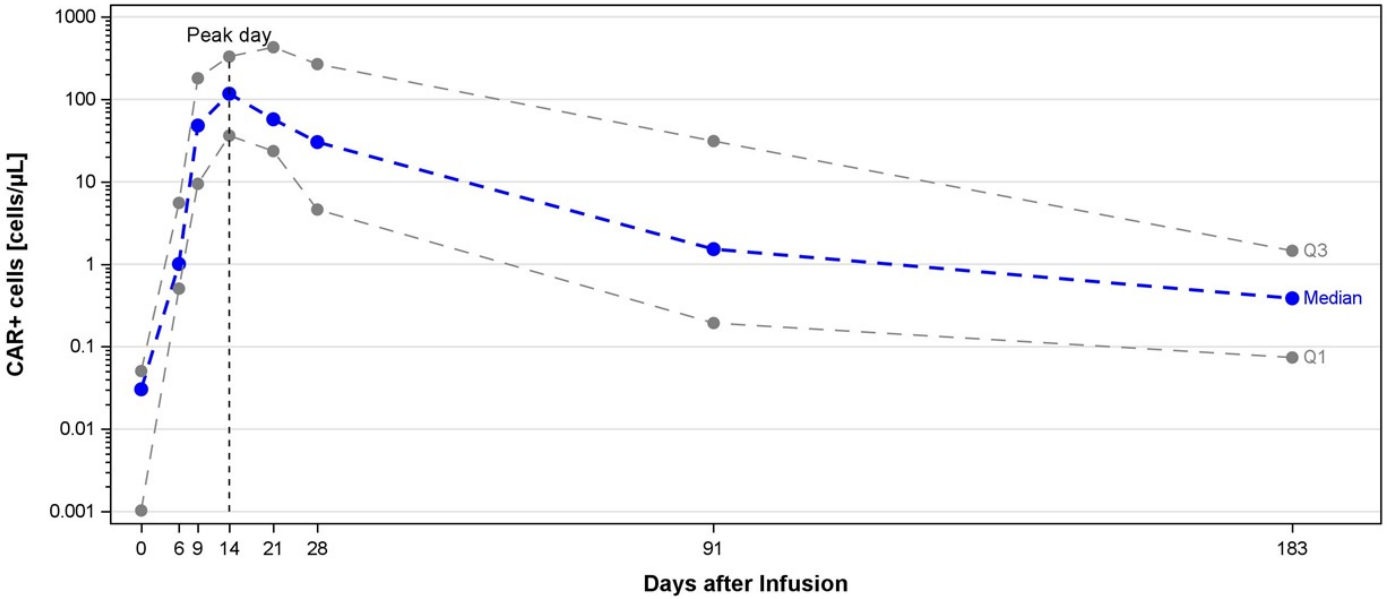
*IRC- Independent Review Committee
** Following PD and a subsequent treatment line/s in 3 to 12 mo after zamto-cel

Case evaluation- 71y white male

Baseline Characteristics and Prior treatment	
ECOG-1, GCB DLBCL, Stage IV, IPI 4 H&N conglomerates, mediastinal LNs, liver, splenic mass, Deauville 5	R-CHOP x 6 - CR R-GDP x 2 - SD



CAR T cell expansion and persistence



Zamto-cel expansion and persistence with median values and interquartile ranges Q1 and Q3.

Durable persistence of CD19/20 CAR T cells

Conclusions

- DALY II USA is the first bispecific anti-CD20/anti-CD19 CAR T trial utilizing fresh infusion with a CAR T-cell product for patients with R/R LBCL who received at least 2L of treatment
- Rapid centralized manufacturing process allowed for 14 days “vein to vein” fresh CAR T cell infusions throughout the United States with LD initiated during this process
- Zamto-cel was well tolerated with only 2 reversible grade 3 ICANS, no grade 3-4 CRS
- Promising responses seen regardless of study population- all treated set is BORR 79%; CRR 46%; 6mo PFS rate 61% and evaluable set is BORR 82%; CRR 50%; 6mo PFS rate 64%
- Patient population reflects advanced disease and contemporary prior treatment algorithms including agents not available in earlier pivotal trials (e.g., CD19 and CD79 targeting agents)

Acknowledgments

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