Poster 355

First-in-human Phase I Study of NKTR-255 in Patients With Relapsed/Refractory Hematologic Malignancies

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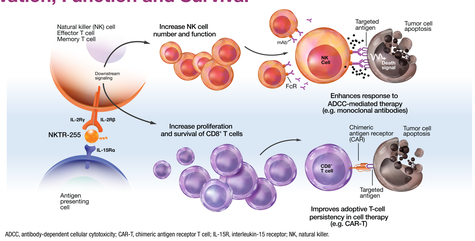
BACKGROUND

NKTR-255 Engages With IL-15Rα/IL-2Rβγ Receptor Complex to Boost NK Cell Number and CD8⁺ T cell Expansion, Proliferation, Activation, Function and Survival

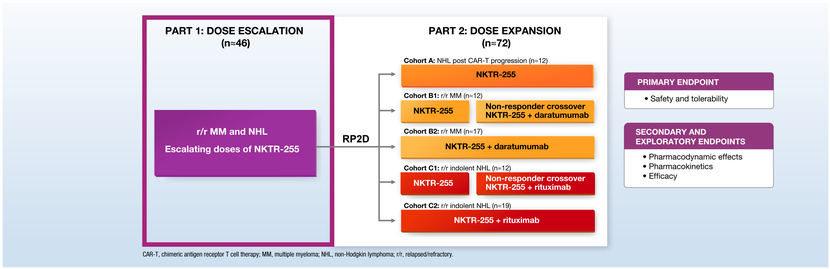
- There is an unmet need for novel agents that can boost natural killer (NK) cell number and function with the aim to aid current approved therapies for multiple myeloma (MM) and non-Hodgkin lymphoma (NHL).
- NKTR-255 is a polymer-conjugated recombinant human IL-15 (rhIL-15) agonist, which provides sustained pharmacodynamic (PD) responses without the need for daily dosing.[1,2]
- This Phase 1 study (NCT04136756) 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, pharmacokinetics (PK), and biomarkers of the dose-escalation portion.**



ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T cell; IL-15R, interleukin-15 receptor; NK, natural killer.

STUDY DESIGN AND PATIENTS

Phase 1, Open-Label, Multicenter Dose-Escalation and Dose-Expansion Study in Patients With R/R MM or NHL



CAR-T, chimeric antigen receptor T cell therapy; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; r/r, relapsed/refractory.

- Patients with relapsed or refractory (r/r) MM or NHL, who had exhausted all available therapeutic options, were eligible for the dose-escalation portion of this study.
- For dose-escalation, successive cohorts of three patients each received escalating doses of NKTR-255 monotherapy to determine the maximum tolerated dose (MTD).
  - Following the first dose, patients were observed for a 3-week dose-limiting toxicity (DLT) window.
  - 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 six patients have been evaluated at a dose and the posterior probability of targeted toxicity is at least 50% for that dose.
- Interim cutoff July 6, 2020 presented.

RESULTS

1. NKTR-255 Was Well Tolerated With No DLTs or Serious AEs (Safety Data During the DLT Period Only)

- As of July 6, 2020, 4 patients aged 59–66 years were enrolled:
  - NKTR-255 1.5 µg/kg
    - Male MM patient (n=1)
    - Female NHL patient (n=1)
    - Male NHL patient (n=1)
  - NKTR-255 3.0 µg/kg
    - Male MM patient (n=1)
- NKTR-255 was well tolerated.
- No serious TRAE, no delayed DLT, and no dose modifications during the DLT period.

Number of AEs, n (%)[a]	NKTR-255 1.5 µg/kg (n=3)	NKTR-255 3.0 µg/kg (n=1)
Patients reporting ≥1 TRAE	3 (100.0)	1 (100.0)
Grade 1/2 TRAE		
Flu-like symptoms[b]	1 (33.3)	1 (100.0)
Headache	0	1 (100.0)
Hypercalcemia	0	1 (100.0)
Hypotension	0	1 (100.0)
Liver function test	0	1 (100.0)
Muscle tightness	1 (33.3)	0
Myalgia	1 (33.3)	0
Platelet count decreased	0	1 (100.0)
Grade 3 TRAE		
Flu-like symptoms[c]	1 (33.3)	0
Lymphocyte count decreased	0	1 (100.0)
White blood cell count decreased	0	1 (100.0)
Patients with AEs leading to discontinuation	0	0

Data cutoff: July 6, 2020. [a]Worst toxicity grades are summarized. [b]Grade 1/2 flu-like symptoms comprise influenza like illness (1 patient: worst Grade 1 [n=1]), pyrexia (2 patients: worst Grade 1 [n=2]), and chills (2 patients: worst Grade 1 [n=1], Grade 2 [n=1]). [c]Grade 3 flu-like symptoms comprise Grade 3 pyrexia (n=1), which resolved <24 hours with over-the-counter medications.

AE, adverse event; DLT, dose-limiting toxicity; TRAE, treatment-related adverse event.

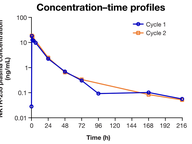
2. NKTR-255 1.5 µg/kg Exhibited a Long Half-life With No Accumulation After Every 21-day Dosing

Preliminary PK analyses

Cycle	N	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng•hr/mL)	$T_{1/2}$ (hr)
1	3	18.1 (46)	212 (69)	27 (10)
2	2	19.8 (26)	250 (39)	27 (67)

PK parameters: Mean (coefficient of variance %).
All pre-dose NKTR-255 concentrations at Cycle 2+ were below the lower limit of quantification of 0.05 ng/mL.

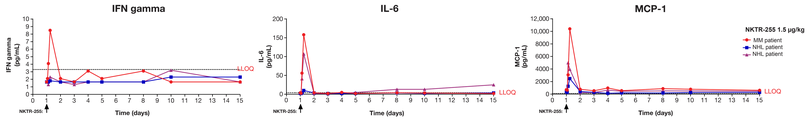
Concentration–time profiles



- Mean plasma NKTR-255 1.5 µg/kg concentration–time profiles were superimposable for cycles 1 and 2.
- Mean half-life of NKTR-255 was 27 hours, which is over 10-fold longer than that reported for rhIL-15 IV dose,[3] with no accumulation following repeat dosing.

Data cutoff: July 6, 2020.
Validated bioassay method was used to measure plasma concentration of NKTR-255, which was expressed in IL-15 content. AUC, area under the curve; C_{max}, peak concentration; PK, pharmacokinetic; $T_{1/2}$, half life.

3. Transient Upregulation and Rapid Decline of Cytokines to Baseline Levels by Day 2 With No Further Increases

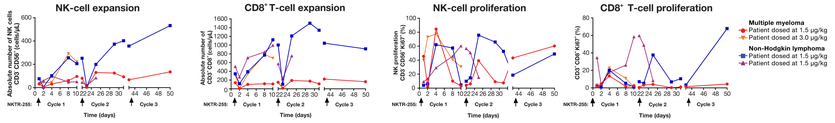


Values below LLOQ are approximate but calculated based on standard control curve.

IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

- NKTR-255-dependent changes in inflammatory cytokines were transient, supporting the safety of NKTR-255.
- No further changes observed after Day 15.

4. NKTR-255 Increased Total Expansion and Proliferative Capacity (Ki67⁺) of NK and CD8⁺ T Cells in Blood, Peaking Around Days 8–10 Per Cycle

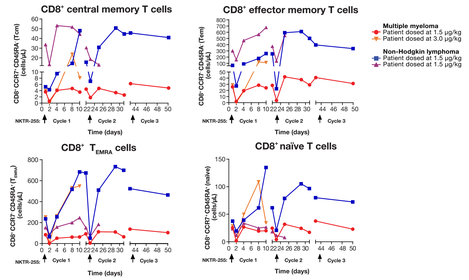


NK, natural killer.

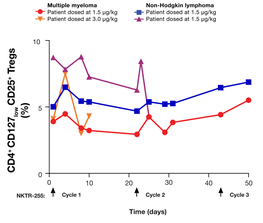
- NKTR-255 1.5 µg/kg expanded NK cells by ~5-fold and CD8⁺ T cells by ~3-fold.
- Proliferative capacity (Ki67⁺) was maintained across multiple cycles of NKTR-255 1.5 µg/kg.
- NKTR-255 3 µg/kg increased NK cell numbers in cycle 1 by ~10-fold in the heavily pretreated patient with MM.
- Differences in 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.

5. NKTR-255 Increased Memory and Naïve CD8⁺ T cell Subpopulations

- NKTR-255 induced CD8⁺ memory T cell expansion in all patients, including a >9-fold increase in one patient receiving NKTR-255 1.5 µg/kg.



6. No Meaningful Changes Were Observed in CD4⁺ Tregs With NKTR-255 Treatment*



*Day 2 timepoint data for cycle 1 and 2 are artifacts of gating and so were removed from the plot.

Clinical Vignette: First Patient Enrolled in the NKTR-255 1.5 µg/kg Cohort (Stable Disease per IMWG)

63-year-old male

ECOG PS = 1; diagnosed with MM (IgG Kappa, with positive +5 and del 13) in August 2017, transplant ineligible

Presented with pancytopenia at initial diagnosis

Prior treatment:
1. RVD (lenalidomide, bortezomib, and dexamethasone)
2. DRD (daratumumab, lenalidomide, and dexamethasone)
3. KD (carfilzomib and dexamethasone)

Current treatment:
4. NKTR-255 1.5 µg/kg
   Baseline: October 2019

- Patient received NKTR-255 as monotherapy at 1.5 µg/kg IV for 9 cycles.

	Baseline (Oct 2019)	Cycle 3 (Dec 2019)	Cycle 7 (Feb 2020)	Cycle 9 (Apr 2020)
K/L chain ratio	638	632	128	554
Lambda/L	2.08	<2.0	5.44	6.0
Kappa K	1328	1265	693	2223
M Protein	1.9	1.9	2.1	2.0
IgG	1340	1757	1928	2004
Bone marrow	44% CD138⁺ core	NA	30% CD138⁺ core	40% CD138⁺ core
Bone marrow FACS	NA	NA	13–17%	6%

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMWG, International Myeloma Working Group; MM, multiple myeloma; NA, not available.

Infusion (Baseline: October 2019)
4–5 hours post-infusion

- Mild rigors (Grade 1) and flu-like symptoms (Grade 1), which were treated with acetaminophen and resolved by Day 2.
  - Reproducible pattern was observed in Cycle 2, 3 and 4
- Neutropenia (Grade 3) and low platelet counts (Grade 3) related to study drug – required stimulating factors and platelet transfusion in order to schedule bone marrow biopsy.

Treatment-related AEs during the DLT period (November 2019)

	NKTR-255 (1.5 µg/kg) MM patient
Grade 1 flu-like symptoms (fever and rigors)	Resolved
Grade 1 muscle aches	Resolved

AEs, adverse events; DLT, dose-limiting toxicity; MM, multiple myeloma.

CONCLUSIONS

- NKTR-255 was well tolerated with low-grade, cytokine-related AEs that were transient and easily managed.
  - No DLTs were observed.
  - No drug-related AEs led to treatment discontinuation, dose delay or dose modification.
- NKTR-255 exhibited a long half-life with no evidence of accumulation.
- NKTR-255 was biologically active and demonstrated consistent expansion of lymphocytes, with durable and sustained increases in NK and CD8⁺ T cells in this highly refractory population of patients with MM and NHL.
- These data support continued dose escalation of NKTR-255, and subsequent evaluation in combination with other anticancer agents.

REFERENCES
1. Miyazaki T, *et al*. Poster presented at ASH 2018; poster 2952.
2. Miyazaki T, *et al*. Poster presented at AACR 2019; poster 3265.
3. Conlon KC, *et al*. *J Clin Oncol*. 2015;33:74–82

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DISCLOSURES
The presenting author, Nina Shah, has the following relationships related to this presentation: held a consulting or advisory role for Amgen, Genentech, GSK, Indapta Therapeutics, Karyopharm, Nektar Therapeutics, Oncopeptides, Precision Biosciences, Sanofi, Seattle Genetics, and Surface Oncology; received research funding from Bluebird Bio, Celgene, Janssen, and Sutro Biopharma; and is a shareholder of Indapta Therapeutics.

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