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TANDEM MEETINGS

Transplantation & Cellular Therapy Meetings *of* ASTCT® and CIBMTR®

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Disclosures

Sairah Ahmed

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NKTR-255 vs Placebo to Enhance Complete Responses and Durability Following CD19-directed CAR-T Therapy in Patients with Relapsed/Refractory (R/R) Large B-cell Lymphoma (LBCL)

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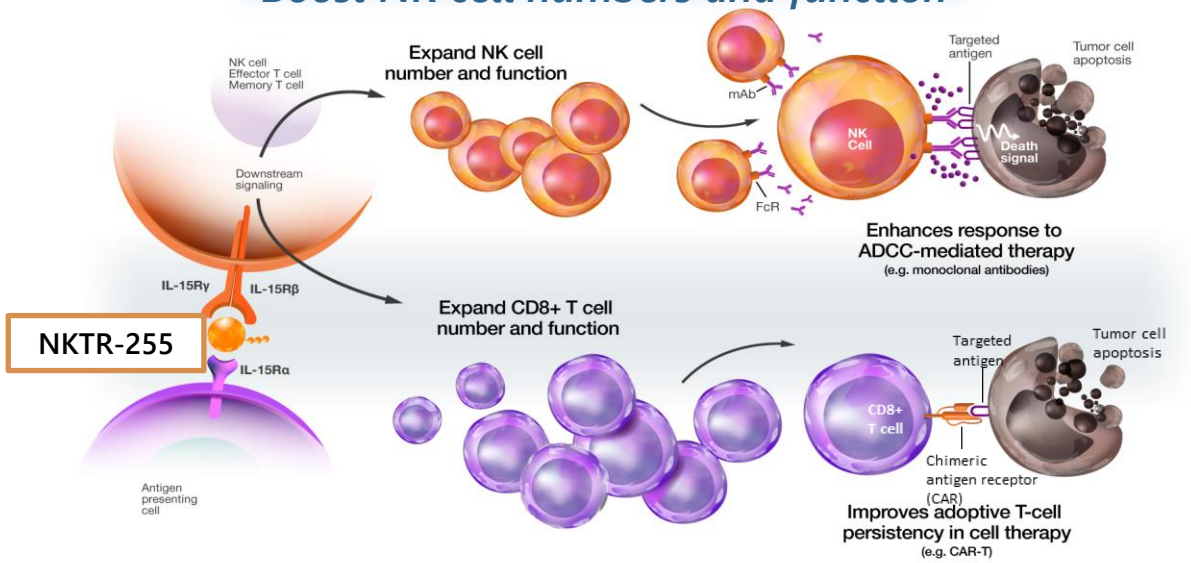
Background

- CAR T-cell therapy has been transformative for treatment of relapsed or refractory (R/R) large B-cell lymphoma (LBCL), however durable responses remain a challenge with more than half of patients with eventual disease relapse or progression
- Relapse after CAR-T cell therapy portends a poor prognosis with a median overall survival (OS) of 8 months; *strategies to improve long-term efficacy are needed*
- In pivotal clinical trials[1], complete response (CR) at 6 months is prognostic of remaining in CR beyond 2 years, therefore therapeutic interventions to improve CR rates at 6 months may improve event-free survival (EFS)
- NKTR-255 is an investigational polymer-conjugated IL-15 agonist, that activates, proliferates and expands natural killer (NK) and CD8+ T-cells in vivo, as well as promotes the survival and expansion of memory CD8+ T cells
- Clinical studies demonstrate NKTR-255 expands CAR-T and CD8+ T cells in patients with R/R NHL who previously received CAR-T therapy (NCT04136756), as well as enhances CAR-T cell trafficking into the tumor microenvironment (Shringesh et al., Blood 2024)

[1]ZUMA-1 (axi-cel) (Locke 2022), JULIET (tisa-cel) (Schuster 2019), and TRANSCEND NHL- 001 (liso-cel) (Abramson 2020)

NKTR-255 IS Designed to Boost NK Cells and Expand CD8+ Effector and Memory T-cells

Boost NK cell numbers and function



Enhancement of ADCC Antibodies

Daratumumab
Rituximab
Cetuximab

Potential to combine with any targeted antibody that utilizes an ADCC MOA

Enhancement of CAR-T Regimens

CD19 CAR-T
BCMA CAR-T
CD38 CAR-T

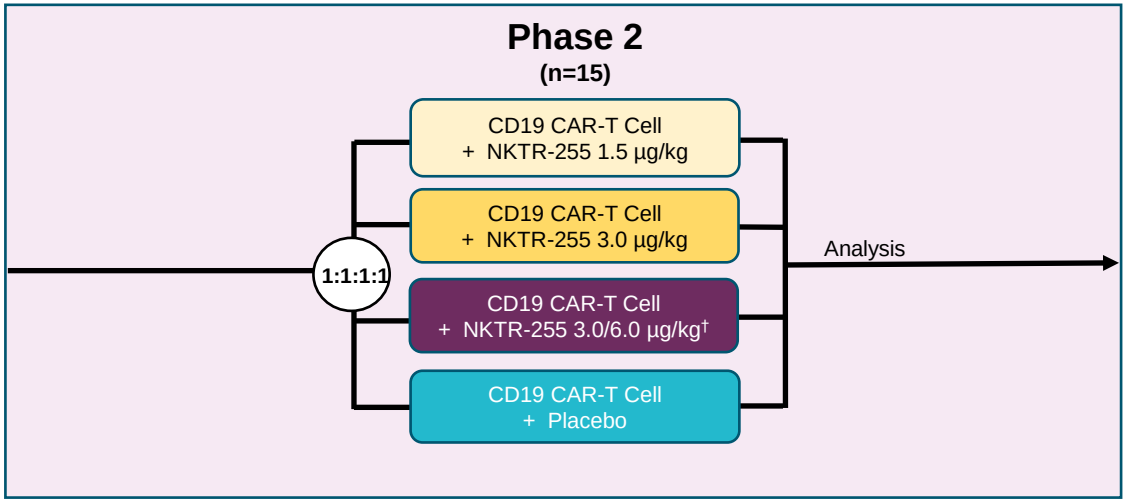
Potential to expand into other hematological and solid tumor CAR-T and cellular therapies

Increase duration of response for CAR-T and cellular therapies

STUDY DESIGN

Patients Eligible:

- Relapse and refractory LBCL
- Planning to receive CD19 CAR T-cell therapy*
- ECOG 0-1

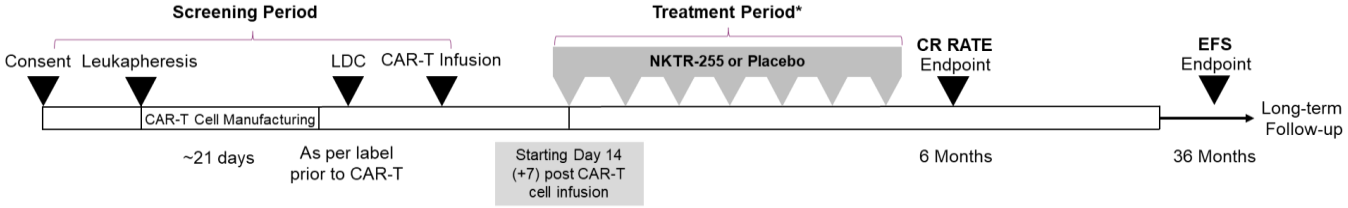


Primary Endpoint:

- CR rate at month 6 of treatment

Secondary Endpoint:

- Safety and tolerability
- PK and PD



Clinicaltrials.gov Identifier: NCT05664217

Study Criteria

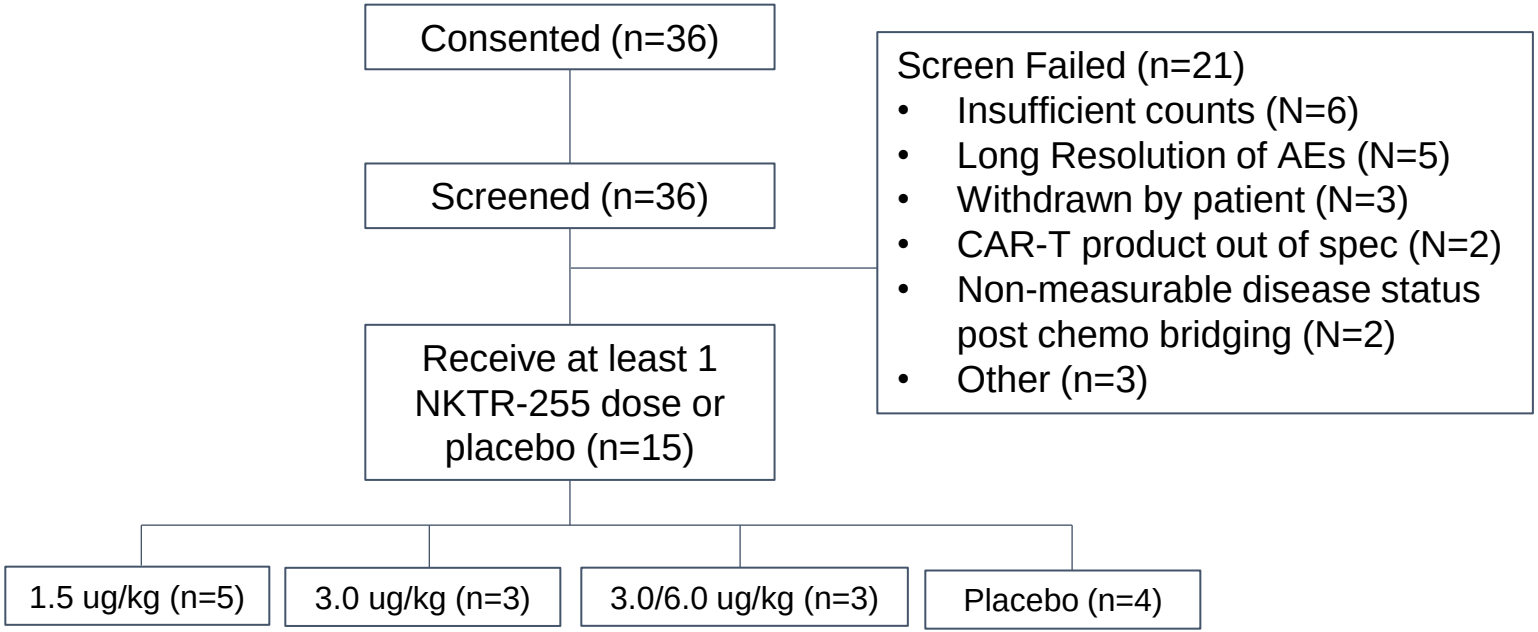
Key Inclusion	Key Exclusion
• Age ≥18 years • Evidence of CD19+ disease • FDG-Avid disease on PET/CT • ECOG Performance of 0 or 1	• Prior treatment with any CD19 CAR-T cell therapy other than planned treatment • Active CNS malignancy • Steroid use of > 5 mg Prednisone or equivalent • Presence of uncontrolled fungal, bacterial, viral, or other infection

Key Study Drug Dosing Criteria

Patients were assessed prior to each study drug infusion to determine if they fulfill the following dosing criteria:

- Appropriate laboratory test results as defined per protocol
- No fever ≥ 38.0°C/Grade ≥ 1 CRS (ASTCT criteria [Lee 2019]) within 24 hours of the planned study drug infusion
- No Grade ≥ 3 CRS (ASTCT criteria) within 72 hours preceding the study drug infusion
- No Grade ≥ 2 ICANS (ASTCT criteria) on the day of the study drug infusion
- No previous Grade 4 IRR to study drug infusion (Cycle 2 and beyond)
- No tocilizumab and/or dexamethasone within 48 hours preceding the study drug infusion

Study Deposition

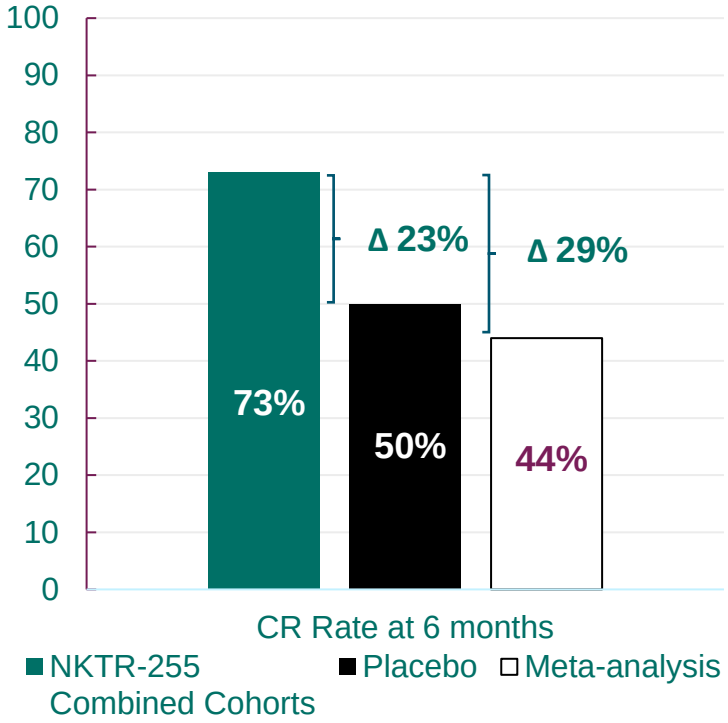


BASELINE CHARACTERISTICS	NKTR-255 1.5 µg/kg (N=5)	NKTR-255 3.0 µg/kg (N=3)	NKTR-255 3.0/6.0 µg/kg (N=3)	Combined NKTR-255 (N=11)	Placebo (N=4)
Age					
Median (range) – years	68 (40-72)	54 (53-72)	62 (61-63)	62 (40-72)	67.5 (44-76)
≥65, n (%)	3 (60)	1 (33)	0	4 (36)	2 (50)
Male, n (%)	4 (80)	2 (67)	2 (67)	8 (73)	0
ECOG Performance of 2, n (%)	3 (60)	2 (66)	0	5 (45)	2 (50)
Disease History, n (%)					
De novo DLBCL	3 (60)	1 (33)	3 (100)	7 (64)	2 (50)
DLBCL transformed from indolent	1 (20)	0	0	0	1 (25)
High grade B-cell lymphoma	0	1 (33)	0	1 (9)	1 (25)
Disease Stage, n (%)					
I or II	2 (40)	0	0	2 (18)	2 (50)
III or IV	3 (60)	3 (100)	3 (100)	9 (82)	2 (50)
Prognostic marker, n (%)					
High-grade B-cell lymphoma, double- or triple-hit	0	0	0	0	1 (25)
Double- or multi-expressor lymphoma*	2 (40)	1 (33)	0	3 (28)	1 (25)
Bulky Disease, one node ≥7cm	1 (20)	2 (67)	1 (33)	4 (36)	2 (50)
CAR-T Product (%)					
Axi-cel	4 (80)	3 (100)	3 (100)	10 (91)	2 (50)
Liso-cel	1 (20)	0	0	1 (9)	2 (50)
No. of Prior Lines of Therapy, n (%)					
1	3 (60)	2 (67)	0	5 (45)	1 (25)
≥2	2 (40)	1 (33)	3 (100)	6 (55)	3 (75)
LDH Median (range) – U/L	160 (147-682)	985 (160-1260)	328 (162-328)	249 (147-1260)	218 (170-602)
Response to first-line therapy n (%)					
Primary Refractory Disease	3 (60)	1 (33)	2 (67)	6 (55)	2 (50)
Relapse ≤12 mo	2 (40)	2 (67)	0	4 (36)	1 (25)
Relapse ≥12 mo	0	0	1 (33)	1 (9)	1 (25)

Grade ≥3 TRAEs: NKTR-255 was Well Tolerated in Combination With CAR-T; Most TRAEs were Transient and Resolved Spontaneously or Using Standard Treatment Protocols; No new cases of CRS or ICANS reported

Select TRAEs; n (%)	NKTR-255 1.5 µg/kg (N=5)	NKTR-255 3.0 µg/kg (N=3)	NKTR-255 3.0/6.0 µg/kg (N=3)	Combined NKTR-255 (N=11)	Placebo (N=4)
Grade 1 or 2 (≥20% of safety population)					
Anemia	1 (20%)	1 (33%)	1 (33%)	3 (27%)	0
Neutrophil count decreased	1 (20%)	1 (33%)	1 (33%)	3 (27%)	1 (25%)
Pyrexia	1 (20%)	1 (33%)	1 (33%)	3 (27%)	0
White blood cell count decreased	1 (20%)	0	2 (67%)	3 (27%)	2 (50%)
Grade 3 (≥20% of safety population)					
Neutrophil count decreased	2 (40%)	0	2 (67%)	4 (36%)	0
Grade 4 (all)					
Neutrophil count decreased	0	1 (33%)	0	1 (9%)	0
Platelet count decreased	0	1 (33%)	0	1 (9%)	0
Pneumonia aspiration	1 (20%)	0	0	1 (9%)	0
White blood cell count decreased	0	1 (33%)	0	1 (9%)	0
Grade 5 (all)					
Guillain-Barre syndrome*	1 (20%)	0	0	1 (9%)	0

NKTR-255 improved Complete Response Rate at 6 Months based on central review

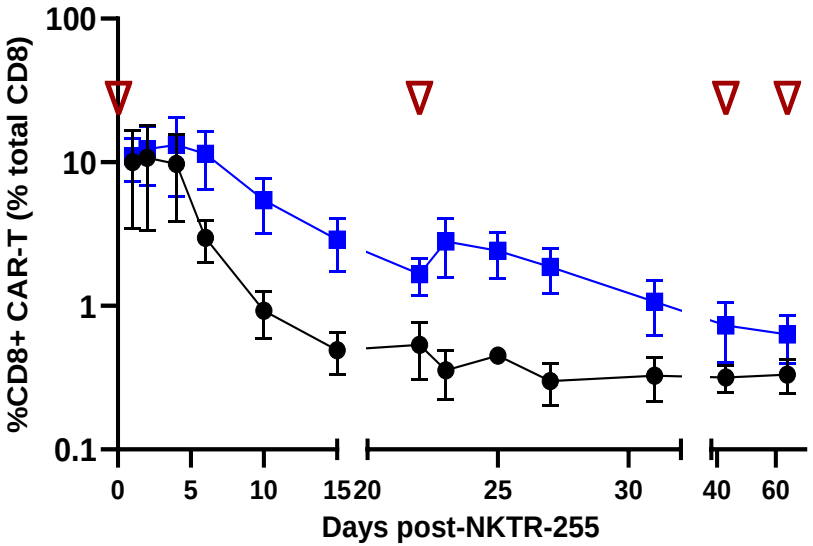


Endpoint	NKTR-255 1.5 mcg/kg	NKTR-255 3.0 mcg/kg	NKTR-255 3.0 mcg/kg/6.0 mcg/kg	NKTR-255 Combined Cohorts	Placebo
Number of patients randomized to cohort	N=5	N=3	N=3	**N=11**	**N=4**
ITT CR Rate per BICR at 6 months	4/5 (80%)	2/3 (67%)	2/3 (67%)	**8/11 (73%)**	**2/4 (50%)**
Efficacy evaluable population* CR Rate per PI at 6 months	4/4 (100%)	2/3 (67%)	2/3 (67%)	**8/10 (80%)**	**2/4 (50%)**
# pts that converted from SD or PR to CR per PI at 6 months	1/5 (20%) SD to PR to CR	1/3 (33%) PR to CR	0	**2/11 (18%)**	**0**

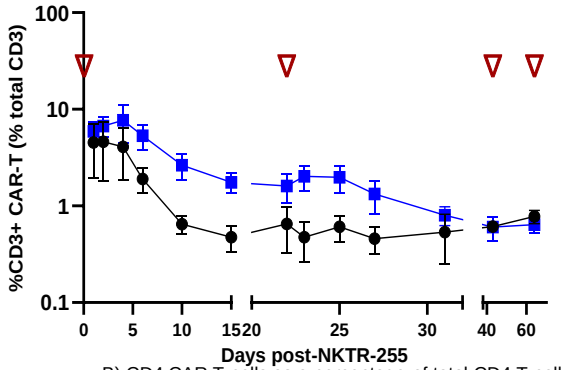
*Efficacy-evaluable population defined as having been dosed with study drug and at least one post baseline scan per PI

1. Frontiers in Pharmacology 2022; Jun Meng; 2. Frontiers in Oncology, 2021

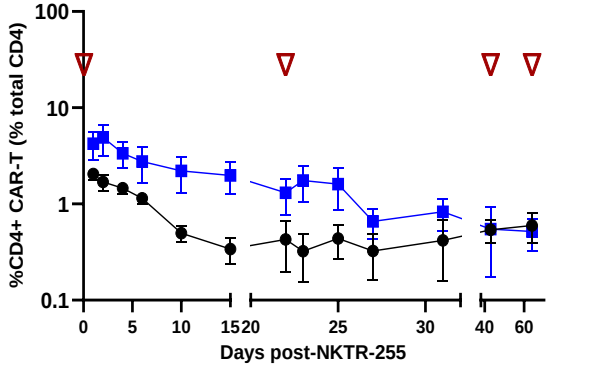
Pharmacodynamic Expansion of CAR T-cells following 1-3 cycles of NKTR-255



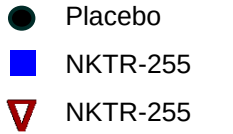
A) Persistence of CD3 CAR T cells as a percentage of total CD3 T-cells



B) CD4 CAR T-cells as a percentage of total CD4 T-cells



C) CD8 CAR T-cells as a percentage of total CD8 T-cells



Preferential expansion of CD8+ CAR-T cells following 1-3 cycles of NKTR-255. Flow cytometry measurement of patient CAR T-cell in the blood after infusion, presented as percentages ± SEM by days post-NKTR-255 treatment.

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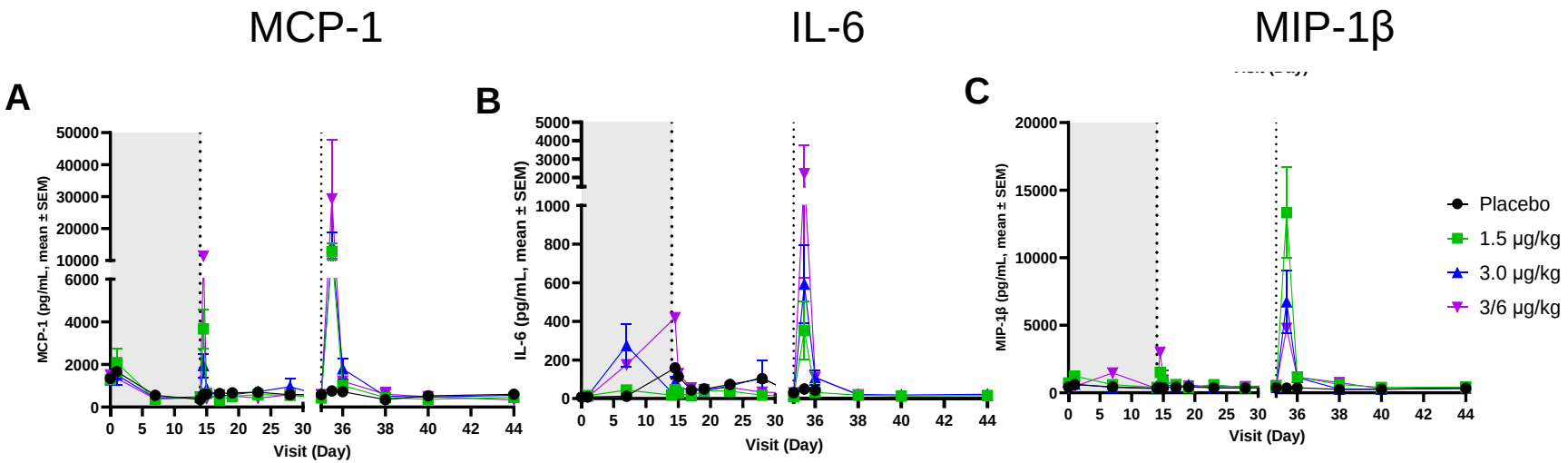
NKTR-255 post-administration cytokine response



Blood samples after NKTR 255 treatment were performed via Luminex assay. Data are presented as mean (pg/mL) ± SEM by visit day.

CAR=chimeric antigen receptor; IL-6=interleukin-6; MCP-1=monocyte chemoattractant protein 1; MIP-1β=macrophage inflammatory protein-1 beta; SEM=standard error of the mean.

Summary

- In conclusion, this study demonstrates that the combination of FDA-approved CD19 CAR T-cell products and NKTR-255 was safe and well-tolerated in patients with LBCL
- NKTR-255 improved the CRR at 6 Months, 8/11 (73%) compared to 2/4 (50%) in the placebo group and exhibited enhanced CAR T-cell kinetics
- The clinical benefit is superior to published historical benchmark data from pivotal and real-world meta-analyses with CAR T-cell therapies
- Further studies are warranted to explore the clinical benefits of NKTR-255 as an adjuvant treatment to CAR T-cell therapy and a broad range of cellular therapies

Acknowledgements

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The study was approved by the institutional review board of each participating site and informed consent is obtained from all patients

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Thank You!