Pharmacodynamic Analysis of CAR-T Cell Persistence in Patients with Hematologic Malignancies Treated with NKTR-255, an IL-15 Receptor Agonist That Enhances CD8+ T-cells: Preliminary Results from a Phase 1 Study

2815

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without written permission from the authors.

Alexandre V. Hirayama[1], Cameron J. Turtle[1,2], Lihua E. Budde[3], Krina K. Patel[4], Miguel-Angel Perales[5], Andrew J. Cowan[1,2], Hayder Saeed[6], Julio C. Chavez[6], Delaney R. Kirchmeier[1], Murali Janakiram[7], Kai Wu[8], Lawrence Fong[8], Zachary Lee[9], Neha Dixit[9], Xiaoli Wang[9], Mario Q. Marcondes[9], Jonathan Zalevsky[9], Nina Shah[8]

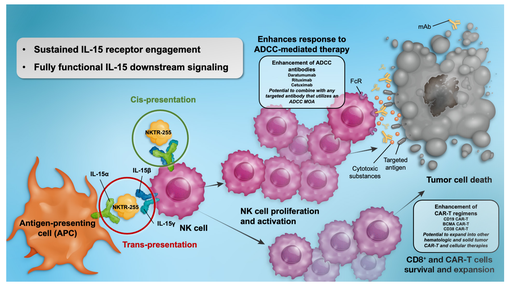
[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]The University of Washington, Seattle, WA, USA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [7]University of Minnesota, Minneapolis, MN, USA; [8]University of California San Francisco, San Francisco, CA, USA.; [9]Nektar Therapeutics, San Francisco, CA, USA

BACKGROUND

- Autologous T cells engineered to express a CD19 or BCMA-specific CAR have shown high overall response rates in treatment-refractory B-cell NHL and BCMA+ MM, respectively
- However, most patients will eventually relapse, and thus strategies are needed to further improve the efficacy and durability of CAR-T cell products
- In the clinical setting, high serum IL-15 levels are associated with effectiveness of CAR-T therapy[1,2]
- NKTR-255 is a polymer-conjugated rhIL-15 agonist, which provides sustained pharmacodynamic responses without the need for daily dosing[3]
- Preclinical data show that administration of NKTR-255 in combination with CD19 CAR-T cells leads to improved anti-tumor efficacy making NKTR-255 an attractive candidate for enhancing CAR-T cell therapy in the clinic.[4,5] NKTR-255 has also shown early evidence of clinical activity in combination with cetuximab in patients with solid tumors[6]
- An ongoing Phase 1 study (NCT04136756)[7] is evaluating NKTR-255 as monotherapy and in combination with daratumumab or rituximab in patients with hematologic malignancies – preliminary safety, PK, and biomarker analyses are reported in Poster 3134

This is the first report of IL-15/NKTR-255 on CAR-T cells from patients with R/R NHL or MM who had progressed or relapsed after CAR-T therapy enrolled in the ongoing Phase 1 study

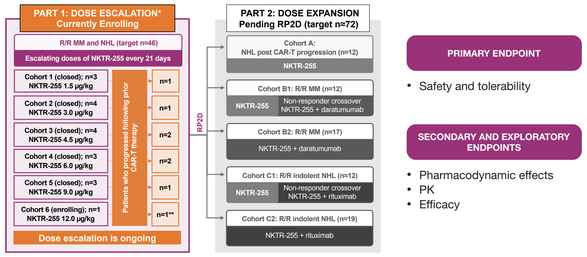
NKTR-255 Retains the Full Spectrum of IL-15 Biology[3]



ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; FcR, Fc receptor; IL-15, interleukin 15; mAb, monoclonal antibody; MOA, mechanism of action; NK, natural killer.

STUDY DESIGN AND METHODS

Analysis of Data from Heavily Pre-treated Patients with R/R NHL or MM who had Prior CAR-T Therapy Enrolled in this Ongoing Phase 1 Study



PRIMARY ENDPOINT

- Safety and tolerability

SECONDARY AND EXPLORATORY ENDPOINTS

- Pharmacodynamic effects
- PK
- Efficacy

*Dose-escalation rules: Successive cohorts each receive escalating doses of NKTR-255 every 21 days to determine the MTD/RP2D. A two-parameter Bayesian logistic regression model employing the escalation with overdose control principle was used to select dose level and determine the MTD. MTD will be declared when at least 6 patients have been evaluated at a dose and the posterior probability of targeted toxicity is at least 50% for that dose. **Patient did not have samples available for analysis (recent enrollment).
CAR-T, chimeric antigen receptor T-cell therapy; MM, multiple myeloma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

PHARMACODYNAMIC ANALYSIS

- Out of 18 patients enrolled in the NKTR-255 study (see abstract 3134), 8 received prior CAR-T therapy. Three patients did not have detectable CAR-T transcripts (or PD method not authorized for publication) and 1 patient did not have samples available for analysis (recent enrollment). All patients enrolled had progressed after achieving biological responses (CR or PR) with CAR-T therapy
- Patients had received commercially and non-commercially available CAR-T/NK (axicabtagene ciloleucel, idecabtagene vicleucel, tisagenlecleucel, and CAR-NK/IL-15) ranging from 111 to 749 (median = 483) days prior to NKTR-255 treatment
- Peripheral blood mononuclear cell samples were obtained at baseline (Day 1, before infusion of NKTR-255 monotherapy) and at intervals following NKTR-255 infusion
- CAR-T cells were identified by flow cytometry using proprietary reagents to detect the CD19-CAR and BCMA-CAR in combination with antibodies to identify CD3+, CD4+, and CD8+ T cells
- Pharmacodynamic data were analyzed for patients with measurable CAR-T cells at baseline; fold-change was calculated from baseline following treatment with NKTR-255 (baseline=1)

RESULTS

Clinical Characteristics and Pharmacodynamic Effects on CAR-T Cells Following NKTR-255 Treatment in Patients with Detectable CAR-T Cells in Peripheral Blood at Baseline

CD3+ CAR-T cell numbers demonstrated a peak average increase of ~2-fold (~100% increase) compared with baseline following NKTR-255 administration

Disease history [date of diagnosis]	Number of therapy lines prior to CAR-T treatment	Prior SCT	CAR-T treatment: Product	CAR-T treatment: Time since infusion (days)	NKTR-255 treatment: Number of cycles	NKTR-255 treatment: Dose (µg/kg)	NKTR-255 treatment: BOR to NKTR-255	Cycle 1 pharmacodynamic effects: Fold change in total CD8+ (cells/µL)	Effects on CAR-T cells (best pharmacodynamic response): CAR-T cells detectable at baseline	Fold change: CD3+ CAR-T (%)	Fold change: CD3+ CAR-T cells (cells/µL)
NHL (DLBCL) [Nov-2019]	4	No	Axicabtagene ciloleucel	111	2	1.5	PD	~2	Yes	1.7	1.4
MM [Jun-2017]	3	No	Idecabtagene vicleucel	440	2	4.5	PD	~1 (No expansion)	Yes	1.5	1.8
NHL (DLBCL) [May-2019]	1	Yes	Axicabtagene ciloleucel	532	5 (Treatment ongoing)	6	SD	~1.05	Yes	1.1	1.8
NHL (High Grade FL)* [Nov-2017]	3	No	Tisagenlecleucel	483	3	9	PD	2.2 -fold	Yes	~1.4	~3.0

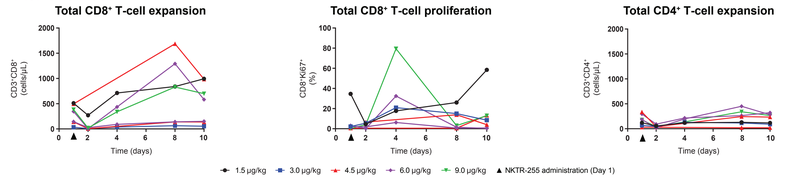
All patients had achieved a partial or complete response to prior CAR-T therapy. PD data were analyzed for patients with measurable CAR-T cells at baseline; fold change was calculated as treatment with NKTR-255 over baseline (baseline=1). *See Clinical Vignette.
BOR, best overall response; CAR-T, chimeric antigen receptor T-cell therapy, CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IL, interleukin; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PD, progressive disease; SD, stable disease.

Clinical Characteristics and Pharmacodynamic Effects Following NKTR-255 Treatment in Patients with No Detectable* CAR-T/CAR-NK Cell Counts at Baseline

Disease history [date of diagnosis]	Number of therapy lines prior to CAR-T treatment	Prior SCT	CAR-T treatment: Product	CAR-T treatment: Time since infusion (days)	NKTR-255 treatment: Number of cycles	NKTR-255 treatment: Dose (µg/kg)	NKTR-255 treatment: BOR to NKTR-255	Cycle 1 pharmacodynamic effects: Fold change in total CD8+ (cells/µL)
NHL (MZL) [Mar-2013]	12	Yes	CAR-NK – IL15**	177	5	4.5	SD	~3.4
MM [Feb-2009]	12	Yes	Idecabtagene vicleucel	742	1	6	PD	~3.7
MM [Jun-2012]	8	Yes	Idecabtagene vicleucel	749	1	3	N/A***	~1.9

For the above patients, CAR-T pharmacodynamic data were analyzed, and no measurable CAR-T cells were detected at baseline and/or after treatment with NKTR-255; fold change was calculated as treatment with NKTR-255 over baseline (baseline=1). One patient (not shown) did not have samples available for analysis (recent enrollment).
*CAR-T cell levels were not available or not determined due to low event counts at baseline and/or post-NKTR-255 treatment. **NCT03579927. ***Patient was not response evaluable due to rapid disease progression. BOR, best overall response; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; IL, interleukin; MM, multiple myeloma; MZL, marginal zone lymphoma; N/A, not evaluable; NHL, non-Hodgkin lymphoma; PD, progressive disease; SD, stable disease.

NKTR-255 Leads to Selective Expansion of CD8+ T cells and Increased Proliferative Capacity of CD8+ T Cells After One Dose



Overall ~2.2-fold increase in total CD8+ T cells

Overall increased proliferation observed in CD8+ T cells

Overall ~1.4-fold increase in total CD4+ T cells

NKTR-255 was Well Tolerated in Patients who had Received Prior CAR-T/CAR-NK Therapy at Doses Studied

TRAEs in >1 Patient who had Received Prior CAR-T/CAR-NK Therapy

Severity	TRAEs	Number of patients (n=8)
Grade 1/2	Flu-like symptom[a]	5
	Infusion-related reaction	6
	Fatigue	3
	Asthenia	2
	Decreased appetite	2
	Back pain	2
	Night sweats	2
	Dyspnea	2
Grade 3/4	Lymphopenia	3

- Most adverse events were transient and resolved spontaneously, or by using standard treatment protocols
- No TRAEs led to discontinuation, change of dose, or death
- Four patients experienced serious TRAEs, all were co-reported with IL-15-mediated symptoms as resolved
  - One cytokine-release syndrome (Grade 1): patient was hospitalized and the event resolved within 2 days using standard treatment protocols (methylprednisolone 100 mg)
  - Three infusion-related reactions (Grade 2) at various doses, all resolved

Data cut: November 3, 2021; [a]Group term includes body temperature increased, chills, headache, hyperhidrosis, hyperpyrexia, influenza-like illness, nausea, pyrexia.
For cytokine data analysis, see ASH Poster #3134.
CAR-T, chimeric antigen receptor T-cell therapy; NK, natural killer; TRAE, treatment-related adverse event.

Patient Treated with NKTR-255 9 µg/kg Demonstrated Increases in CD3+ CAR-T Cells Within One Cycle

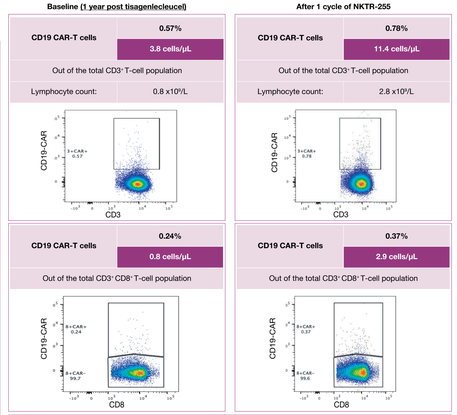
CASE VIGNETTE

59-year-old, Female
High-grade FL

Prior treatment:
1. Bendamustine + rituximab
2. Obinutuzumab
3. R-EPOCH
4. Tisagenlecleucel
5. Polatuzumab + bendamustine + rituximab
6. Tazemetostat hydrobromide

Current treatment:
NKTR-255 9 µg/kg

CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma.



~1.4-fold increase in percentage CD3+ CAR-T cells
~3-fold increase in CD3+ CAR-T cell counts
~4-fold increase in CD3+ CD8+ CAR-T cell counts

CONCLUSIONS

- This report from the ongoing Phase 1 study is the first clinical safety and pharmacodynamic assessment of the effects of IL-15/NKTR-255 on CAR-T cell counts in R/R NHL or MM patients who had progressed or relapsed after CAR-T therapy
- Of the patients with detected CAR-T cells in blood at baseline, 4/4 (100%) showed an increase of CD3+ CAR-T cells following NKTR-255 treatment
- NKTR-255 induced proliferation of CD8+ T cells and an increase of the total CD8+ cell fraction in all patients with detected CAR-T cells at baseline
- Although preliminary, these data suggest that NKTR-255 administration represents a potentially novel means of CAR-T augmentation through enhancement of CD8+ T cells and provides promising evidence of CAR-T cell rescue
- Results support planned evaluation of NKTR-255 in combination with CAR-T therapy as a potential strategy to enhance the efficacy of CAR-T therapy
- Evaluation of NKTR-255 in patients with NHL post CAR-T progression in the dose-expansion part of this study is ongoing (NCT04136756). Dose escalation of NKTR-255 + cetuximab in patients with R/R HNSCC and CRC is also ongoing (NCT04616196)

ACKNOWLEDGMENTS

This study is funded by Nektar Therapeutics, San Francisco, CA. Medical writing assistance was provided by Suzanne Patel PhD of BOLDSCIENCE Inc., and was funded by Nektar Therapeutics. The study was approved by the institutional review board of each participating site and informed consent is obtained from all patients.

DISCLOSURES

The presenting author, Alexandre Hirayama, has received honoraria from Bristol Myers Squibb and Novartis within the last 24 months.

ABBREVIATIONS

ADCC, antibody-dependent cellular cytotoxicity; BCMA, B-cell maturation antigen; BOR, best overall response; CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CR, complete response; CRC, colorectal carcinoma; DLBCL, diffuse large B-cell lymphoma; FcR, Fc receptor; FL, follicular lymphoma; HNSCC, head and neck squamous cell carcinoma; IL, interleukin; IL-15, interleukin-15; mAb, monoclonal antibody; MM, multiple myeloma; MOA, mechanism of action; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NK, natural killer; PD, progressive disease; PK, pharmacokinetics; PR, partial response; rhIL-15, recombinant human interleukin 15; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SD, stable disease; TRAE, treatment-related adverse event.

REFERENCES

1. Kochekderfer JN, et al. *J Clin Oncol* 2017;35:1803; 2. Rossi J, et al. *Blood* 2018;132:804–814; 3. Miyazaki T, et al. *J Immunother Cancer* 2021;9:e002024; 4. Chou C, et al *HernaSphere* 2019;3:550; 5. Chou C, et al. *Blood* 2019;134:2866; 6. Altan M, et al. *J Immunother Cancer* 2021;9(Suppl. 2):A1007; 7. Shah N, et al. *Future Oncol* 2021;17:3549–3560.