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Safety, Tolerability, PK/PD, and Preliminary Efficacy of NKTR-255, a Novel IL-15 Receptor Agonist, in Patients with Relapsed/Refractory Hematologic Malignancies

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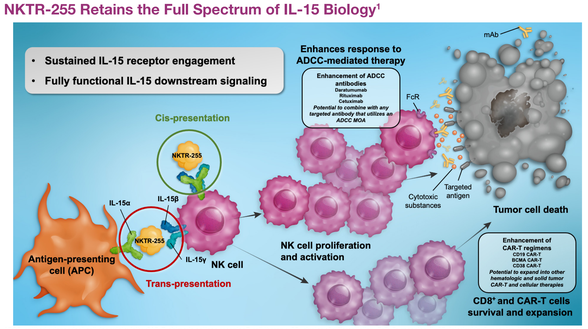
BACKGROUND

- There is an unmet need for novel agents that can boost NK cell number and function with the aim to aid current approved therapies for MM and NHL
- NKTR-255 is a polymer-conjugated rhIL-15 agonist, which provides sustained PD responses without the need for daily dosing[1]
- In preclinical models, NKTR-255 induced proliferation and activation of NK cells and promoted survival and expansion of CD8$^+$ T cells.[1] NKTR-255 also enhanced the antitumor activity of tumor-targeted antibodies that function by an ADCC mechanism,[2,3] and has shown early evidence of clinical activity in combination with cetuximab in patients with solid tumors[4]
- This Phase 1 study (NCT04136756)[5] evaluates the safety and tolerability of NKTR-255 monotherapy and in combination with daratumumab or rituximab in patients with hematologic malignancies

Here we report preliminary data on safety, PK, and PD biomarkers from patients (n=18) treated in the ongoing dose-escalation part of the study

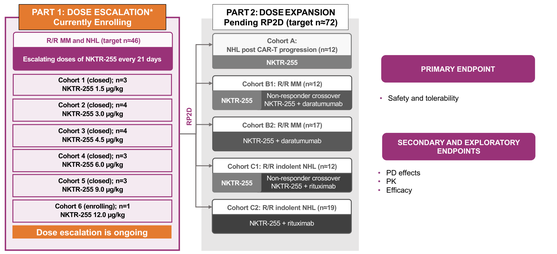
NKTR-255 Retains the Full Spectrum of IL-15 Biology[1]



ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; FcR, Fc receptor; IL-2R, interleukin-2 receptor; IL-15R, interleukin-15 receptor; mAb, monoclonal antibody; MOA, mechanism of action; NK, natural killer.

STUDY DESIGN AND PATIENTS

Preliminary Safety, PK, and PD Biomarker Data from the Ongoing Dose-Escalation Part of a Phase 1 Study in Patients With R/R MM or NHL (n=18)



*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. CAR-T, chimeric antigen receptor T-cell therapy; MM, multiple myeloma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; PD, pharmacodynamic; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Study Procedures and Assessments

SAFETY AND TOLERABILITY	PK AND PD BIOMARKERS	EFFICACY
• AEs were assessed by CTCAE v5.0 • Safety population: all patients who received ≥1 dose of treatment • Data cutoff: November 3, 2021	• PK with concentration–time profiles • PD – Assessment of NK cells, CD8$^+$ T cells, and CD4$^+$ T cells – Evaluation of inflammatory cytokines	• Objective efficacy response: evaluated using IMWG for MM patients; Lugano for NHL patients • Response-evaluable population: patients with ≥1 dose, measurable disease at baseline, and ≥1 post-baseline response assessment • Disease efficacy response measurements according to protocol: – Amendment 1: MM Q2 cycles; NHL C5D8, then Q4 cycles – Amendment 2: MM Q2 cycles; NHL C2D8, then Q4 cycles – Amendment 3: MM Q1 cycle; NHL C2D8, then Q4 cycles • Data cutoff: October 14, 2021

CD, cluster of differentiation; CTCAE, Common Terminology Criteria for Adverse Events; IMWG, International Myeloma Working Group; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PD, pharmacodynamic; PK, pharmacokinetic.

RESULTS

Heavily Pre-treated Population Enrolled in Dose-Escalation Phase (n=18)

Patient Demographics and Disease Characteristics

Patients with NHL (n=7)		
Median age (range), years		66 (59–80)
Sex, n (%)	Female Male	4 (57) 3 (43)
Median (range) time since diagnosis, months		62.6 (12.9–226)
Median (range) number of prior therapies		3 (1–12)
Disease subtype, n (%)	Large B-cell lymphoma Diffuse large B-cell lymphoma Follicular lymphoma Other/missing	1 (14) 3 (43) 2 (29) 1 (14)
Bulky disease, n (%)	Yes No Unknown	1 (14) 5 (71) 1 (14)
Pathological classification, n (%)	Germinal center B-cell like Non-germinal center B-cell like Unknown	2 (29) 1 (14) 4 (57)
Prior therapies of interest, n (%)	Autologous stem cell transplants Allogenic stem cell transplants CAR-T	2 (29) 1 (14) 4 (57)
CD20-containing regimens, n (%)	Rituximab	7 (100)
International Prognostic Index score, n (%)	0–1 3 4–5	1 (14) 3 (43) 3 (43)

Patients with MM (n=11)		
Median age (range), years		66 (49–78)
Sex, n (%)	Female Male	3 (27) 8 (73)
Median (range) time since diagnosis, months		70.9 (25.2–231.7)
Median (range) number of prior therapies		5 (3–12)
Cytogenetic risk, n (%)	Standard High Unknown	6 (55) 3 (27) 2 (18)
Paraprotein type, n (%)	IgG IgA Light chain myeloma Unknown	6 (55) 3 (27) 1 (9) 1 (9)
Prior therapies of interest, n (%)	Autologous stem cell transplants Allogenic stem cell transplants CAR-T	7 (64) 0 4 (36)
Prior therapies of interest, n (%)	IMiD Protease inhibitor Lenalidomide	8 (73) 11 (100) 11 (100)
CD38 experience, n (%)	Daratumumab Elotuzumab Both agents	9 (82) 4 (36) 2 (18)
ISS stage at screening, n (%)	I II II Not available	5 (46) 3 (27) 1 (9) 2 (18)

Data cutoff: November 3, 2021.
CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; IgA/G, immunoglobulin A/G; IMiD, immunomodulatory imide drugs; ISS, International Staging System; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

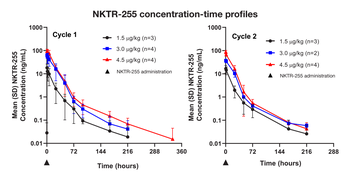
NKTR-255 was Well Tolerated; Most TRAEs were Transient and Resolved Spontaneously or Using Standard Treatment Protocols

Selected TRAEs; n (%)	1.5 µg/kg (n=3)	3 µg/kg (n=4)	4.5 µg/kg (n=4)	6 µg/kg (n=3)	9 µg/kg (n=3)	12 µg/kg (n=1)	Total (N=18)
Grade 1 or 2 (≥25% of total population)							
Flu-like symptoms[a]	2 (67)	4 (100)	4 (100)	3 (100)	1 (33)	0	14 (78)
Infusion-related reaction	0	0	3 (75)	2 (67)	1 (33)	1 (100)	7 (39)
Fatigue	0	2 (50)	1 (25)	2 (67)	1 (33)	0	6 (33)
Grade 3 (all)							
Lymphopenia[b]	0	1 (25)	0	0	0	1 (100)	2 (11)
Neutropenia[c]	0	1 (25)	1 (25)	1 (33)	1 (33)	1 (100)	5 (28)
Thrombocytopenia	0	0	0	1 (33)	1 (33)	0	2 (11)
Hypophosphatasemia	1 (33)	0	0	0	0	0	1 (6)
Anemia	0	0	0	0	1 (33)	0	1 (6)
Hypertension	0	1 (25)	0	0	0	0	1 (6)
Grade 4 (all)							
Lymphopenia	0	0	2 (50)	2 (67)	1 (33)	0	5 (28)

Data cutoff: November 3, 2021. [a]Group term includes body temperature increased, chills, headache, hyperhidrosis, hyperpyrexia, influenza like illness, nausea, pyrexia; [b]Group term includes lymphopenia and lymphocyte count decreased; [c]Group term includes neutropenia, leukopenia and white blood cell count decreased.

- No DLTs were observed, and no patients discontinued NKTR-255 due to adverse events
- Serious TRAEs were observed in 1 patient in the 3.0 µg/kg group (Grade 2 fever), 4 patients in the 4.5 µg/kg group (CRS and confusion, n=1; CRS, n=1; infusion-related reaction, n=2), 2 patients in the 9.0 µg/kg group (pyrexia, neutropenia, n=1; infusion-related reaction, n=1) and 1 patient in the 12.0 µg/kg group (infusion-related reaction, n=1)
- None of the serious AEs met the criteria for DLT, as defined by the protocol

NKTR-255 Demonstrated Extended Half-life with Minimal Accumulation

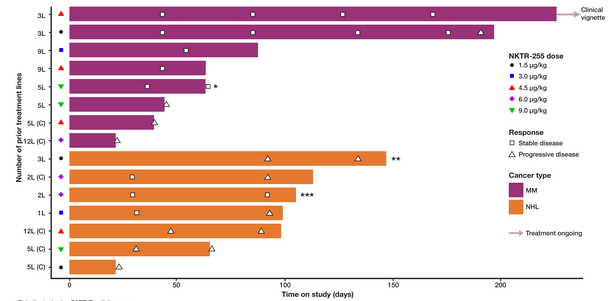


- Preliminary PK analyses showed target-mediated drug disposition at the lowest dose level (1.5 µg/kg) and linear PK toward higher dose levels (>3.0 µg/kg), with clearance of higher doses ~50% of that estimated for 1.5 µg/kg
- The average half-life of NKTR-255 was 27–48 hours, which is ~11–19 fold longer than that reported for rhIL-15,[6] with no accumulation following repeated dosing on a once every three-week dosing regimen

Data cutoff: May 3, 2021. Validated bioassay method was used to measure plasma concentration of NKTR-255, which was expressed in IL-15 content. Below limit of quantification samples were treated as 0 in summarizing NKTR-255 concentration–time profiles. PK, pharmacokinetic; SD, standard deviation.

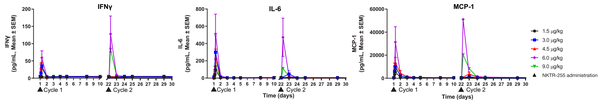
NKTR-255 Shows Evidence of Preliminary Efficacy

- Among the 15 response-evaluable patients, 8 (53%) reported disease stabilization (5/8 [63%] patients with MM; 3/7 [43%] patients with NHL)



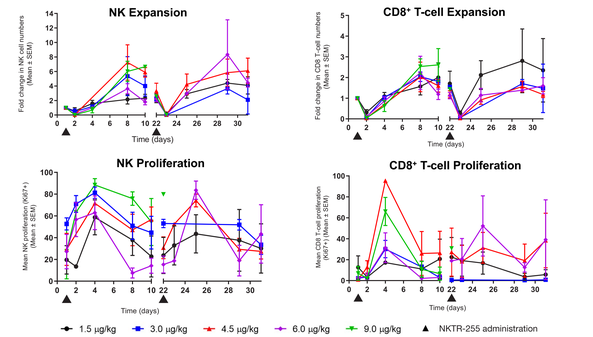
(C) Indicated prior CART-T cell therapy.
*Discontinued treatment due to unrelated AE. **This patient was enrolled under protocol amendment 2, which specifies the first response evaluation at Cycle 5. All other patients had first response evaluation at Cycle 2, Day 8. One additional MM patient had PD assessment after the data cut. ***Patient withdrew consent due to unrelated AE. Three patients (not shown) had clinical progression prior to disease assessment and were not included in the efficacy- evaluable population (one was a prior CAR-T recipient). One additional patient did not reach the primary disease assessment at the time of the data cut.
CAR-T, chimeric antigen receptor T-cell therapy; MM, multiple myeloma; NHL, non-Hodgkin lymphoma

NKTR-255 Does Not Cause Sustained Upregulation of Inflammatory Cytokines Commonly Associated with CRS, Supporting the Safety of Treatment



Data cutoff: August 2021.
Dotted line represents lower limit of quantification; values below this line are approximate but calculated based on standard control curve. Cycle 2, 6-hour timepoint added in protocol amendment 3.0, data only available for dose level 6 µg/kg and beyond. CRS, cytokine release syndrome; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; SEM, standard error of the mean

NKTR-255 Led to Expansion and Increased Proliferative Capacity of NK and CD8$^+$ T cells



Data cutoff: August 19, 2021 (n=16). Differences in baseline levels and fold increases of NK and CD8$^+$ cells may be due to different disease types (MM vs NHL), disease severity and bone marrow capacity. Cycle 2, Day 4 CD8$^+$ proliferation data readout for patients at the 3 µg/kg dose level is unavailable. CD, cluster of differentiation; NK, natural killer; SEM, standard error of the mean.

- NKTR-255 induced NK and CD8$^+$ T-cell expansion, with peak fold changes in NK numbers of ~8-fold at the 6.0 µg/kg dose in Cycle 2 and ~3-fold change in number of CD8$^+$ T cells at the 9.0 µg/kg dose in Cycle 1
- Evidence of continued NK expansion following NKTR-255 administration across multiple patients and cycles
- Proliferative capacity of NK and CD8$^+$ T cells was maintained across multiple cycles of NKTR-255

Minimal changes in CD4$^+$ Tregs were observed with NKTR-255 (data not shown)

CASE VIGNETTE

Stable Disease (per IMWG) in Patient Dosed with NKTR-255 4.5 µg/kg Treatment Ongoing for 12 Cycles

49-year-old, male

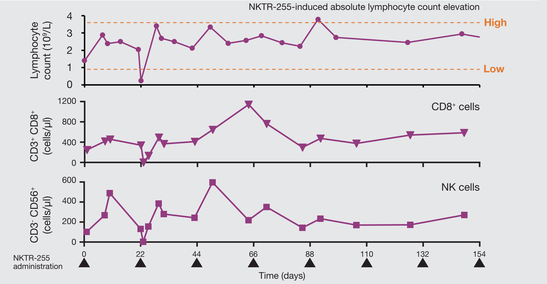
Initial MM diagnosis: Feb-2017, MM IgG lambda

Prior treatment [best overall response]:

1. RVd (lenalidomide, bortezomib, and dexamethasone; Mar-2017 to Jun-2017, melphalan [Jul-2017] plus lenalidomide maintenance [Oct-2017 to Nov-2018]) [PR]
2. DRd (daratumumab, lenalidomide, and dexamethasone; Jan-2019 to Oct-2019) [SD]
3. KPd (carfilzomib, pomalidomide, and dexamethasone; Oct-2019 to Jan-2021) [SD]

Current treatment:
NKTR-255 4.5 µg/kg for 12 cycles; first dose Mar-2021

	Baseline (Mar-2021)	Cycle 3 (Apr-2021)	Cycle 5 (May-2021)	Cycle 7 (Jul-2021)	Cycle 9 (Aug-2021)	Cycle 11 (Sep-2021)
Kappa/Lambda chain ratio	0.16	0.16	0.13	0.16	0.15	0.2
Kappa (mg/L)	8.7	10.1	9.6	8.7	9.6	10.8
Lambda (mg/L)	56.1	63.1	71.4	55.2	64.7	53.8
M protein (g/dL)	1.2	1.2	1.2	1.2	1.2	1.2
IgG (mg/dL)	1704	1654	1678	1770	1813	1871
Beta-2 microglobulin (mg/L)	2.1	n.a.	2.0	2.0	2.0	1.6



Achieved longer disease stabilization with NKTR-255 as a single agent, compared to prior combination therapy. IgG, immunoglobulin G; IMWG; International Myeloma Working Group; MM, multiple myeloma; PR, partial response; SD, stable disease.

CONCLUSIONS

- **NKTR-255 was well tolerated in this heavily pre-treated population of patients with hematologic malignancies. TRAEs were generally low-grade, transient, and easily managed**
- **Evidence of on-target biological activity was observed despite highly compromised bone marrow hematopoietic capacity: NKTR-255 led to expansion and proliferation of NK and CD8$^+$ T cells**
- **Early evidence of clinical activity was observed in this heavily pre-treated and highly refractory patient population**
- **The MTD/RP2D has not yet been reached and dose escalation of NKTR-255 is ongoing**
- **Results support subsequent evaluation in combination with other anticancer agents**

ACKNOWLEDGMENTS
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DISCLOSURES
The presenting author, Nina Shah, has had the following relationships within the last 24 months: held a consulting role for Amgen, CareDx, CSL Behring, GSK, Indapta Therapeutics, Karyopharm, Kite, Oncopeptides and Sanofi; received research funding from Bluebird Bio, BMS/Celgene, Janssen, Nektar, Poseida, Precision Biosciences, Sutro Biopharma, and Teneobio.

ABBREVIATIONS
ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CRS, cytokine-release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; FcR, Fc receptor; IFN, interferon; IgG, immunoglobulin IgA/G, immunoglobulin A/G; IL, interleukin; IL-15R, interleukin-15 receptor; IL-2R, interleukin-2 receptor; IMWG, International Myeloma Working Group; ISS, International Staging System; mAb, monoclonal antibody; MCP, monocyte chemoattractant protein; MM, multiple myeloma; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; NK, natural killer; PD, pharmacodynamic; PK, pharmacokinetic; PR, partial response; R/R, relapsed/refractory; rhIL-15, recombinant human interleukin 15; RP2D, recommended phase 2 dose; SD, standard deviation; SEM, standard error of the mean; TRAE, treatment-related adverse event; Tregs, regulatory T cells.

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