A Phase 2/3, Randomized, Double Blind, Placebo-Controlled, Multicenter Study Of NKTR-255 Vs Placebo Following CD19-Directed CAR-T Cell Therapy In Patients With Relapsed/Refractory Large B-Cell Lymphoma

3335

Miguel-Angel Perales, MD[1]*, Sairah Ahmed, MD[2]*, Saurabh Dahiya, MD[3], Peter A. Riedell, MD[4], Joseph P. McGuirk, DO[5], Olalekan O. Oluwole, MBBS, MPH, MD[6], Sohail Chaudhry, MD, PhD[7], Zachary Lee, PharmD[7], Stanley Dai, MAS[7], Neha Dixit, PhD[7], Christie Fanton, PhD[7], Xiaoli Wang, PhD[7], Danni Yu, PhD[7], Mario Q. Marcondes, MD, PhD[7], Jonathan Zalevsky, PhD[7], Mary A. Tagliaferri, MD[7] and Cameron J. Turtle, MBBS, PhD[8]

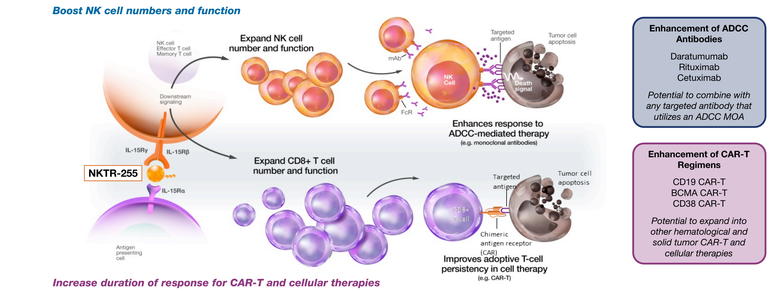
[1]Adult Bone Marrow Transplant Service, Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Lymphoma/Myeloma and Stem Cell Transplantation, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University – School of Medicine - Hematology/Oncology, Stanford University, Palo Alto, CA; [4]University of Chicago, Chicago, IL; [5]Division of Hematologic Malignancies & Cellular Therapeutics, The University of Kansas Cancer Center, Westwood, KS; [6]Vanderbilt University Medical Center, Nashville, TN; [7]Nektar Therapeutics, San Francisco, CA; [8]Fred Hutchinson Cancer Research Ctr., Seattle, WA

*Co-primary Authors

BACKGROUND

- Autologous T cells engineered to express a CD19-directed chimeric antigen receptor (CAR) have shown high overall response rates in treatment-refractory CD19$^+$ large B-cell lymphoma (LBCL).[1,2] However, over half of these patients will have lymphoma that fails to achieve remission or will relapse.[1,2] Thus, strategies to further improve the long-term efficacy of CAR-T cell products are needed.
- High serum IL-15 levels have been associated with effectiveness of CAR-T cell therapy.[3,4] IL-15 is crucial in the development, function, and survival of CD8$^+$ T cells, NK cells, and NK T cells.[5]
- NKTR-255 is a novel investigational polymer-conjugated IL-15 agonist, designed to activate, proliferate and expand natural killer (NK) and CD8$^+$ T cells *in vivo* (**Figure 1**). NKTR-255 also promotes the survival and expansion of memory CD8$^+$ T cells.[5-9]
- Preclinical data in B-cell lymphoma xenograft models have shown that NKTR-255 enhanced expansion, survival, and anti-tumor activity of human CD19 CAR-T cells.[9,10]
- NKTR-255 has demonstrated CD8$^+$ T cell expansion in patients with relapsed/refractory (r/r) multiple myeloma (MM) and non-Hodgkin lymphoma (NHL) as monotherapy (NCT04136756), including patients who previously received CAR-T cell therapy targeting CD19 or BCMA.[7,9]
- Two ongoing Investigator-sponsored trials are evaluating safety and tolerability of NKTR-255 following CAR-T cell therapy: one following treatment with an investigational CD19/CD22-directed CAR-T cell therapy (NCT03233854) in patients with B-cell acute lymphoblastic leukemia (ALL) and the other following treatment with lisocabtagene maraleucel (NCT05359211) in patients with LBCL.
- Here, we describe a planned Phase 2/3 clinical trial of NKTR-255 versus placebo following CD19-directed CAR-T cell therapy in patients with r/r LBCL.

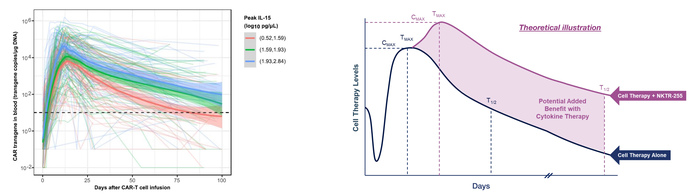
Figure 1. NKTR-255 Designed to Boost NK Cells and Expand CD8$^+$ Effector and Memory T cells



ADCC = Antibody-dependent cellular cytotoxicity; IL-15 = interleukin-15

Figure 2. Combining Cell Therapy with Exogenous Cytokine May Increase C_{max} and Extend CAR-T Cell Persistence in LBCL[10]

Higher peak IL-15 levels correlate with higher CD19 CAR-T cell $AUC_{0\text{-}28}$ in humans.



CAR transgene (FlapEF1$_\alpha$ copies/µg DNA) is shown as polynomial regression lines for three distinct tertiles of serum IL-15 peak concentration. Shaded areas represent 95% CI of the LOESS estimates.[11]

Factors that Correlate with Responses in CD19 CAR-T Recipients

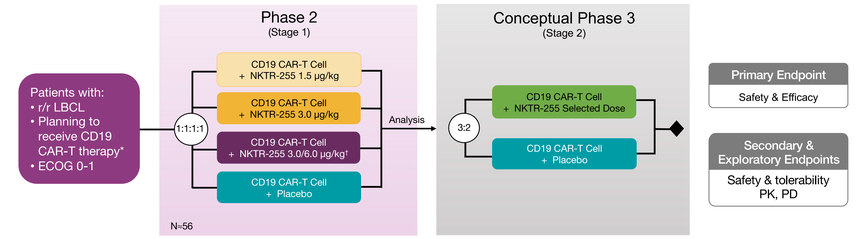
Serum IL-15 Levels	CAR-T Cell Kinetics
• Higher serum IL-15 levels are associated with effectiveness of CD19 CAR-T cell therapy[3,4]	• Peak CD19 CAR-T cell count (C_{max}) • CD19 CAR-T cell exposure during first 28 days ($AUC_{0\text{-}28}$) are associated with effectiveness of CAR-T cell therapy[12]

A full-spectrum IL-15 agonist (like NKTR-255) can potentially positively impact all factors known to correlate with responses in CD19 CAR-T cell recipients[10]

Persistence	Enhance stemness of the cellular product
Expansion	Enhance CD8$^+$ cellular composition
Function	Revert cellular exhaustion

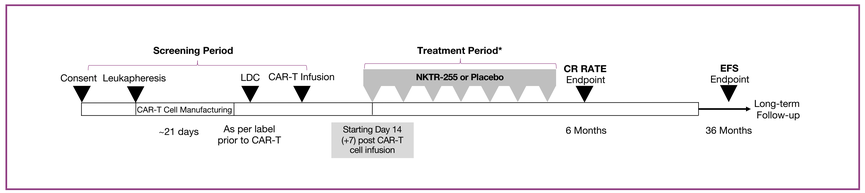
STUDY DESIGN

Figure 3. Phase 2/3 Randomized Double-Blind, Placebo-Controlled Study of NKTR-255 vs Placebo Following CD19-Directed CAR-T Cell Therapy in LBCL



LBCL=large B-cell lymphoma; CAR-T=chimeric antigen receptor T cell therapy; DL=dose level; PK=pharmacokinetics; PD=pharmacodynamics; r/r=relapse and refractory. *CD19 CAR-T cell therapy includes axi-cel or liso-cel (or tiso-cel in Stage 2). †Step-up dose regimen initiating with 3.0 µg/kg NKTR-255 in Cycle 1 and continuing in Cycle 2 and beyond with 6.0 µg/kg NKTR-255. Randomization will be stratified according to the cellular product that the patient receives (i.e., axi-cel or liso-cel [or tisa-cel in Stage 2]) and baseline LDH, and should take place no more than 1 day prior to the first study drug administration.

Figure 4. NKTR-255 or Placebo Dosed Following Commercially Approved CD19-Directed CAR-T Cell Therapy



*Study drug (NKTR-255 or placebo) infusion will be administered every 3 weeks (q3w) for up to 7 cycles or 5 months, whichever is earlier.

NKTR-255 Following Commercial CD19 CAR-T Cell Therapy Treatment

- This is a Phase 2/3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of multiple doses of NKTR-255 versus placebo following CD19-directed CAR-T cell therapy in patients with R/R LBCL. The study will be conducted in two stages:
  - **In Stage 1 (Phase 2)**, approximately 56 patients with R/R LBCL being treated with commercial CAR-T cell therapy will be randomized (following CAR-T cell therapy) in a 1:1:1:1 ratio with approximately 14 patients in each cohort (**Figure 3**).
  - **In Stage 2 (Phase 3)**, patients with R/R LBCL, following treatment with commercial CD19-directed CAR-T cell infusion, will be randomized in a 3:2 ratio to receive either NKTR-255 (at a dose determined in Stage 1) or placebo.
- Patients will be treated with NKTR-255 or placebo ~14 days after commercial CAR-T cell therapy. Treatment may be delayed up to 7 days until a patient meets the randomization criteria (**Figure 4**).

Key inclusion criteria

- ✓ Age ≥18 years
- ✓ CD19 positive disease
- ✓ FDG-Avid disease on PET/CT
- ✓ ECOG PS 0 or 1
- ✓ Planned FDA approved CD19-directed CAR-T cell therapy and LDC to treat R/R LBCL according to commercial label

YESCARTA® (axicabtagene ciloleucel) Gilead Kite
Breyanzi® (lisocabtagene maraleucel) BMS

Key exclusion criteria

- ✗ Prior treatment with any CD19 CAR-T cell therapy other than the planned treatment per protocol screening period
- ✗ Active CNS malignancy involvement
- ✗ Steroid use of > 5 mg Prednisone or equivalent
- ✗ Prior treatment with any IL-2 or IL-15 agonist and/or biosimilar agents
- ✗ Presence of uncontrolled fungal, bacterial, viral, or other infection

Primary Endpoints

- To compare the CR rate by BICR at month 6 of treatment of NKTR-255 arms vs Placebo (Phase 2).

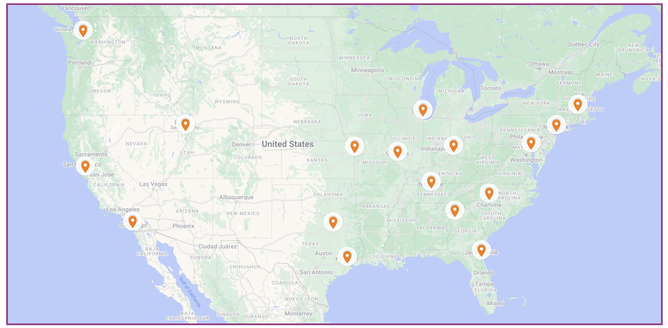
Secondary Endpoints

- To evaluate the safety and tolerability of NKTR-255 vs placebo.
- To compare DOR and PFS by BICR, EFS and OS of NKTR-255 arms vs placebo.
- To characterize the PD effects on other immune cell subsets and plasma cytokines in the blood.
- To characterize the PK of NKTR-255 and CAR-T cells.
- To assess rates of B-cell aplasia, infection, and usage of IVIG of NKTR-255 vs placebo.

Based upon results of the Phase 2 portion of the study, final design of the Phase 3 portion of the study will be determined, including NKTR-255 dose, sample size and endpoints of the study

STUDY STATUS

Figure 5. Locations of active or planned US clinical trial sites (Stage 1)



- When completed, this study will show whether treatment with NKTR-255 following CD19-directed CAR-T cell therapy can deepen overall response rates, improve durability of response and event-free survival vs CAR-T cell therapy alone. In addition, the safety and tolerability of the combination regimens will be reported.
- This study is initiating in the United States (**Figure 5**) and is expected to enroll approximately 56 patients in Stage 1.
- Please visit ClinicalTrials.gov to find out the latest information about this study.

ACKNOWLEDGMENTS

This study is funded by Nektar Therapeutics, San Francisco, CA. The study was approved by the institutional review board of each participating site and informed consent is obtained from all patients.

ABBREVIATIONS

1L, first-line therapy; 2L, second-line therapy; ADCC, antibody-dependent cellular cytotoxicity; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T cell therapy; CD, cluster of differentiations; CPI, checkpoint inhibitor; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; LDC, lymphodepleting chemotherapy; IL, interleukin; IV, intravenous; mAb, monoclonal antibody; MTD, maximum tolerated dose, NK, natural killer; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetics; Q21D, every 21 days; RECIST, Response Evaluation Criteria in Solid Tumors; rh, recombinant human; RP2D, recommended phase 2 dose; r/r, relapse/refractory; IVIG, Intravenous Immunoglobulin.

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).

Poster presented at the ASH Annual Meeting | Dec 10–13, 2022.
Corresponding author Miguel Perales: peralesm@mskcc.org