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

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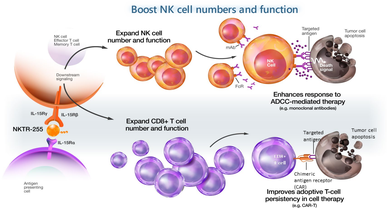
Background

- Autologous CAR T-cell therapy has emerged as a transformative approach for the treatment of relapsed/refractory (R/R) large B-cell malignancies (LBCL). However, durable responses remain a challenge, as more than half of patients fail to achieve remission and/or eventually relapse.
- Patients who relapse after CAR-T cell therapy have a poor prognosis with a median overall survival of 8 months. Thus, strategies to improve long-term efficacy of CAR-T cell products are needed.
- In pivotal clinical trials ZUMA-1 (axi-cel) (Locke 2022), JULIET (tisa-cel) (Schuster 2019), and TRANSCEND NHL- 001 (liso-cel) (Abramson 2020), patients who achieve CR at 6 months are highly likely to remain in CR beyond 2 years. Therapeutic interventions to improve CR rates at 6 months is anticipated to translate into an improvement of 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 promote the survival and expansion of memory CD8+ T cells.
- Clinical studies have shown that 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).

Figure 1. Mechanism of Action



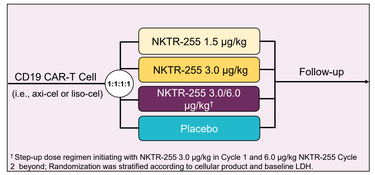
Enhancement of CAR-T Regimens:
CD19 CAR-T
BCMA CAR-T
CD38 CAR-T
Potential to expand into other hematological and solid tumor CAR-T and cellular therapies

Methods

- This is a multi-center phase 2 randomized, double-blind, placebo-controlled study of NKTR-255 vs placebo following standard of care lymphodepleting chemotherapy (LDC) and one of two FDA-approved CAR-T products (axicabtagene-ciloleucel or lisocabtagene-maraleucel).
- Eligible, adult patients (≥18 years old) with R/R LBCL received Study Drug (NKTR-255 or Placebo) intravenously starting +14 days following CAR-T infusion for up to 5 months.
- Patients received one of three different regimens of NKTR-255 or placebo intravenously as a 30-minute infusion 14 days after CAR T-cell infusion, with continued dosing every 21 days until the primary efficacy assessment.
- Efficacy response was measured by Blinded Independent Central Review (BICR).

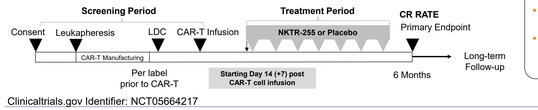
Figure 2. Study Design

Patients with:
- Relapse or refractory LBCL
- Planning to receive commercial CD19 CAR T-cell therapy
- ECOG 0-1



Primary Objective
- To compare the CR rate by BICR at month 6 of treatment with NKTR-255 vs placebo in patients who have received CAR-T cell therapy.
  - Efficacy assessed by PET-CT according to Lugano at Months 3, 6, 9 and 12

Key Secondary Objectives
- To evaluate safety and tolerability of NKTR-255 vs placebo following treatment with CAR-T.
- To characterize PK of NKTR-255 following treatment with CAR-T.
- To characterize PD effects on immune cell subsets and plasma cytokines after treatment with NKTR-255 following treatment CAR-T.



Clinicaltrials.gov Identifier: NCT05664217

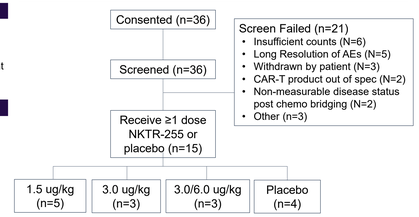
Table 1. Key inclusion and dosing criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥ 18 years • Evidence of CD19+ disease • FDG-Avid disease on PET/CT • ECOG 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 prior to each study drug infusion:
- No fever ≥ 38.0°C/Grade ≥ 1 CRS (Lee 201) within 24 hours of infusion.
- No Grade ≥ 3 CRS (ASTCT criteria) within 72 hours preceding infusion.
- No Grade ≥ 2 ICANS (ASTCT criteria) on the day of infusion.
- No previous Grade 4 IRR to infusion (Cycle 2 and beyond).
- No tocilizumab and/or dexamethasone within 48 hours preceding infusion.
- Appropriate laboratory test results as defined per protocol.

Figure 3. Study Deposition



Results

Table 2. Patient Demographics and Disease Characteristics

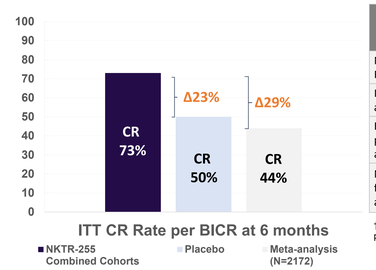
Characteristic	NKTR-255 1.5 µg/kg (N=5)	NTKR-255 3.0 µg/kg (N=3)	NTKR-255 3.0/6.0 µg/kg (N=3)	NKTR-255 Combined (N=11)	Placebo (N=4)
Age					
Median (range) – years	68 (40-72)	54 (53-72)	62 (61-63)	62 (40-72)	67.5 (44-76)
≥65, n (%)	3 (60)	1 (33)	0	4 (36)	2 (50)
Male, n (%)	4 (80)	2 (67)	2 (67)	8 (73)	0
ECOG Performance 0-1, n (%)	2 (40)	1 (33)	3 (100)	6 (55)	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)
Lugano 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)
None	1 (20)	2 (67)	1 (33)	4 (36)	2 (50)
Other**	2 (40)	0	2 (67)	4 (36)	0
Molecular subgroup per investigator, n (%)					
Germinal center B-cell–like	3 (60)	1 (33)	2 (67)	6 (55)	0
Activated B-cell–like	0	0	1 (33)	1 (9)	1 (25)
Unknown/Missing	2 (40)	2 (67)	0	4 (36)	3 (75)
Bulky Disease, one node ≥7cm	1 (20)	2 (67)	1 (33)	4 (36)	2 (50)
Tumor Burden Median (SPD), mm²	1320	3121	1056	1408	939
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)
Median Lines of Prior Therapy, n (range)	1 (1-2)	1 (1-3)	2 (2-3)	2 (1-3)	2 (1-2)
Response to first-line therapy , n (%)					
Primary Refractory Disease	3 (60)	1 (33)	2 (67)	6 (55)	2 (50)
Relapse ≤12 mo. after receipt first-line therapy	2 (40)	2 (67)	0	4 (36)	1 (25)
Relapse ≥12 mo. after receipt of first-line therapy	0	0	1 (33)	1 (9)	1 (25)

Table 3. Safety

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)	NKTR-255 Combined (N=11)	Placebo (N=4)
Grade 1 or 2 (>1 patient)					
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 (>1 patient)					
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[9]	1 (20%)	0	0	1 (9%)	0

CTCAE v5 grading criteria; [9]A fatal AE of Guillain-Barré-syndrome: Neurological symptoms including lower extremity weakness were first observed 7 days after administration of axi-cel and prior to first infusion of NKTR-255 (1.5 µg/kg). Prior to randomization, the patient experienced G1 CRS and G3 ICANS with mild confusion and difficulty finding words 8-9 days after CAR T infusion. 21 days following CAR T-cell infusion, NKTR-255 was administered based on resolution of AEs and fulfillment of eligibility criteria. Analysis of CAR-T cellular expansion and safety cytokine panel did not indicate any persistent cellular re-expansion or up-regulation of MCP-1, interferon gamma or IL-8. To assess the potential relationship of the grade 5 event, an independent DMC reviewed the case with a final decision that NKTR-255 had no causality to the event.

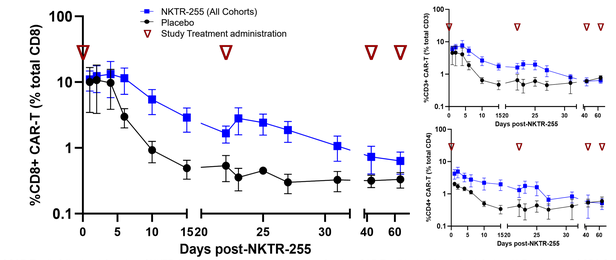
Figure 4. NKTR-255 improved Complete Response Rate at 6 Months based on central review



	NKTR-255 1.5 µg/kg	NKTR-255 3.0 µg/kg	NKTR-255 3.0/6.0 µg/kg	NKTR-255 Combined	Placebo
No. Patients Randomized	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 at 6 mo per PI††	4/4 (100%)	2/3 (67%)	2/3 (67%)	8/10 (80%)	2/4 (50%)
No. Pts. Converting from SD or PR to CR at 6 mo per PI††	1/5 (20%) SD to PR to CR	1/3 (33%) PR to CR	0	2/11 (18%)	0

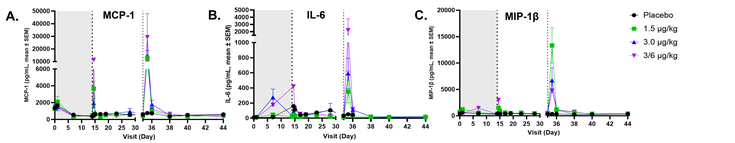
†Efficacy evaluable population defined as pts who received ≥1 dose NKTR-255 and ≥ 1 post-baseline scan per PI. ††Per PI assessment includes additional timepoint of 1mo post-CAR-T; ITT = Intent-to-treat

Figure 5. Re-expansion of CD8+ T cells supports MOA of NKTR-255 following CAR-T therapy



Expansion of CAR-T cells following 1-3 cycles of NKTR-255. Flow cytometry measurement of patient CAR T-cell in the blood after infusion. 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, and C) CD8 CAR T-cells as a percentage of total CD8 T-cells) presented as percentages ± SEM by days post-NKTR-255 treatment. Black symbol: placebo, blue symbol, and inverted triangle: NKTR 255 administration: NKTR-255. CAR=chimeric antigen receptor; SEM=standard error of the mean.

Figure 6. Fast normalization of MCP-1, IL-6, MIP cytokines supports favorable safety profile



NKTR-255 post-administration cytokine evaluation. Measurements of **A)** MCP-1, **B)** IL-6, and **C)** MIP-1β in patient blood samples after NKTR 255 treatment were performed via Luminex assay. Data are presented as mean (pg/mL) ± SEM by visit day. Gray shaded area denotes when CAR T infusion took place, while dotted black lines shows day of NKTR-255 administration. Black symbol: placebo, green: 1.5 µg/kg NKTR-255, blue: 3.0 µg/kg NKTR-255, and magenta: 3.0/6.0 µg/kg NKTR-255. One patient in the 1.5 µg/kg group had outlier IL-6 values and is omitted here for visualization. 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.

Conclusion

- The combination of FDA-approved CD19 CAR T-cell products and NKTR-255 was safe and well-tolerated in patients with relapsed/refractory LBCL.
- NKTR-255 improved the Complete Response Rate at 6 Months.
  - 8/11 (73%) of the NKTR-255 combined group compared to 2/4 (50%) in the placebo group achieved a CR at 6 months.
  - The clinical benefit is superior to published historical benchmark data from pivotal and real-world meta-analyses with CAR-T cell therapies
- Notably in this trial, two patients treated with NKTR-255 converted from SD or PR to CR at month 6, in comparison no conversions were observed in the placebo group.
- NKTR-255 enhanced CAR T-cell kinetics; the improved CD8 CAR T AUC0-15 was 5.8-fold greater than placebo-controls.
- 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. NKTR-255 is currently being studied in combination with Tumor-infiltrating-lymphocyte (TIL) cell therapies (NCT05676749).

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Disclosures:
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Abbreviations:
ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CR, Complete Response; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; FcR, Fc receptor; ICANS, Immune effector cell-associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; IL-15R, interleukin-15 receptor; IL-2R, interleukin-2 receptor; IV, intravenous; LDC, lymphodepleting chemotherapy; mAb, monoclonal antibody; MCP, monocyte chemoattractant protein; NHL, non-Hodgkin lymphoma; NK, natural killer; PD, pharmacodynamic; PK, pharmacokinetic; PR, partial response; R/R, relapsed/refractory; rhIL-15, recombinant human interleukin 15; SD, standard deviation; SEM, standard error of the mean; SPD, Sum of Product Diameters; TRAE, treatment-related

References:
1. Locke FL, et al. NEJM 2022; 386:640-654. **2.** Kamdar M, et al. Lancet 2022; p2294-2308 **3.** Rossi J, et al. Blood. 2018 Aug 23; 132(8): 804-814; **4.** Kochenderfer J., et al. J Clin Oncol. 2017 Jun 1;35(16): 1803-1813. **5.** Chou C, et al. Blood 2019;134(Suppl 1) 2866. **6.** Shah N, et al. Blood 2019;134:4459. **7.** Shah N, et al. Future Oncol 2021. doi: 10.2217/fon-2021-0576. **8.** Miyazaki T, et al. J Immunother Cancer 2021;9(5):e002024. **9.** Shah N, et al. J Immunother Cancer 2020;8. Abstract 355. **10.** Hirayama A, et al. Blood Advances 2022. **11.** Hirayama A, et al. Blood. 2019;133(17):1876-1887. **12.** Ogasawara, K., et al. Clin Pharmacokinetics 60, 1621–1633 (2021). **13.** Ying Z et al., Front Pharmacol 2022. **14.** Meng J et al., Front Oncol 2021. **14.** Alarcon Tomas A, et al., Leukemia 2023;37(1):154-163. DOI: 10.1038/s41375-022-01739-2.