A Phase 1, open-label, multi-center, dose-escalation and dose-expansion study of NKTR-255 as a single agent in relapsed or refractory hematologic malignancies and in combination with daratumumab as a salvage regimen for multiple myeloma

Abstract: 4459

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BACKGROUND

- Natural killer (NK) cells are effector cells of the innate immune system, with a critical role in immunosurveillance against malignancy, including multiple myeloma (MM) and non-Hodgkin lymphoma (NHL).
- In MM, NK cell-mediated immunity is impaired, especially in advanced disease.[1]
  - NK cell-mediated cytotoxicity is important for the antitumor action of approved monoclonal antibodies (mAb) for MM, including the anti-CD38 mAb daratumumab.[1]
- In NHL, low peripheral blood NK cell counts have been associated with poor clinical outcome of patients receiving anti-CD20-based immunochemotherapy (e.g. rituximab).[2,3]
- There is an unmet need for novel agents that can boost NK cell number and function with the purpose of aiding current approved therapies for MM and NHL.

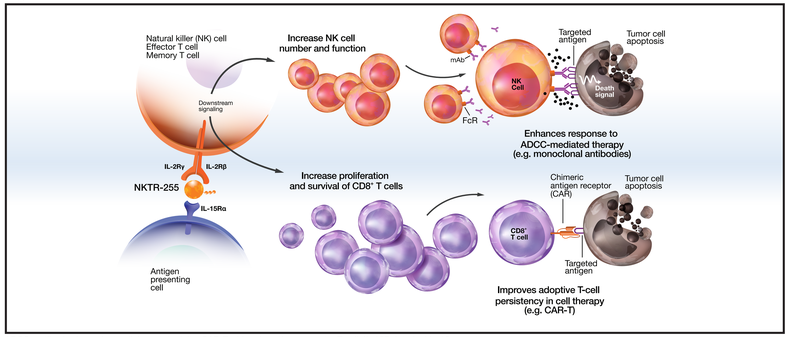
IL-15

- IL-15 is a cytokine that preferentially stimulates the proliferation and cytotoxic functions of NK cells and memory $CD8^+$ T cells leading to enhanced antitumor responses.[4]
  - While initially showing promise for cancer therapy, the efficacy of native IL-15 is limited by its short *in vivo* half-life.[4]

NKTR-255

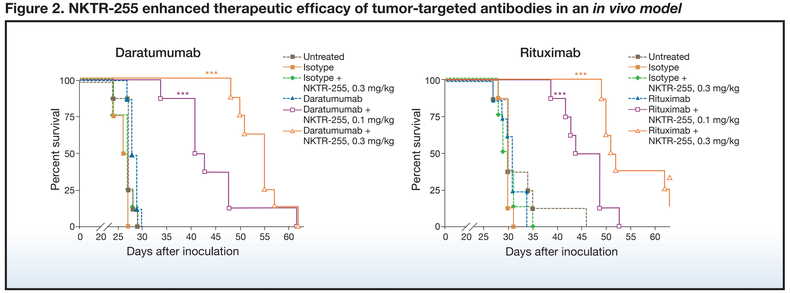
- NKTR-255 is an investigational immunotherapeutic drug. It consists of polymer conjugated IL-15 that exhibits improved pharmacokinetics vs unconjugated IL-15, thereby providing sustained pharmacodynamic responses without the need for daily dosing.[5]
- NKTR-255 engages with IL-15Rα/IL-2Rβγ receptor complex to boost NK number and function, and increase proliferation and survival of $CD8^+$ T cells **(Figure 1)**.
  - In a preclinical study, NKTR-255 enhanced NK cell function and synergized with daratumumab to enhance ADCC of a MM cell line.[6]
  - Furthermore, in a model of Daudi B-cell lymphoma, mice treated with NKTR-255 in combination with either rituximab or daratumumab showed extended survival compared with either drug as a single agent **(Figure 2)**.[6]
  - NKTR-255 increased the accumulation and persistence of CAR-T in the bone marrow of rats *in vivo*, resulting in decreased tumor burden and increased survival vs CAR-T alone.[7]
- In this Phase 1 dose-escalation and dose-expansion study we will evaluate the safety and tolerability of NKTR-255 both as a single agent and in combination with daratumumab in patients rel/ref MM or NHL.

Figure 1. Mechanism of action of NKTR-255



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

Figure 2. NKTR-255 enhanced therapeutic efficacy of tumor-targeted antibodies in an *in vivo model*



SCID mice (n=8/group) inoculated intravenously with Daudi cells were treated with a single dose of daratumumab (0.5 mg/kg, 14 days after inoculation) or two doses of rituximab (40 mg/kg, 14 and 17 days after inoculation) and three doses of NKTR-255 (14, 21 and 28 days after tumor inoculation). The survival endpoint was measured by hind limb paralysis onset and body condition. *** NKTR-255 combination with rituximab or daratumumab significantly increases median survival compared with single-agent treatments ($p<0.05$, Log-Rank test).

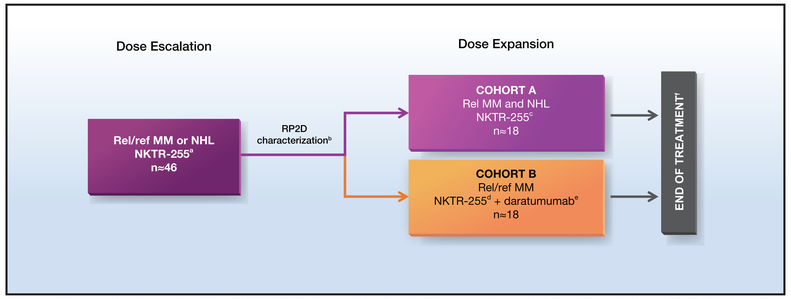
Miyazaki T, et al. Cancer Research 2019; 79:3265 (Suppl).

STUDY

Design

- This is a Phase 1, open-label, multi-center, dose-escalation and dose-expansion study in patients with rel/ref MM or NHL **(Figure 3)**.
- In the dose-escalation portion, successive cohorts of three patients each will receive single escalating doses of NKTR-255 until the MTD is determined.
  - Patients to be observed for a 3-week DLT window following the first NKTR-255 dose.
  - A two-parameter Bayesian logistic regression model employing the escalation with overdose control principle[8] will be used for dose level selection and for determination of the MTD.
  - The MTD of NKTR-255 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.
- In the dose-expansion portion, patients will be treated with NKTR-255 at the RP2D in two expansion cohorts (A and B):
  - Cohort A will expand NKTR-255 monotherapy in patients with relapsed MM or NHL as a salvage regimen
  - Cohort B will combine NKTR-255 with daratumumab in patients with MM with progressive disease who have had at least three prior lines of treatment.

Figure 3. Study design



[a]Starting dose of 1.5 µg/kg, administered intravenously every 21 days. [b]The RP2D of NKTR-255 will be chosen at a dose not exceeding the final recommendation from dose escalation and will be based upon review of all available data on pharmacokinetics, pharmacodynamics, and the clinical and biologic effects of NKTR-255. [c]RP2D of NKTR-255 as a single agent every 21 days until disease progression. [d]RP2D starting on Cycle 1 Day 1. Each cycle is every 21 days. [e]Intravenous daratumumab 16 mg/kg will be administered weekly starting on Cycle 1 Day 8 for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter. [f]Patients will be treated until confirmed disease progression, intolerable toxicity, symptomatic deterioration, achievement of maximal response, loss to follow-up, patient withdrawal of consent, physician's decision, or death (treatment may continue beyond progression if there is clinical benefit as determined by the investigator). MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ref, refractory; rel, relapsed; RP2D, recommended Phase 2 dose.

Assessments

- Safety assessments will include the incidence of adverse events, clinical laboratory tests, vital signs, physical examinations, ECGs and cardiac function tests.
- Blood samples for NKTR-255 and daratumumab pharmacokinetic analysis will be collected from all patients.
- Systemic and tumor tissue-based pharmacodynamic effects of NKTR-255 with and without daratumumab will be examined.
- Efficacy assessments will include:
  - For MM: measurements of myeloma protein in serum and urine, serum calcium corrected for albumin, β2-microglobulin and albumin, bone marrow examination, skeletal survey and documentation of extramedullary plasmacytomas
  - For NHL: FDG-PET every 3 months.

Objectives

Primary objectives

- Part 1 (dose escalation):
  - Evaluate the safety, tolerability, MTD and RP2D of NKTR-255 as a single agent.
- Part 2 (dose expansion):
  - Evaluate the safety and tolerability of NKTR-255 in patients with relapsed MM or NHL.
  - Evaluate the safety and tolerability of NKTR-255 in combination with daratumumab in patients with rel/ref MM.

Secondary objectives

- Characterize the phamacodynamic effects and change from baseline in immune cell populations, tumor cells, cytokine levels, and changes in gene expression after NKTR-255 monotherapy.
- Characterize the pharmacokinetics of NKTR-255.

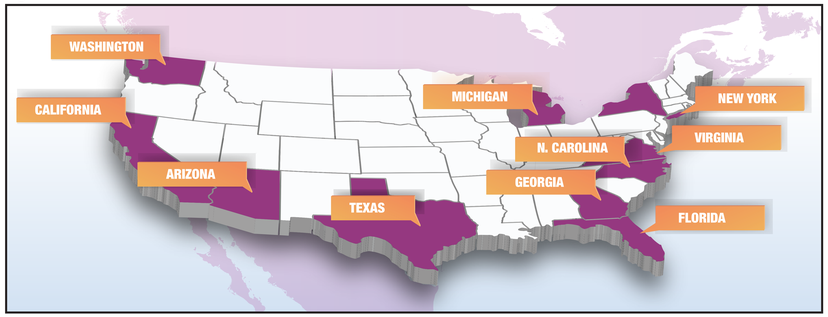
Selected exploratory objectives

- Evaluate the efficacy of NKTR-255 in combination with daratumumab in rel/ref MM by assessing the rate of minimal residual disease prior to progressive disease and complete response by IMWG criteria.
- Evaluate the efficacy of NKTR-255 in NHL by assessing the complete response rate and duration of response based on the Lugano classification.[9]
- Characterize levels of genetically modified cells in patients who have previously received treatment with CD19 CAR-T for NHL or BCMA CAR-T for MM.

Status

- Dose escalation is ongoing with two patients treated.
- The study is currently enrolling in the United States **(Figure 4)**.
- For participating trial sites, please visit https://clinicaltrials.gov, and search NCT04136756.

Figure 4. Location of clinical trial sites within the United States



Eligibility criteria (all tumor types)

Key inclusion criteria

- Rel/ref MM or NHL with no available therapies that would confer clinical benefit for their primary disease and meets disease-specific criteria (see right).
- Documented evidence of progressive disease as defined by the IMWG criteria (for MM) or the Lugano criteria (for NHL) on or after their last regimen.[9]
- ECOG performance status of ≤2.
- Prior CD19 CAR-T for NHL, or BCMA CAR-T or anti-CD38 therapies for MM, are eligible after confirmation of relapse of the primary disease.
- Previous response (partial response or better) to at least one prior regimen.
- Life expectancy of >3 months with treatment.
- Adequate organ and bone marrow function.

Key exclusion criteria

- Active, known, or suspected autoimmune disease.
- Prior daratumumab or other anti-CD38 therapies within 6 months of initiating study drug(s).
- Prior IL-2 or IL-15 therapy.

Eligibility criteria (by disease)

Multiple myeloma

- Measurable rel/ref MM as defined by the IMWG criteria following treatment with at least three lines of therapy with no other available treatment that would confer benefit.
- Progression on, or within 60 days of completion of the last therapy and measurable disease within at least one of the following:
  - Serum M-protein level ≥ 0.5 g/dL
  - Urine M-protein level ≥ 200 mg/24 hours
  - Serum FLC assay: involved FLC level ≥ 0.5 g/dL and an abnormal serum FLC ratio (< 0.26 or > 1.65)
  - Biopsy proven plasmacytoma (measured within 28 days of screening).

Non-Hodgkin lymphoma

- Histologically confirmed CD19/CD20-positive NHL (including large B-cell lymphoma, high grade B-cell lymphoma, PMBCL, or DLBCL, arising from follicular lymphoma) confirmed by archived tumor biopsy tissue from last relapse and corresponding pathology report.
- Measurable or detectable disease according to the Lugano classification.
  - Extranodal disease that is measurable by FDG-PET imaging only will also be allowed.[10]

ABBREVIATIONS

ADCC: antibody-dependent cellular cytotoxicity **BCMA:** B-cell maturation antigen **CAR-T:** chimeric antigen receptor T-cell **DLBCL:** diffuse large B-cell lymphoma **DLT:** dose-limiting toxicity **ECG:** electrocardiogram **ECOG:** Eastern Cooperative Oncology Group **FDG-PET:** fluorodeoxyglucose-positron emission tomography **FLC:** free light chain **IL:** interleukin **IMWG:** International Myeloma Working Group **IV:** intravenous **MM:** multiple myeloma **MTD:** maximum tolerated dose **NK:** natural killer **NHL:** non-Hodgkin lymphoma **PMBCL:** primary mediastinal large B-cell lymphoma **POEMS:** polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes **Rel/ref:** relapsed or refractory **RP2D:** recommended phase 2 dose

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DISCLOSURES

N Shah has served on advisory boards for Amgen, Genentech, GSK, Indapta Therapeutics, Karyopharm, Nektar Therapeutics, Oncopeptides, Precision Biosciences, Sanofi, Seattle Genetics, and Surface Oncology; has received research funding from Bluebird Bio, Celgene, Janssen, and Sutro Biopharma; and is a shareholder of Indapta Therapeutics. **C Turtle** has served on advisory boards for Allogene, Caribou Biosciences, Eureka Therapeutics, Humanigen, Kite/Gilead, Nektar Therapeutics, Novartis, Precision Biosciences, and T-CURX; has received research funding and/or royalties from Juno Therapeutics and Nektar Therapeutics; and is a shareholder of Caribou Biosciences, Eureka Therapeutics, and Precision Biosciences. **A Cowan** has received consultancy fees and/or research funding from AbbVie, Celgene, Cellectar Biosciences, and Janssen. **J Chavez** has served on advisory boards and/or speakers' bureau for Bayer, Celgene, Genentech, Karyopharm, Kite, and Novartis. **E Budde** has received consultancy fees from AstraZeneca, Genentech, and Gilead; and research funding from Amgen and Merck. **A Tan** has no relevant relationships to disclose. **AM Marcondes, Z Lee, W Lin, J Zalevsky,** and **M Tagliferri** are employees and/or shareholders of Nektar Therapeutics. **K Patel** has received consultancy fees and/or research funding from AbbVie, BMS, Celgene, Cellectis, Janssen, Nektar Therapeutics, Oncopeptides, Poseida Therapeutics, Precision Biosciences, and Takeda.

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