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

Nina Shah1, Cameron J. Turtle2, Andrew J. Cowan1, Julio C. Chavez2, Lihua E. Budde3, Alan Tan4, Mario Q. Marcondes5, Zachary Lee6, Wei Lin7, Jonathan Zalesky2, Mary Tagliaferri8, Krina K. Patel4
1University of California, San Francisco, San Francisco, CA; 2Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 3Division of Medical Oncology, University of Washington, Seattle, WA; 4Lee Moffitt Cancer Center and Research Institute, Tampa, FL; 5City of Hope Comprehensive Cancer Center, Duarte, CA; 6University of Arizona College of Medicine – Phoenix, Cancer Treatment Centers of America, Goodyear, AZ; 7Nektar Therapeutics, San Francisco, CA; 8Department of Lymphoma and Myeloma, The University of Texas M.D. Anderson Cancer Center, Houston, TX

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BACKGROUND

• Natural killer (NK) cells are effectors 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 immune response is impaired, especially in advanced disease.

• NK cell-mediated cytotoxicity is important for the antitumor action of approved monoclonal antibodies (mAbs) for MM, including the anti-CD38 mAb daratumumab.

• In NHL, low peripheral blood NK cell counts have been associated with poor clinical outcome of patients receiving anti-CD20-based immunotherapy (e.g. rituximab).

• 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.

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 of frequent dosing.

• NKTR-255 engages with IL-15Rα expressed by NK cells, T cells, and tumor cells.

• NKTR-255 enhances NK cell function and synergizes with daratumumab to enhance ADCOC of a MM cell line.

• 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.

• 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.

• In this Phase 1 dose-escalation and dose-expansion study, NKTR-255 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. Patients will be treated until confirmed disease progression, intolerable toxicity, symptomatic deterioration, achievement of a complete response, or death.

• Dose escalation is ongoing with two patients treated.

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 relapsed MM.

Secondary objectives:

• Characterize the pharmacokinetic effects and changes in baseline in immune cell populations, tumor cells, cytokine levels, and changes in gene expression after NKTR-255 monotherapy and NKTR-255-mobility.

• Characterize the pharmacokinetics of NKTR-255.

Selected exploratory objectives:

• Evaluate the efficacy of NKTR-255 in combination with daratumumab in rel/rel MM by assessing the rate of minimal residual disease below the limit of detection on next-generation sequencing.

• Evaluate the efficacy of NKTR-255 as a single agent 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.

Eligibility criteria (by disease type)

MM:

• Relapsed or refractory MM (MM) as defined by the IWG criteria following treatment with at least three prior lines of therapy with no prior exposure to daratumumab that would confer benefit.

• Progression on, or within 60 days of completion of the last therapy and measurable disease at one of the relapse criteria (low risk).

NHL:

• Documented evidence of progressive disease as defined by the IWG criteria for MM or the Lugano criteria (for NHL) on or after their last regimen.9

• ECOG performance status of 1/2.

• Prior CD19 CAR-T for NHL or BCMA CAR-T or anti-CD38 therapies for MM are eligible after confirmation of relapse and/or progression of the primary disease.

• Bone marrow involvement with/without extramedullary involvement.

• Adequate organ and bone marrow function.

Eligibility criteria (all tumor types)

• Previous response (partial response or better) to at least one prior line of therapy for the primary disease.

• Availability of an adequate number of tumor cells (minimum of at least 1010 cells).

• Adequate organ and bone marrow function.

• Adequate hepatic function.

• Adequate renal function.

• Adequate end-organ function.

Key exclusion criteria

• Active, known, or suspected autoimmune disease.

• Prior chemotherapy, radiation therapy, or biologic therapy within 6 months of initiating study drug(s).

• Prior CAR-T therapy.

• Prior   120 days of screening.

• Prior intravenous immunoglobulin therapy within 28 days of screening.

Non-Hodgkin lymphomas:

• Histologically confirmed CD19/CD20-positive NHL including large B-cell lymphoma, high grade B-cell lymphoma, PDLC, or DLBCL, arising from follicular lymphoma, B-cell lymphoma, or marginal zone lymphoma.

• Eligibility criteria from last relapse and corresponding pathologist reporting.

• Measurable or detectable disease according to the Lugano classification.

• Extramedullary disease that is measurable by FDG-PET imaging only will also be allowed.10

DISCLOSURES

The phase 1 clinical trial of NKTR-255 is registered with ClinicalTrials.gov NCT03413576.

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