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

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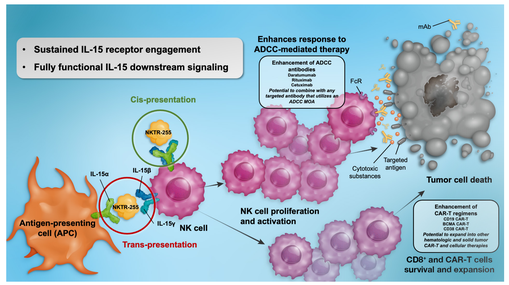
BACKGROUND

- 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

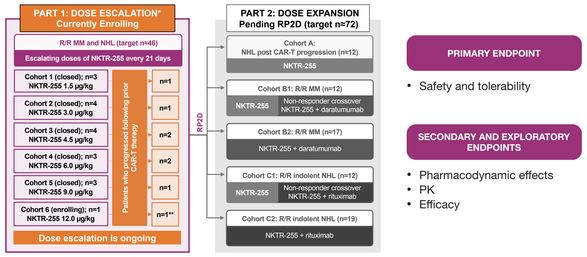
NKTR-255 Retains the Full Spectrum of IL-15 Biology[3]



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

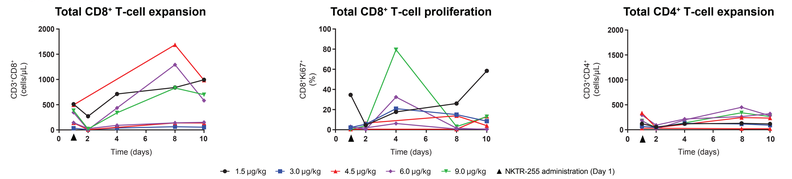
All patients had achieved a partial or complete response to prior CAR-T therapy. PD data were analyzed for patients with measurable CAR-T cells at baseline; fold change was calculated as treatment with NKTR-255 over baseline (baseline=1). *See Clinical Vignette.
BOR, best overall response; CAR-T, chimeric 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.

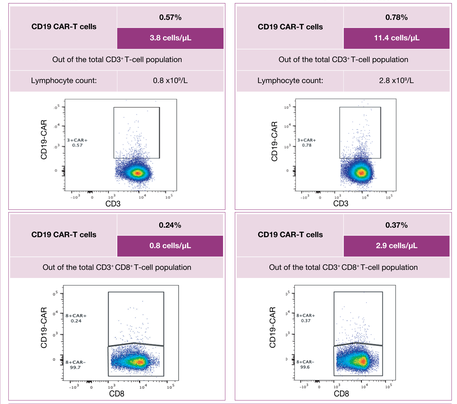
Patient Treated with NKTR-255 9 µg/kg Demonstrated Increases in CD3⁺ CAR-T Cells Within One Cycle

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



~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

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

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

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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.

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