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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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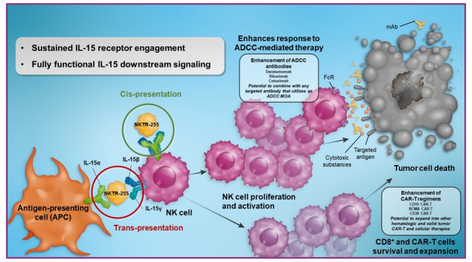
BACKGROUND

- The therapeutic potential of daratumumab for advanced multiple myeloma (MM) is limited by the on-target cytotoxic effect on CD38 expressing NK cells.[1,2]
- Natural killer (NK) cells are important for daratumumab-mediated antibody-dependent cellular cytotoxicity (ADCC).
- CD38$^+$ NK cells are an unexplored therapeutic target for priming the immune system of MM patients and strategies to enhance NK cell population and function may improve outcomes.[3]
- IL-15Rβγ are highly expressed on NK cells and receptor activation leads to expansion and enhancement of NK cell function.[4]
- NKTR-255 is a polymer-conjugated rhIL-15 agonist with ≥10-fold longer half-life than rhIL-15 and has been shown to induce proliferation and activation of NK cells and promote survival and expansion of CD8$^+$ T cells in the clinic.[5,6,7]
- NKTR-255 also enhanced the antitumor activity of tumor-targeted antibodies that function by an ADCC mechanism,[8] and has shown early evidence of clinical activity in combination with cetuximab in patients with solid tumors (NCT04616196).[9]
- This Phase 1 study (NCT04136756)[10] 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 26 patients treated with NKTR-255, including 4 patients treated in combination with daratumumab

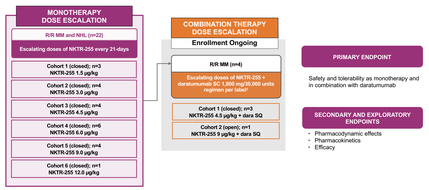
NKTR-255 Retains the Full Spectrum of IL-15 Biology[3]



ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; FcR, Fc receptor; IL-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 Biomarkers Data from the Ongoing Dose-Escalation Part of a Phase 1 Study in Patients With R/R MM or NHL (n=26)



*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 are evaluated at a dose and the posterior probability of targeted toxicity is at least 50% for that dose. †Darzalex Faspro® SC 4-week cycle regimen: Weeks 1–8: once weekly, Weeks 9–24: q2weeks, then Week 25 onwards q4weeks; NKTR-255 in Cycles 1–3 is administered on Day 2 (i.e., one day after daratumumab of the cycle and on Day 1 (i.e., same day) Cycle 4 beyond.

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 study drug	• PK – Derive PK parameters from concentration-time profiles • PD – Assessment of NK cells, CD8$^+$ T cells, and CD4$^+$ T cells – Evaluation of inflammatory cytokines	• Objective response: evaluated using IMWG for MM patients; Lugano for NHL patients • Response-evaluable population: patients with ≥1 dose of study drug 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&4: MM Q1 cycle; NHL C2D8, then Q4 cycles

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 NKTR-255 Dose-Escalation Phase (n=26)

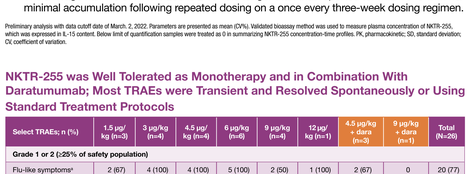
Patient Demographics and Disease Characteristics

Patients with NHL (n=8)		
Median age (range), years		65.5 (59–80)
Sex, n (%)	Female Male	4 (50) 4 (50)
Median (range) time since diagnosis, months		53.6 (12.9–226.0)
Median (range) number of prior therapies		4 (1–12)
Disease subtype, n (%)	Large B-cell lymphoma Diffuse large B-cell Lymphoma Follicular lymphoma Other/missing	1 (13) 4 (50) 2 (25) 1 (13)
Bulky disease, n (%)	Yes No Unknown	1 (13) 6 (75) 1 (13)
Prior therapies of interest, n (%)	Autologous stem cell transplants Allogenic stem cell transplants CAR-T	2 (25) 1 (13) 4 (50)
CD20 containing regimens, n (%)	Rituximab	8 (100)
International Prognostic Index score, n (%)	0–1 2–3 4–5 Unknown	1 (13) 3 (38) 3 (38) 1 (13)

Patients with MM (n=18)			
	NKTR-255 monotherapy (n=14)		NKTR-255 + Dara (n=4)
Median age (range), years		64.0 (49–78)	61.5 (52–70)
Sex, n (%)	Female Male	4 (29) 10 (71)	2 (50) 2 (50)
Median (range) time since diagnosis, months		86.0 (25.2–231.7)	122.4 (90.9–174.3)
Median (range) number of prior therapies		6 (3–16)	5.5 (5–10)
Cytogenetic risk, n (%)	Standard Intermediate High Not Available	7 (50) 0 5 (38) 2 (14)	2 (50) 1 (25) 1 (25) 0
Paraprotein type, n (%)	IgG IgA Light chain myeloma Unknown	7 (50) 3 (21) 2 (14) 2 (14)	1 (25) 1 (25) 2 (50) 0
Prior therapies of interest, n (%)	Autologous stem cell transplants Allogenic stem cell transplants CAR-T IMiD Lenalidomide Proteasome inhibitor	9 (64) 1 (7) 6 (43) 14 (100) 13 (93) 14 (100)	3 (75) 1 (25) 3 (75) 4 (100) 4 (100) 4 (100)
CD38 experience, n (%)	Yes	14 (100)	4 (100)
ISS stage at screening, n (%)	I II III IV Not Available	7 (50) 4 (28) 1 (7) 0 2 (14)	2 (50) 1 (25) 0 0 1 (25)

Clinical cutoff: October 20, 2022.
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 Monotherapy Demonstrates Extended Half-life with No/Minimal Accumulation



Summary of PK parameters (Cycle 1)

DOSE	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	$T_{1/2}$ (hr)	CL (L/hr)
1.5 µg/kg (n=3)	16.1 (45.5)	212 (66.7)	29.5 (9.90)	0.61 (38.8)
3.0 µg/kg (n=4)	43.7 (26.0)	993 (60.8)	34.4 (47.9)	0.29 (45.0)
4.5 µg/kg (n=4)	93.3 (24.4)	1572 (29.7)	47.9 (22.3)	0.30 (37.8)
6.0 µg/kg (n=5)	98.0 (32.3)	1945 (50.5)	58.1 (28.1)	0.36 (44.2)
9.0 µg/kg (n=5)	183 (12.1)	4016 (46.0)	68.0 (56.6)	0.20 (41.0)
12.0 µg/kg (n = 1)	225	4308	86.7	0.20

- 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).
- The average half-life of NKTR-255 is ≥ 10-fold longer than that reported for rhIL-15, 6 with no/minimal accumulation following repeated dosing on a once every three-week dosing regimen.

Preliminary analysis with data cutoff date of March, 2, 2022. Parameters are presented as mean (CV%). 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; CV, coefficient of variation.

NKTR-255 was Well Tolerated as Monotherapy and in Combination With Daratumumab; Most TRAEs were Transient and Resolved Spontaneously or Using Standard Treatment Protocols

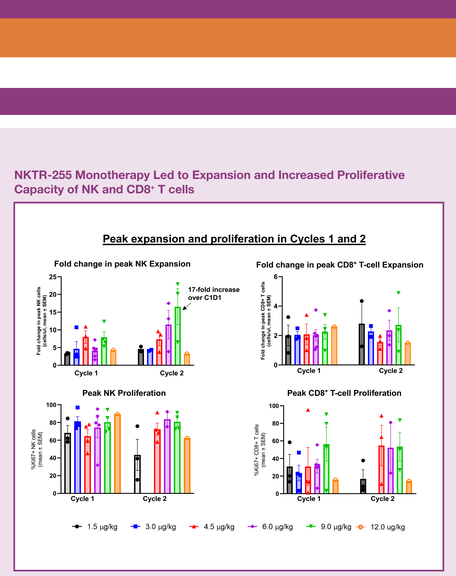
Select TRAEs; n (%)	1.5 µg/kg (n=3)	3 µg/kg (n=4)	4.5 µg/kg (n=4)	6 µg/kg (n=6)	9 µg/kg (n=4)	12 µg/kg (n=1)	4.5 µg/kg + dara (n=3)	9 µg/kg + dara (n=1)	Total (N=26)
Grade 1 or 2 (≥25% of safety population)									
Flu-like symptoms[a]	2 (67)	4 (100)	4 (100)	5 (100)	2 (50)	1 (100)	2 (67)	0	20 (77)
Infusion-related reaction	0	0	3 (75)	3 (50)	2 (50)	1 (100)	1 (33)	1 (100)	11 (42)
Fatigue	0	2 (50)	1 (25)	3 (50)	2 (50)	1 (100)	2 (66)	0	11 (42)
Grade 3 (≥5% of safety population)									
Neutropenia[a]	0	1 (25)	1 (25)	0)	1 (25)	1 (100)	0	0	4 (18)
Anemia	0	0	0	1 (17)	1 (25)	0	0	0	2 (8)
Thrombocytopenia	0	0	0	1 (17)	1 (25)	0	0	0	2 (8)
Lymphopenia[c]	0	1 (25)	0	0	0	1 (100)	0	0	2 (8)
Grade 4 (all)									
Lymphopenia[c]	0	0	0	2 (50)	2 (33)	1 (25)	0	0	5 (19)

Clinical cutoff: October 20, 2022; During the first cycle, patients were not allowed to receive pre-medications (antipyretic/antihistamines). A patient is only counted once within each preferred term or grouped term, using highest toxicity grade. [a]Group term includes body temperature increase, chills, headache, myalgia, hyperhidrosis, hyperpyrexia, influenza like illness, nausea, and pyrexia; [c]Group term includes neutropenia, leukopenia and white blood cell count decrease. [c]Group term includes lymphopenia and lymphocyte count decrease.

- 12 (46%) patients experienced serious TEAEs, of which 8 (31%) were NKTR-255 related. Serious TEAEs that occurred in 2 or more patients are IRR (Grade 1-2, n=5), CRS (Grade 1, n=2)
- Grade ≥3 lymphopenia occurred in 27% (7/26) of patients receiving NKTR-255. The median time to baseline recovery for these lymphopenia events was 3 days (range: 2 to 9 days).
- No ADAs detected in 54 samples collected from 17 subjects treated with NKTR-255 monotherapy for up to 8 cycles over the dose range of 1.5 to 9 µg/kg.

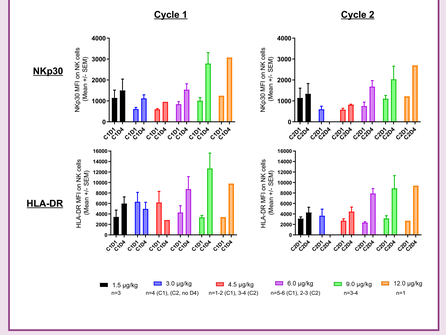
Clinical cutoff: October 20, 2022; During the first cycle, patients were not allowed to receive pre-medications (antipyretic/antihistamines). A patient is only counted once within each preferred term or grouped term, using highest toxicity grade. [a]Group term includes body temperature increase, chills, headache, myalgia, hyperhidrosis, hyperpyrexia, influenza like illness, nausea, and pyrexia; [c]Group term includes neutropenia, leukopenia and white blood cell count decrease. [c]Group term includes lymphopenia and lymphocyte count decrease.

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



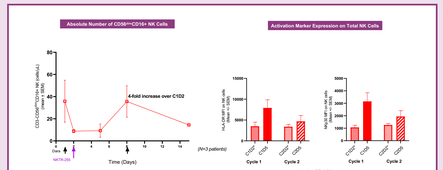
Fold change in cell numbers calculated from C1D1/predose; peak response of cellular expansion at D8-D10 of each cycle. Peak proliferative response at D4 for most patients; no Ki67 data available for 3.0 µg/kg patients in C2.

NKTR-255 Monotherapy Increases Activation Markers on NK cells



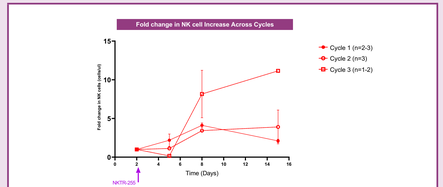
NKp30 is key activation marker linked to enhancement of NK cell cytotoxicity and cytokine secretion. HLA-DR is functional marker and increases lead to greater functional activity (enhanced degranulation and cytokine secretion) in NK cells.

Absolute Number of CD16$^+$ NK cells and NK Activation Markers Increased in Response to 4.5 µg/kg NKTR-255 After Administration of Daratumumab



Daratumumab administered weekly (Weeks 1–8), q2w (Weeks 9–24); q4w (Week 25+); NKTR-255 in Cycles 1–3 is administered on Day 2 of the cycle and on Day 1 Cycle 4+.

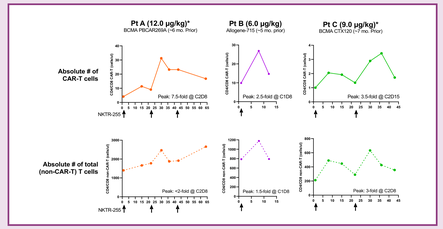
Absolute Number of NK cells rescued with NKTR-255 After Daratumumab Administration Over Multiple Cycles in Patients with ≥5 Prior lines of Treatment



- NK cell expansion was maintained in subsequent cycles of treatment with NKTR-255.
- All of the patients receiving combination therapy showed disease stabilization.

Fold change calculated from day of NKTR-255 administration for each cycle (CxD2).

Allo-Reactivity to CAR-T Cells was Not Induced With NKTR-255 Monotherapy Treatment Amongst Patients Previously Treated with Off-the-Shelf Allogeneic CAR-T Cells



*Continued expansion of CAR-T cell numbers with repeat administration of NKTR-255 (Pts A & C).

CASE VIGNETTE

Stable Disease (per IMWG) in Patient Dosed with NKTR-255 4.5 µg/kg and Daratumumab: Treatment Ongoing for 7+ months

70 year-old, male

Initial MM diagnosis: Apr-2012, MM IgG kappa light chain disease

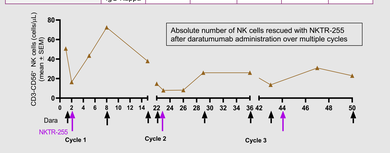
Prior treatment [best overall response]:

1. RVd (lenalidomide, bortezomib, and dexamethasone; Jun-2012 to Aug-2012, plus lenalidomide maintenance [Feb-2013 to Mar-2015]) [CR]
2. Pom-dex (pomalidomide and dexamethasone; May-2016 to Jul-2017) [SD]
3. DVd (daratumumab, bortezomib, and dexamethasone; Jul-2017 to Sep-2018) [PR]
4. Belantamab Mafodotin (Dec-2018 to Sep-2020) [PD]
5. BMCA CAR-T (clinical trial Jan 2021) [CR]

Current treatment:

NKTR-255 4.5 µg/kg + dara for 7+ months; first dose 07-Apr-2022

	Baseline (Mar-2022)	Cycle 2 (Apr-2022)	Cycle 3 (May-2022)	Cycle 4 (Jul-2022)	Cycle 5 (Aug-2022)	Cycle 6 (Sep-2022)
Kappa/Lambda chain ratio	28.6	83.5	-	63.8	93.2	89.9
Kappa (mg/L)	28.9	19.2	17.2	18.5	27.0	25.2
Lambda (mg/L)	1.01	0.2	-	0.3	0.3	0.3
M protein (g/dL)	0.7	0.7	0.5	0.6	0.7	0.7
Urine Immunofixation	Positive IgG Kappa	Positive	Positive	Positive	Positive	Positive



Achieved disease stabilization with NKTR-255 + dara following relapse from prior BCMA CAR-T IgG, immunoglobulin G; IMWG, International Myeloma Working Group; MM, multiple myeloma; PR, partial response; SD, stable disease.

CONCLUSIONS

- NKTR-255 was well tolerated in heavily pre-treated patients with hematologic malignancies (NHL and MM) in doses up to 12 mcg/kg and in combination with dara in doses up to 9 mcg/kg (in MM). The majority of TRAEs were low-grade, transient, and easily managed. The MTD was not reached.
- No new safety signals or overlapping toxicities were observed with the doublet and dose escalation is ongoing.
- Early evidence of clinical activity was observed in this heavily pre-treated and highly refractory patient population with the doublet (NKTR-255 + dara).
- Peak fold-changes of ~17-fold NK cell and ~2-fold in CD8$^+$ T cell expansion were observed in the first 2 cycles with NKTR-255 monotherapy doses up to 12 µg/kg. Sustained proliferative ability of NK and CD8$^+$ T cells across multiple cycles indicated no evidence of tachyphylaxis.
- Preliminary data from patients previously treated with off-the-shelf allogenic CAR-T cells indicates that allo-CAR-T cells persisted with NKTR-255 monotherapy, **suggesting no alloreactivity to off-the-shelf allo-CAR-T cells.**
- With combination therapy, NK cell rescue was observed with sustained increases in NK and CD8$^+$ T cells despite daratumumab's on-target depletion of CD38 expressing NK cells.
- Based on these findings, Nektar is conducting a Phase 2/3 study in combination with commercially approved CAR-T cells in LBCL/NHL to potentially enhance responses and durability of cellular therapies.

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.

DISCLOSURES

The presenting author, Krina Patel, has had the following relationships within the last 24 months: Legend, Pfizer, Celgene, Merck, Poseida, PrecisionBi, Arcellx, Caribou, Nektar, Oncopeptides: Consultancy.

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; 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; IV, intravenous; 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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