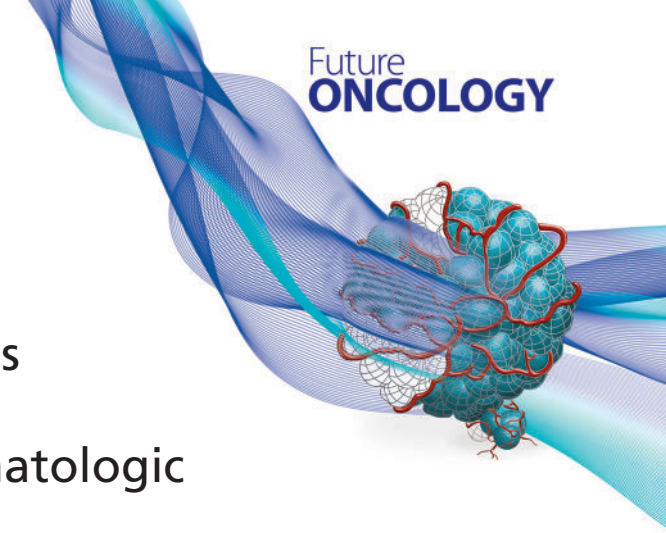
Clinical Trial Protocol

For reprint orders, please contact: reprints@futuremedicine.com



Phase I study protocol: NKTR-255 as monotherapy or combined with daratumumab or rituximab in hematologic malignancies

Nina Shah*[,1], Miguel-Angel Perales[2], Cameron J Turtle[3,4], Mitchell S Cairo[5], Andrew J Cowan[3,4], Hayder Saeed[6], Lihua E Budde[7], Alan Tan[8], Zachary Lee[9], Kazuharu Kai[9], Mario Q Marcondes[9], Jonathan Zalevsky[10], Mary A Tagliaferri[9] & Krina K Patel[11]

[1]Department of Medicine University of California San Francisco, San Francisco, CA 94158, USA
[2]Department of Medical Oncology, Memorial Sloan Kettering Cancer Centre, New York, NY 10065, USA
[3]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[4]Division of Medical Oncology, University of Washington, Seattle, WA 98195, USA
[5]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, New York Medical College, Valhalla, NY 10595, USA
[6]Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA
[7]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA
[8]Division of Hematology, Rush University Medical Center, Chicago, IL 60612, USA
[9]Clinical Development, Nektar Therapeutics, San Francisco, CA 94158, USA
[10]Research & Development, Nektar Therapeutics, San Francisco, CA 94158, USA
[11]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
*Author for correspondence: Tel.: +1 415 353 2737; Nina.Shah@ucsf.edu

NKTR-255 is an investigational polyethylene glycol-modified recombinant human IL-15 (rhIL-15) receptor agonist, designed to improve the immunotherapeutic and anti-cancer benefit observed with rhIL-15 while circumventing the toxicities associated with this therapy. In preclinical studies, NKTR-255 has demonstrated enhanced proliferation and function of $CD8^+$ T cells and natural killer cells, as well as enhanced anti-tumor activity and survival both as monotherapy and in combination with monoclonal antibodies in multiple cancer models. Here, we describe the rationale and design of the first-in-human Phase I, dose-escalation and dose-expansion study of NKTR-255 alone and in combination with daratumumab or rituximab in adults with relapsed/refractory multiple myeloma or non-Hodgkin's lymphoma that will determine the maximum tolerated dose and recommended Phase II dose for NKTR-255.

Lay abstract: Interleukin-15 (IL-15) is a protein that helps the body's natural immune system to defend itself against infections and diseases like cancer. This article discusses a clinical trial in patients with multiple myeloma or non-Hodgkin's lymphoma that evaluates a new investigational medicine, NKTR-255, a polymer-modified form of IL-15 that has been engineered to improve its ability to provide a sustained anti-tumor immune response. The trial will explore different doses of NKTR-255 to determine patient side effects and to find the highest acceptable dose that patients can tolerate. Based on this, a dose will be chosen that offers an optimal balance between having a positive anti-cancer effect and minimizing side effects. This dose will be tested further in patients who have had different treatments in the past. If the side effects are acceptable, this dose will be tested in a new trial in a large number of patients.

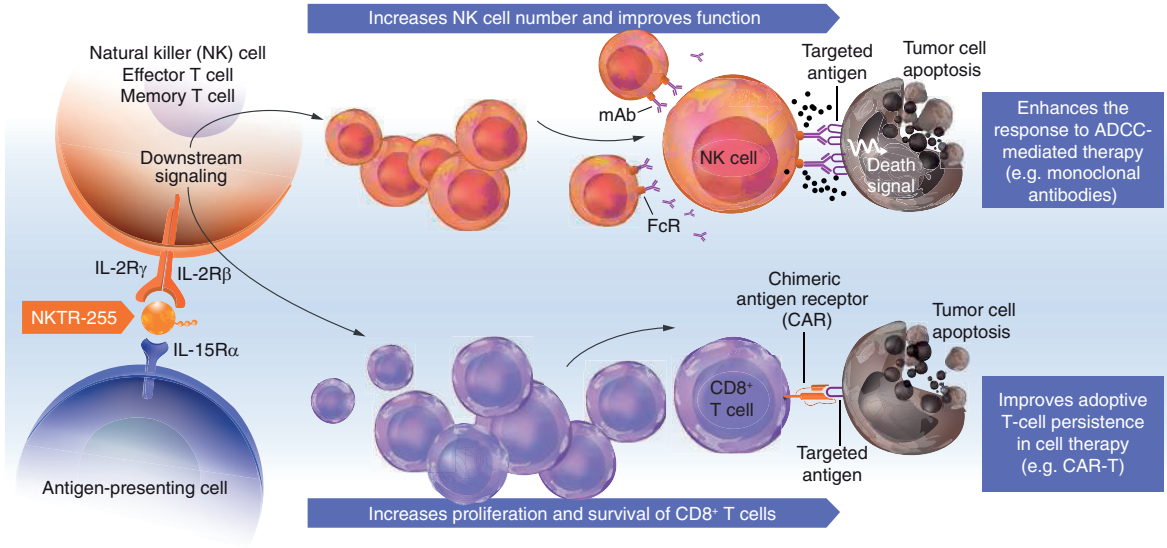
Clinical Trial Registration: NCT04136756 (ClinicalTrials.gov)

First draft submitted: 7 May 2021; Accepted for publication: 2 June 2021; Published online: 22 June 2021

Keywords: daratumumab • IL-15 • multiple myeloma • NKTR-255 • non-Hodgkin lymphoma • rituximab • study protocol

Future Medicine

Graphical abstract:



A first-in-human Phase I, dose-escalation, dose-expansion study will assess the safety and efficacy of NKTR-255 alone and in combination with daratumumab or rituximab in patients with relapsed/refractory hematologic malignancies (NCT04136756)

Natural killer (NK) cells are powerful cytotoxic immune cells that play a vital role in immune surveillance against tumors [1]. NK cell defects have been observed in some hematologic cancers and allow tumors to escape the NK cell tumor surveillance [2]. Mechanisms involved in this escape include a deficiency in NK cell proliferation, increased expression of NK cell inhibitory receptors, impaired NK cell differentiation and impaired NK cell cytokine production [2]. As a result, there is ongoing interest in the immunobiology and clinical significance of reversing NK cell dysfunction using novel immunotherapeutic agents for the treatment of relapsed/refractory hematologic malignancies [3].

Multiple myeloma (MM) is a malignancy characterized by the abnormal growth of plasma cells in the bone marrow [4]. MM is also characterized by immune dysregulation, including reduced proliferation and function of NK cells, especially in advanced disease [5,6]. *In vitro*, NK cells have been shown to detect and destroy MM cells [7]. Therefore, NK cell immunomodulation has been investigated using various therapeutic approaches to enhance NK cell activity [5,6]. Standard treatment options for newly diagnosed patients with MM who are transplant eligible include multiple anti-MM agents, followed by autologous hematopoietic stem cell transplantation, which is usually pre-conditioned by high dose melphalan [8]. Therapies for these patients with MM include immunomodulatory therapies (e.g., lenalidomide), proteasome inhibitors (e.g., bortezomib) and corticosteroids (e.g., dexamethasone) [8]. Despite lenalidomide being among the mainstay of initial therapy for patients with MM, it has a limited stimulatory effect on NK cell activity [7]. Novel immunotherapeutics have recently been developed that induce antibody-dependent cellular cytotoxicity (ADCC) driven by NK cells. Those are the CD38-targeted monoclonal antibody (mAb), daratumumab, and the signaling lymphocytic activation molecule F7 (SLAMF7)-targeting mAb, elotuzumab [9,10]. However, MM eventually becomes resistant or even refractory to these mAbs [9,11,12]. As such, there is an unmet medical need for improved novel immunomodulatory treatments to enhance NK cell function in order to overcome primary or acquired resistance to these mAbs.

In non-Hodgkin lymphoma (NHL), a lack of NK cells and impaired function have been associated with poorer prognosis [13,14]. Lower NK cell count in patients with diffuse large B cell lymphoma (DLBCL) or follicular lymphoma treated with anti-CD20-based (e.g., rituximab) regimens was associated with shorter progression-free survival (PFS) and overall survival (OS) compared with higher NK cell counts [13,14]. Despite treatment advances in the last three decades with combination therapy, a significant fraction of patients with NHL eventually relapse or are refractory from the initial treatment [15]. With NK cells increasingly recognized as important in tumor recognition and elimination, there is an unmet need for novel agents that can boost NK cell number and function in patients with MM and NHL.

Immunotherapy with IL-15

Interleukin-15 (IL-15) is a cytokine that primarily stimulates the proliferation and cytotoxic function of NK cells and $CD8^+$ memory T cells to provide potentially enhanced immune surveillance against malignant cells. It has therefore gained interest as a potential immunotherapeutic agent for enhancing the antitumor response [16], and was ranked as the top potential cancer immunotherapy agent by the National Cancer Institute [17]. Preclinical studies in nonhuman primates have demonstrated the profound effect of IL-15 in maintaining T-cell responses through the expansion of $CD8^+$ memory, $CD4^+$ T and NK cells [18,19], but with minimal increases in regulatory T cells [18]. In preclinical mouse models, DNA encoding IL-15 was shown to increase tumor-specific T-cell responses and was among the most potent adjuvants when combined with anti-tumor DNA vaccines [20]. Furthermore, in a murine tumor model of LA795 adenocarcinoma, treatment with recombinant human IL-15 (rhIL-15) inhibited tumor growth and markedly reduced tumor recurrence and metastases [21]. While the immune effects of rhIL15 observed in preclinical studies were also seen in a single agent Phase I human study that included patients with melanoma and renal cell carcinoma, no objective improvement in disease was observed [22,23]. Preliminary analyses suggested that the lack of response may have been in part due to the poor pharmacokinetic (PK) profile of rhIL-15; even in the two highest dose cohorts, the 24-h mean serum rhIL-15 concentration had fallen by more than one log from the 4-h peak value [23]. Such unfavorable PK, exemplified as a short half-life and rapid clearance from plasma, necessitates a need to administer a high daily dose to achieve functional responses *in vivo* [16,24]; or multiday continuous infusions to achieve optimal activity in the clinical setting [22,23]. In two clinical studies of daily or multi-day rhIL-15 monotherapy in advanced solid tumors [22,23], rhIL-15 was associated with toxicities including lymphopenia, neutropenia and increased aspartate and/or alanine aminotransferase. Interestingly, capillary leak syndrome has not been associated with IL-15 treatment [24], unlike with other cytokine therapy such as IL-2 [25].

NKTR-255

NKTR-255 is an investigational polyethylene glycol-modified rhIL-15 receptor agonist that is in clinical development. The molecule was designed to optimally engage with all known IL-15R-binding interactions, including the IL-15Rα/IL-2Rβγ complex, to achieve extended exposure and sustainable activation of the IL-15 pathway (Figure 1), and thus overcome the challenges of rhIL-15 therapy. Optimal engagement with IL-15 pathway by NKTR-255 is driven by an extended half-life [26] and an IL-15Rα-binding preference [27]. It is anticipated that such optimal engagement can enhance formation of long-term immunologic memory, and lead to antitumor immune responses, without the need for daily dosing.

In vitro, NKTR-255 has been shown to retain IL-15Rα binding, which is important for its immunomodulatory activity [27]. *In vivo*, NKTR-255 induces proliferation and activation of NK cells and $CD8^+$ T-cells, and increased the $CD8^+$:Treg ratio in mice [26]. PK analyses have revealed that NKTR-255 exhibited reduced clearance and a longer effective half-life than IL-15 [28], thus giving rise to the potential for administering lower doses at a reduced dosing frequency. These findings have been confirmed in preclinical studies in cynomolgus monkeys [29]. Furthermore, NKTR-255 can attenuate progression of metastatic disease in a murine model of colon carcinoma (CT-26) [26].

Compared with other engineered forms of IL-15, specifically precomplexed rhIL-15/IL-15Rα cytokines, NKTR-255 demonstrates an enhanced IL-15 signaling profile as well as more persistent expansion of NK cells and prolonged survival in Balb/c mice [30]. Treatments that stimulate the proliferation and function of NK cells have the potential to synergize with tumor-targeting antibody therapies to enhance ADCC. Therefore, studies have been carried out to evaluate whether NKTR-255 can enhance tumor-directed mAb activity in preclinical cancer models, including MM, lymphoma and solid tumors. In an MM cell line, NKTR-255 boosted NK cell proliferation and activation that translated into enhanced daratumumab-mediated *in vitro* ADCC [31]. Furthermore, in a Daudi B-cell lymphoma mouse model, NKTR-255 combined with daratumumab or rituximab prolonged the survival of treated animals compared with single-agent treatment [31]. These observations were extended further in human tumor xenograft models in which NKTR-255 combined with cetuximab induced NK cell expansion and increased functional activation, as well as delayed or inhibited tumor growth [32]. Enhanced efficacy was also observed with NKTR-255 in combination with trastuzumab versus either agent alone [32].

Immunotherapy with CD19 chimeric antigen receptor T cells (CAR-T) can achieve durable responses in some patients with relapse/refractory B-cell malignancies but disease progression and loss of CAR-T-cell persistence remains a common issue [33]. IL-15 promotes T-cell proliferation and survival and thus, could enhance CAR-T cell

10.2217/fon-2021-0576

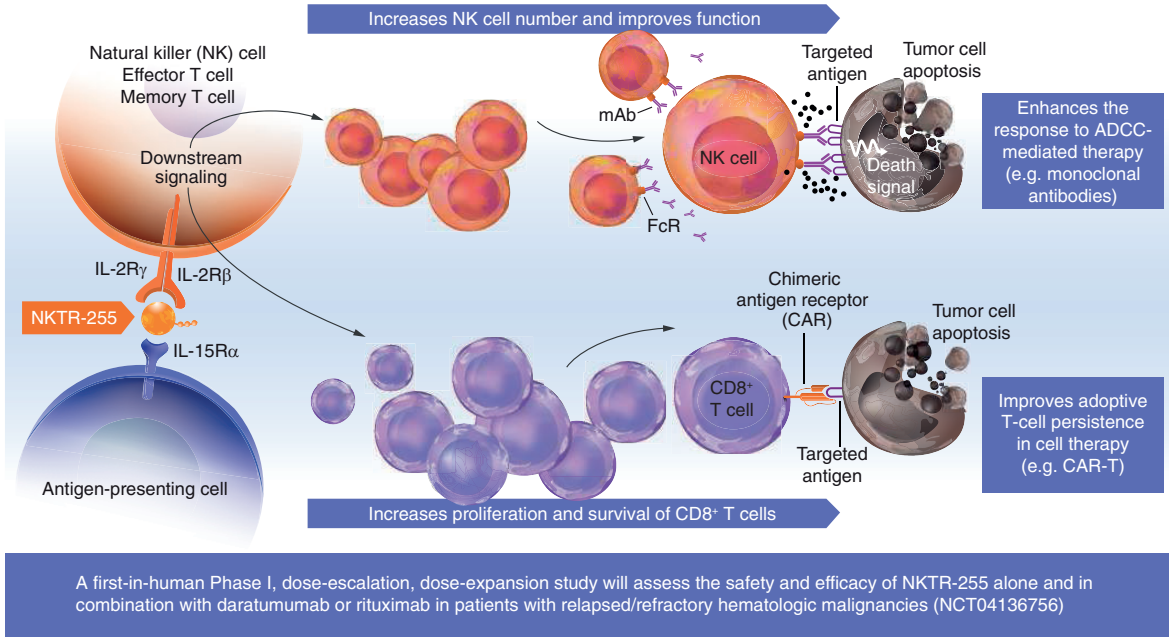


Figure 1. Mechanism of action of NKTR-255.
ADCC: Antibody-dependent cellular cytotoxicity; CAR-T: Chimeric antigen receptor T cell; mAb: Monoclonal antibody. Image reproduced with permission from Nektar Therapeutics. The copyright for this figure is retained by Nektar Therapeutics.

efficacy. However, this has been challenging due to the unfavorable PK and toxicity profile of IL-15 [33]. Preclinical studies of NKTR-255 have shown increased accumulation and persistence of CD19 CAR-T in the bone marrow of mice, resulting in decreased tumor burden and increased survival compared with CAR-T therapy alone [33].

Taken together, these observations warrant the clinical investigation of NKTR-255 as a single agent therapy or in combination with targeted antibody therapies to evaluate the safety and efficacy in patients with hematologic malignancies.

NKTR-255 Phase I trial

We report the design and methods for an ongoing Phase I study of NKTR-255 as monotherapy and in combination with either daratumumab or rituximab in patients with relapsed/refractory hematologic malignancies (NCT04136756). This study began enrollment in October 2019 with 14 sites in the USA.

Study design

This Phase I, open-label multicenter, dose-escalation and dose-expansion study is investigating the safety and tolerability of NKTR-255 as monotherapy, or in combination with daratumumab or rituximab in patients with relapsed/refractory MM, NHL or indolent NHL (iNHL) (Figure 2). In the dose-escalation phase, successive groups of three patients each will be treated with increasing doses of NKTR-255 (starting dose 1.5 µg/kg intravenously every 21 days), and observed during a 21-day dose-limiting toxicity (DLT) window until the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) is determined. The MTD will be declared when at least six patients have been evaluated at one dose level and determined based on targeted toxicity probability of a two-parameter Bayesian logistic regression model.

Exact doses will be determined based on the review of safety data by the Safety Review Committee after a minimum of three patients have been enrolled in each group. The RP2D of NKTR-255 will be based upon review of all available data on PK, PD as well as the clinical and biological effects of NKTR-255. A group of six patients will receive NKTR-255 at the RP2D every 28 days to determine the optimal schedule for dose expansion. Additional patients may be enrolled to refine the RP2D; a minimum of six patients will be required to determine the RP2D.

In the dose-expansion phase, patients will be treated with NKTR-255 at the RP2D at either an every 21- or 28-day dosing schedule, as determined prior to starting this phase, in three expansion cohorts (A, B and C) to

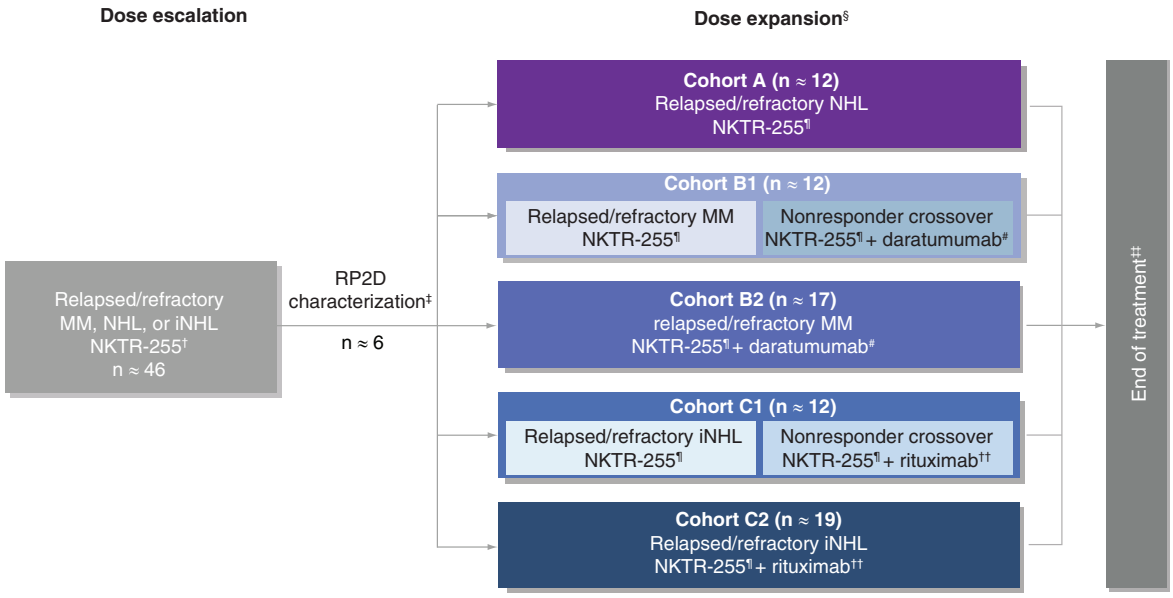


Figure 2. Study design.
†Starting dose of 1.5 μg/kg, administered intravenously every 21 days.
‡A group of six patients will receive NKTR-255 at the RP2D every 28 days to determine the optimal schedule for dose expansion. The RP2D and schedule of NKTR-255 will be chosen at a dose not exceeding the final 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.
§Patients who have received prior investigational CAR-T are eligible after confirmation of relapse of their primary disease.
¶RP2D of NKTR-255 every 21 or 28 days.
#Subcutaneous daratumumab 1800 mg once weekly starting on cycle 1 day 8 for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter.
††Induction treatment with intravenous rituximab 375 mg/m^2 once a week for 4 weeks, combined with three doses of NKTR-255 at the RP2D (every 21 or 28 days for 3 cycles). Patients who achieve CR/PR or clinical benefit will receive maintenance treatment with four additional doses of rituximab administered every other 28-day cycle in combination with NKTR-255 every 28 days. The dose of NKTR-255 during maintenance will be the selected RP2D dose.
‡‡Patients will be treated until confirmed disease progression, unacceptable toxicity, clinically assessed symptomatic deterioration, achievement of maximal response, loss to follow-up, patient withdrawal of consent, patient or physician's decision, Nektar Therapeutics or regulatory bodies terminate the study or death. Treatment may continue beyond progression if there is clinical benefit as determined by the investigator.
CAR-T: Chimeric antigen receptor T cell; CR: Complete response; iNHL: Indolent non-Hodgkin lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; PR: Partial response; RP2D: Recommended Phase II dose.

further characterize safety and tolerability (Figure 2). Cohort A will expand NKTR-255 in patients with NHL who have relapsed after CAR-T therapy as a salvage regimen, Cohort B will evaluate NKTR-255 in patients with MM with progressive disease who have had at least three prior lines of therapy, and Cohort C will evaluate NKTR-255 in patients with iNHL after treatment with at least one prior rituximab-containing regimen. Cohort B consists of Cohort B1 that will assess NKTR-255 as a single agent, and Cohort B2 that will assess NKTR-255 in combination with daratumumab (1800 mg subcutaneously [SC] once weekly starting on cycle 1 day 8 for 7 weeks, then every 2 weeks for 16 weeks and every 4 weeks thereafter). Cohort C comprises Cohort C1 that will assess NKTR-255 as a single agent, and Cohort C2 that will assess NKTR-255 in combination with rituximab (induction period: 375 mg/m^2 once weekly for 4 weeks, combined with three doses of NKTR-255 at the RP2D given at either every 21 or 28 days for three cycles; patients who achieve complete response [CR], partial response [PR] or clinical benefit will receive maintenance treatment with four additional doses of rituximab every other 28-day cycle in combination with NKTR-255 every 28 days). During maintenance, NKTR-255 will be dosed at the RP2D. Patients in Cohorts B1 and C1 who fail to respond to treatment are permitted to cross over to the combination Cohorts B2 and C2, respectively, after at least one disease assessment.

10.2217/fon-2021-0576

Patients will be treated until confirmed disease progression, unacceptable toxicity, clinically assessed symptomatic deterioration, achievement of maximal response, loss to follow-up, patient withdrawal of consent, patient or physician's decision, study sponsor or regulatory bodies terminates the study or death. Treatment may continue beyond progression if there is clinical benefit as determined by the investigator.

Eligibility criteria

This study includes general eligibility criteria for all tumor types and according to disease type, with specific criteria for the dose-expansion phase. All patients must be aged ≥18 years and provide written informed consent prior to enrollment. A full list of eligibility criteria can be found in Supplementary Table 1.

All tumor types

Eligible patients must have relapsed/refractory MM or NHL with documented disease progression on or after their last regimen, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and achieved a PR or better on at least one prior regimen. Participants will be excluded if they have an autoimmune disease, prior IL-2 or IL-15 therapy, or surgery/radiotherapy within 14 days of initiating study drug. Patients who have received prior investigational CAR-T are eligible after confirmation of relapse of their primary disease.

Multiple myeloma

Patients with MM must have measurable relapsed/refractory disease as defined by the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma [34], have received at least three prior lines of therapy, and have exhausted all available treatment options that could confer clinical benefit for their primary disease. Eligible patients must have measurable disease within at least one of the following: serum M-protein level ≥0.5 g/dl, urine M-protein level ≥200 mg/24 h, serum-free light chain (FLC) level ≥10 mg/dl and an abnormal serum FLC ratio (<0.26 or >1.65) or extramedullary plasmacytoma (measured within 28 days of screening). Patients who have received daratumumab (or any other anti-CD38 therapy) are eligible, provided they have undergone a 3-month washout period. In the dose-expansion cohort, patients must have relapsed/refractory disease (IMWG criteria) defined as progressive disease while on or within 60 days of therapy. Patients are required to have previous exposure to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 therapy (and responded at least once to prior daratumumab). Patients who previously received daratumumab or other anti-CD38 therapies must respect a 3-month washout prior to study enrollment.

Non-Hodgkin lymphoma

Patients with NHL must have histologically confirmed CD19-/CD20-positive disease that is measurable according to the Lugano classification [35] and/or extranodal disease measurable by ^{18}F-labeled fluoro-2-deoxy-D-glucose–positron emission tomography (^{18}F-FDG-PET) imaging. Patients who have received prior CD19 CAR-T therapy are eligible following confirmation of relapse of their primary disease. Patients with active central nervous system involvement will be excluded. In the dose-expansion phase, patients must have progressed on a commercially approved CD19 CAR-T therapy, and the first dose of NKTR-255 should be administered within 30 days of disease progression.

Indolent non-Hodgkin lymphoma

Patients with iNHL must have histologically confirmed CD19-/CD20-positive disease after treatment with at least one prior rituximab-containing regimen. Patients with either anti-CD20 mAb therapy refractory or sensitive disease are eligible. In the dose-expansion phase, patients must have progressed during or following at least one prior anti-CD20 mAb therapy.

Study procedures

Safety assessment will encompass an ongoing review of adverse events (AEs), including incidence of AEs, serious AEs (SAEs), clinical laboratory tests (blood and urine sampling), vital signs, physical examination, electrocardiograms, cardiac function tests and concomitant medication. Reporting of all AEs, except SAEs, will begin from the administration of the first study drug(s) until 30 days after the last dose of NKTR-255 and 90 days after the last dose of daratumumab or rituximab, or until a new antineoplastic regimen has been initiated. Severity of AEs will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [36], with the exception of cytokine-release syndrome which is graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading [37]. All ongoing AEs will

Box 1. Study end points

Primary end point

Dose-escalation phase

- Safety, tolerability, MTD, RP2D of single-agent NKTR-255.

Dose-expansion phase

- Safety and tolerability of single-agent NKTR-255 in patients with relapsed NHL who have progressed on CAR-T therapy, relapsed/refractory MM or relapsed/refractory iNHL.
- Safety and tolerability of NKTR-255 plus daratumumab in patients with relapsed/refractory MM.
- Safety and tolerability of NKTR-255 plus rituximab in patients with relapsed/refractory iNHL.

Secondary end points

- With single-agent NKTR-255 and in combination with daratumumab or rituximab:
  - ORR;
  - Pharmacokinetic parameters;
  - Pharmacodynamic parameters.

CAR-T: Chimeric antigen receptor T cell; CR: Complete response; iNHL: Indolent non-Hodgkin lymphoma; MM: Multiple myeloma; MTD: Maximum tolerated dose; NHL: Non-Hodgkin lymphoma; ORR: Objective response rate; RP2D: Recommended Phase II dose.

be followed until resolution, the patient is lost to follow-up, death, 30 days after the last dose of NKTR-255 or 90 days after the last dose of daratumumab or rituximab.

Tumor assessments will be performed at screening and routinely after cycle 1 day 1 until the patient withdraws consent or starts a new antineoplastic regimen. For patients with MM, treatment response will be measured using the IMWG criteria, and assessments will be carried out every cycle. For patients with NHL/iNHL, tumor response will be evaluated using the Lugano classification. Computed tomography (CT) and PET scans will be performed to evaluate disease status. The same method of assessment and the same technique for acquisition of images must be used for all study assessments. Baseline imaging should be done at the same institution/facility, and radiographic assessments and efficacy analyses will be conducted by the investigator site.

Blood samples for PK analyses will be collected before and during treatment to estimate maximum observed concentration, area under the concentration–time curve, clearance, volume of distribution and half-life where possible. Pharmacodynamic analyses will also be performed to assess the effects of NKTR-255 on the number and activation of immune cell populations (including NK cells, $CD8^+$ T cells and $CD8^+$ memory cells), as well as changes in cytokine levels and gene expression. For patients previously treated with CD19 CAR-T for NHL or any other experimental CAR-T therapy for MM, characterization of the genetically modified cells will be performed in peripheral blood by flow cytometry as well as quantitative polymerase chain reaction before and after treatment with NKTR-255.

Plasma and serum samples will be collected to assess the presence and timing of anti-NKTR-255 antibodies.

Outcome measures/end points

The primary objective of the dose-escalation phase is to evaluate the safety, tolerability, MTD and RP2D of single-agent NKTR-255 (Box 1). The primary objective of the dose-expansion phase is to evaluate the safety and tolerability of: NKTR-255 monotherapy in patients who have progressed on CAR-T therapy with relapsed/refractory NHL, MM or iNHL; NKTR-255 in combination with daratumumab in patients with relapsed/refractory MM; and NKTR-255 in combination with rituximab in patients with relapsed/refractory iNHL.

Secondary objectives are the objective response rate (ORR), PK, and PD of single-agent NKTR-255 and in combination with daratumumab or rituximab.

Statistics

It is estimated that 46 patients will be enrolled in the dose-escalation phase. Successive groups of three patients will be treated at each dose level until the MTD or RP2D is determined. Additional patients may be enrolled into each cohort for further evaluation of safety and tolerability.

Approximately 72 patients will be enrolled in the dose-expansion phase to be treated at the RP2D (Cohort A:12; Cohort B1:12; Cohort B2:17; Cohort C1:12; and Cohort C2:19). A Fleming's two-stage design guided the sample size calculation, with a one-sided alpha of 0.05 and power of 0.85. The Fleming's 2-stage design allows early stopping for futility as well as an expansion of enrollment if a strong antitumor activity signal is observed.

Populations for analysis include the response-evaluable population (defined as patients who receive at least one dose of study drug, have measurable disease at baseline, and at least one post-baseline planned response assessment) and the safety population (defined as all patients who receive at least one dose [or partial dose] of study drug).

Efficacy analyses will be performed for evaluation of ORR, CR rate and rate of minimal residual disease negativity (for MM patients); these measures will be summarized using 95% CI from the exact binomial method. For efficacy end points including ORR, the summary will be based on the response-evaluable population.

Conclusion

This Phase I trial will be the first to investigate the safety and efficacy of NKTR-255 in humans. The primary goal is to determine the safety and tolerability, MTD and RP2D of NKTR-255 as monotherapy and in combination with mAbs daratumumab or rituximab in the setting of relapsed/refractory MM, NHL and iNHL. Results from this trial will guide the future development of NKTR-255, with a view to address the unmet need for new treatments that can boost NK cell number and function and thereby increase the effectiveness of approved therapies for MM and NHL.

Executive summary

Background & rationale

- There is ongoing interest in the immunobiology and clinical significance of circumventing natural killer (NK) dysfunction through immunotherapy in hematologic malignancies.
- Interleukin-15 (IL-15) is a cytokine that primarily stimulates the proliferation and cytotoxic function of NK and $CD8^+$ memory T cells, and has potential as an immunotherapeutic approach for enhancing the antitumor response.
- Traditionally, recombinant human (rhIL-15) has a short half-life, requires high and frequent doses to achieve functional responses *in vivo*, and is associated with toxicities including lymphopenia, neutropenia and increased aspartate and/or alanine aminotransferase.

NKTR-255

- NKTR-255 is an investigational polyethylene glycol-modified rhIL-15 receptor agonist that optimally engages with all IL-15R, including the IL-15Rα/IL–2Rβγ complex, to achieve durable and controlled activation of the IL-15 pathway.
- Preclinical studies have demonstrated that *in vitro* NKTR-255 monotherapy retains IL-15Rα-binding affinity, induces the proliferation and activation of NK and $CD8^+$ T cells, increases the $CD8^+$: regulatory T cell ratio and increases the accumulation and persistence of CD19 chimeric antigen receptor T cells in the bone marrow, resulting in decreased tumor burden and prolonged survival.
- Studies have also shown that NKTR-255 synergizes with monoclonal antibodies, such as daratumumab, to enhance antibody-dependent cellular cytotoxicity (ADCC) in cancer models, including multiple myeloma (MM), lymphoma and solid tumors.

NKTR-255 Phase I trial

- This is a Phase I, open-label, multicenter, dose-escalation and dose-expansion study of NKTR-255 alone or in combination with daratumumab or rituximab in patients with relapsed/refractory MM, non-Hodgkin lymphoma (NHL) or indolent NHL (iNHL).
- Eligible patients will have relapsed/refractory MM, NHL or iNHL with documented disease progression on or after their last regimen, an Eastern Cooperative Oncology Group performance status of ≤ 2 and achieved a partial response or better to ≥ 1 prior regimen.
- The primary objective of the dose-escalation phase is to evaluate the safety, tolerability, maximum tolerated dose and recommended Phase II dose of single-agent NKTR-255.
- The primary objective of the dose-expansion phase is to evaluate the safety and tolerability of NKTR-255 monotherapy in patients with relapsed NHL who have progressed on CAR-T therapy or relapsed/refractory MM or iNHL, NKTR-255 plus daratumumab in patients with relapsed/refractory MM and NKTR-255 plus rituximab in patients with relapsed/refractory iNHL.
- Approximately 46 and 72 patients will be enrolled in the dose-escalation and dose-expansion phases, respectively.
- Results from this study will inform the optimal dose for future studies of NKTR-255, and may provide an initial indication of whether NKTR-255, either as monotherapy or in combination with daratumumab or rituximab, has the potential to address the unmet need for novel agents that can boost NK cell number and function for hematologic malignancies.
- This trial is expected to enroll at approximately 14 sites in the USA; for participating trial sites, please visit: https://clinicaltrials.gov and search NCT04136756.

Supplementary data

An infographic also accompanies this paper at the end of the references section. To view the supplementary data and infographic that accompanies this paper please visit the journal website: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0576

Author contributions

N Shah, M-A Perales, CJ Turtle, MS Cairo, AJ Cowan, H Saeed, LE Budde, A Tan, Z Lee, MQ Marcondes, J Zalevsky, MA Tagliaferri, KK Patel conceived, designed or planned the study. N Shah, M-A Perales, CJ Turtle, MS Cairo, AJ Cowan, H Saeed, LE Budde, A Tan, Z Lee, K Kai, MQ Marcondes, J Zalevsky, MA Tagliaferri, KK Patel drafted, critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the final version and are in agreement with the content and approved of the decision to submit.

Acknowledgments

The authors would like to thank all patients, their families and the investigators who are participating in this study.

Financial & competing interests disclosure

This study is sponsored by Nektar Therapeutics, San Francisco, CA, USA. The authors have no other relevant affiliations or financial involvement with any organization or entity in conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. N Shah has served on the advisory boards for Amgen, Genentech, GSK, Indapta Therapeutics, Karoypharm, 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. M-A Perales reports honoraria from Abbvie, Astellas, Bristol-Myers Squibb, Celgene, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros and Takeda. He serves on data and safety monitoring boards for Cidara Therapeutics, Medigene, and Servier, and the scientific advisory board of NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec and Novartis. He serves in a volunteer capacity as a member of the board of directors of Be The Match (National Marrow Donor Program, NMDP), as well as on the Centre for International Blood and Marrow Transplant Research (CIBMTR) Cellular Immunotherapy Data Resource (CIDR) executive committee. CJ Turtle receives research funding from AstraZeneca, Juno Therapeutics/BMS, Nektar Therapeutics and TCR^2 Therapeutics; serves on scientific advisory boards for ArsenalBio, Caribou Biosciences, Century Therapeutics, Eureka Therapeutics, Myeloid Therapeutics, Precision Biosciences and T-CURX and has served as an ad hoc advisor for Allogene, Amgen, Asher Bio, AstraZeneca, Nektar Therapeutics and PACT Pharma; has stock options with ArsenalBio, Caribou Biosciences, Eureka Therapeutics, Myeloid Therapeutics, and Precision Biosciences; and is an inventor on patents licensed or optioned to Juno Therapeutics. MS Cairo serves on an advisory board for Nektar Therapeutics and has a research materials transfer agreement in place with same company. AJ Cowan has received consultancy fees and/or research funding from AbbVie, Celgene, Cellectar Biosciences, Harpoon, Janssen and Sanofi-Aventis. H Saeed has served as on advisory boards for MorphoSys, Sanofi Genzyme, and Seattle Genetics; and has received consultancy fees and/or honoraria from Cardinal Health, Epizyme, MorphoSys, PRIME Education LLC, Sanofi Genzyme, and Seattle Genetics. LE 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. Z Lee is an employee of and has ownership interest (including stock, patents, etc.) in Nektar. K Kai is an employee of and has ownership interest (including stock, patents, etc.) in Nektar. MQ Marcondes is an employee of and has ownership interest (including stock, patents, etc.) in Nektar. J Zalevsky is an employee of and has ownership interest (including stock, patents, etc.) in Nektar. MA Tagliaferri is an employee of and has ownership interest (including stock, patents, etc.) in Nektar. KK Patel has received consultancy fees and/or research funding from AbbVie, BMS, Celgene, Cellectis, Janssen, Nektar Therapeutics, Oncopeptides, Poseida Therapeutics, Precision Biosciences and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing assistance was provided by S Shaw of BOLDSCIENCE Inc., and was funded by Nektar Therapeutics.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent has been obtained from the participants involved.

Data sharing statement

Nektar is committed to sharing anonymized individual patient-level data and supporting clinical documents from eligible studies with qualified scientific researchers. These requests are reviewed and approved by an independent review panel. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Trial data availability is according to the criteria and process described on http://www.clinicalstudydatarequest.com.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Gonzalez-Rodriguez AP, Villa-Álvarez M, Sordo-Bahamonde C, Lorenzo-Herrero S, Gonzalez S. NK cells in the treatment of hematological malignancies. *J. Clin. Med.* 8(10), 1557 (2019).
2. Farnault L, Sanchez C, Baier C, Le Treut T, Costello RT. Hematological malignancies escape from NK cell innate immune surveillance: mechanisms and therapeutic implications. *Clin. Dev. Immunol.* 2012, 421702 (2012).
3. Hu W, Wang G, Huang D, Sui M, Xu Y. Cancer immunotherapy based on natural killer cells: current progress and new opportunities. *Front. Immunol.* 10, 1205 (2019).
4. Fairfield H, Falank C, Avery L, Reagan MR. Multiple myeloma in the marrow: pathogenesis and treatments. *Ann. NY Acad. Sci.* 1364(1), 32–51 (2016).
5. Pittari G, Vago L, Festuccia M *et al.* Restoring natural killer cell immunity against multiple myeloma in the era of new drugs. *Front. Immunol.* 8, 1444 (2017).
6. Osterborg A, Nilsson B, Björkholm M, Holm G, Mellstedt H. Natural killer cell activity in monoclonal gammopathies: relation to disease activity. *Eur. J. Haematol.* 45(3), 153–157 (1990).
7. Besson L, Charrier E, Karlin L *et al.* One-year follow-up of natural killer cell activity in multiple myeloma patients treated with adjuvant lenalidomide therapy. *Front. Immunol.* 9, 704 (2018).
8. Mikhael J, Ismaila N, Cheung MC *et al.* Treatment of multiple myeloma: ASCO and CCO joint clinical practice guideline. *J. Clin. Oncol.* 37(14), 1228–1263 (2019).
9. Darzalex (daratumumab) Prescribing Information. (2020). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761036s029lbl.pdf
10. Empliciti (elotuzumab) Prescribing Information. (2019). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761035s010lbl.pdf
11. Ishibashi M, Soeda S, Sasaki M *et al.* Clinical impact of serum soluble SLAMF7 in multiple myeloma. *Oncotarget* 9(78), 34784–34793 (2018).
12. Nijhof IS, Casneuf T, van Velzen J *et al.* CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. *Blood* 128(7), 959–970 (2016).
13. Kim J-K, Chung J-S, Shin H-J *et al.* Influence of NK cell count on the survival of patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood Res* 49(3), 162–169 (2014).
14. Klanova M, Oestergaard MZ, Trněný M *et al.* Prognostic impact of natural killer cell count in follicular lymphoma and diffuse large B-cell lymphoma patients treated with immunochemotherapy. *Clin. Cancer Res.* 25(15), 4634–4643 (2019).
15. National Institute for Health and Care Excellence (NICE). Non-Hodgkin's lymphoma: diagnosis and management. (2016). https://www.nice.org.uk/guidance/ng52
16. Robinson TO, Schluns KS. The potential and promise of IL-15 in immuno-oncogenic therapies. *Immunol. Lett.* 190, 159–168 (2017).
17. Cheever MA. Twelve immunotherapy drugs that could cure cancers. *Immunol. Rev.* 222, 357–368 (2008).
18. Berger C, Berger M, Hackman RC *et al.* Safety and immunologic effects of IL-15 administration in nonhuman primates. *Blood* 114(12), 2417–2426 (2009).
19. Lugli E, Goldman CK, Perera LP *et al.* Transient and persistent effects of IL-15 on lymphocyte homeostasis in nonhuman primates. *Blood* 116(17), 3238–3248 (2010).
20. Ferrone CR, Perales M-A, Goldberg SM *et al.* Adjuvanticity of plasmid DNA encoding cytokines fused to immunoglobulin Fc domains. *Clin. Cancer Res.* 12(18), 5511–5519 (2006).
21. Tang F, Zhao LT, Jiang Y, Ba DN, Cui LX, He W. Activity of recombinant human interleukin-15 against tumor recurrence and metastasis in mice. *Cell. Mol. Immunol.* 5(3), 189–196 (2008).

22. Conlon KC, Potter EL, Pittaluga S *et al.* IL15 by continuous intravenous infusion to adult patients with solid tumors in a Phase I trial induced dramatic NK-cell subset expansion. *Clin. Cancer Res.* 25(16), 4945–4954 (2019).

23. Miller JS, Morishima C, McNeel DG *et al.* A first-in-human Phase I study of subcutaneous outpatient recombinant human IL15 (rhIL15) in adults with advanced solid tumors. *Clin. Cancer Res.* 24(7), 1525–1535 (2018).

24. Waldmann TA, Lugli E, Roederer M *et al.* Safety (toxicity), pharmacokinetics, immunogenicity, and impact on elements of the normal immune system of recombinant human IL-15 in rhesus macaques. *Blood* 117(18), 4787–4795 (2011).

25. Rosenstein M, Ettinghausen SE, Rosenberg SA. Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin 2. *J. Immunol.* 137(5), 1735–1742 (1986).

26. Kuo P, Kirk P, Addepalli M *et al.* Preclinical efficacy and tolerability of NKTR-255, a polymer conjugated IL-15 for immuno-oncology. *Poster presented at: 32nd Annual Meeting of the Society for Immunotherapy of Cancer.* National Harbor, MD, USA, 8–12 November 2017 (Poster P332).

- **Preclinical data for NKTR-255 supporting the tolerability and antitumor activity.**

27. Miyazaki T, Maiti M, Hennessy M *et al.* NKTR-255, a novel polymer-conjugated rhIL-15 with potent antitumor efficacy. *J. Immunother. Cancer* 9(5), e002024 (2021).

- **Preclinical data for NKTR-255 supporting the mechanism of action and antitumor activity.**

28. Bhasi K, Obalapur P, Cetz J *et al.* First-in-human pharmacokinetic (PK) prediction of NKTR-255, an interleukin-15 (IL-15) receptor agonist, based on a target-mediated drug disposition (TMDD) model. *Presented at: 11th American Conference on Pharmacometrics.* Denver, CO, USA, 4–7 October 2020 (Abstract THU-045).

- **Preclinical data for NKTR-255 supporting the mechanism of action and antitumor activity.**

29. Miyazaki T, Kuo P, Maiti M *et al.* Pharmacokinetic and pharmacodynamic study of NKTR-255, a polymer-conjugated IL-15, in cynomolgus monkey. *Poster presented at: 60th American Society of Hematology Annual Meeting.* San Diego, CA, USA 1–4 December 2018 (Abstract 2952).

- **Preclinical data for NKTR-255 supporting the pharmacokinetic and pharmacokinetic profile.**

30. Miyazaki T, Maiti M, Sheibani S, Zemska O, Kivimäe S, Hennessy M *et al.* Characterization and comparison of NKTR-255, a polymer-conjugated IL-15 versus IL-15 superagonist. *Poster presented at: 34th Annual Meeting of the Society for Immunotherapy of Cancer.* National Harbor, MD, USA, 6–10 November 2019 (Poster P622).

- **Poster presentation of the pharmacological properties of NKR-255 in comparison with IL-15 superagonists.**

31. Miyazaki T, Kivimäe S, Pena R *et al.* NKTR-255: a polymer-conjugated IL-15 enhances anti-tumor NK cell responses and synergizes with monoclonal antibodies to provide long-term survival in human lymphoma model. *Poster presented at: The American Association for Cancer Research Annual Meeting.* Atlanta, GA, USA, 29 March–3 April 2019 (Abstract 3265).

- **Preclinical data for NKTR-255 supporting the pharmacological properties and antitumor activity in a B cell lymphoma model.**

32. Kivimae S *et al.* NKTR-255: a polymer-conjugated IL-15 receptor agonist, enhances efficacy of therapeutic monoclonal antibodies with ADCC activity in solid tumor models. *Poster presented at: 34th Annual Meeting of the Society for Immunotherapy of Cancer.* National Harbor, MD, USA, 6–10 November 2019 (Abstract P619).

- **Preclinical data for NKTR-255 supporting the pharmacological properties and antitumor activity in a B cell lymphoma model.**

33. Chou C, Fraessle S, Steinmetz R *et al.* Combination of NKTR-255, a polymer conjugated human IL-15, with CD19 CAR T cell immunotherapy in a preclinical lymphoma model. *Blood* 134(Suppl. 1), 2866–2866 (2019).

34. Kumar S, Paiva B, Anderson KC *et al.* International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 17(8), e328–e346 (2016).

35. Cheson BD, Fisher RI, Barrington SF *et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: the Lugano classification. *JCO* 32(27), 3059–3067 (2014).

36. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. (2017). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

37. Lee D, Santomasso B, Locke F *et al.* ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol. Blood Marrow Transplant.* 25(4), 625–638 (2019).

Phase 1 study protocol: NKTR-255 as monotherapy or combined with daratumumab or rituximab in hematologic malignancies

Authors

Nina Shah, Miguel-Angel Perales, Cameron J Turtle, Mitchell S Cairo, Andrew J Cowan, Hayder Saeed, Lihua E Budde, Alan Tan, Zachary Lee, Kazuharu Kai, Mario Q Marcondes, Jonathan Zalevsky, Mary A Tagliaferri & Krina K Patel

Article URL

www.futuremedicine.com/doi/10.2217/fon-2021-0576

Trial registration number

NCT04136756

Study Outcomes

Primary outcomes

Dose-escalation phase: safety and tolerability, MTD and RP2D of NKTR-255 monotherapy

Dose-expansion phase: safety and tolerability of:

- NKTR-255 monotherapy in patients who have progressed on a CAR-T therapy with relapsed/refractory MM, NHL or iNHL
- NKTR-255 plus daratumumab in patients with relapsed/refractory MM
- NKTR-255 plus rituximab in patients with relapsed/refractory iNHL

Secondary key outcomes

ORR, PK, and PD of NKTR-255 monotherapy and in combination with daratumumab or rituximab

Key Eligibility Criteria

- Aged ≥18 years
- Relapsed/refractory MM or NHL with progressive disease on/after their last regimen
- ECOG PS ≤ 2
- Response to at least 1 prior line of treatment
- All patients who received prior investigational CAR-T are eligible after confirmation of relapse of their primary disease
- Patients with MM: measurable disease (defined by the IMWG criteria) with ≥ 3 prior lines of therapy with no other available treatment options
- Patients with NHL or iNHL: histologically confirmed CD19-/CD20-positive disease

Study Design and Treatment

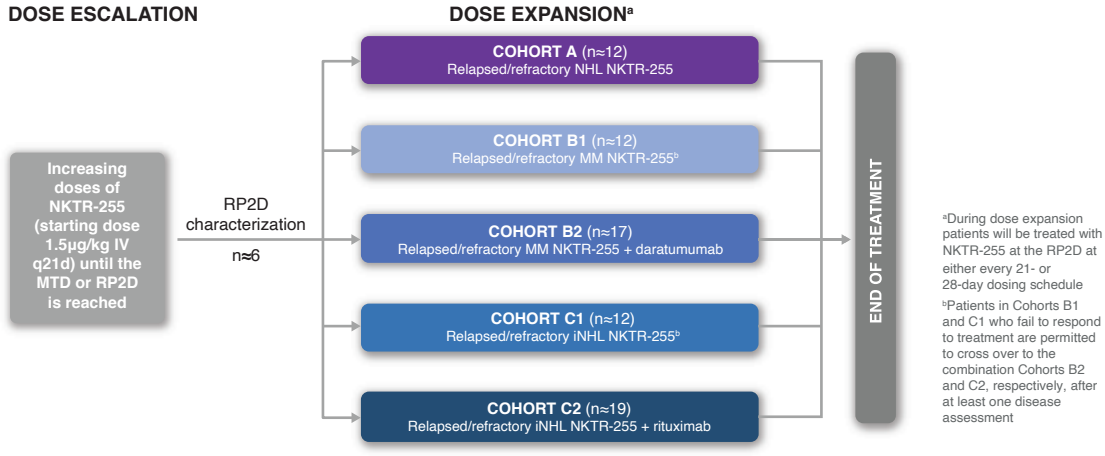
P1

Phase 1

Open label

Multicenter

Dose escalation (n≈46)
Dose expansion (n≈72)



[a]During dose expansion patients will be treated with NKTR-255 at the RP2D at either every 21- or 28-day dosing schedule

[b]Patients in Cohorts B1 and C1 who fail to respond to treatment are permitted to cross over to the combination Cohorts B2 and C2, respectively, after at least one disease assessment

Glossary

CAR-T: Chimeric antigen receptor T cell; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IMWG: International Myeloma Working Group; iNHL: Indolent non-Hodgkin lymphoma; IV: Intravenously; MM: Multiple myeloma; MTD: Maximum tolerated dose; NHL: Non-Hodgkin lymphoma; ORR: Objective response rate; PD: Pharmacodynamics; PK: Pharmacokinetics; q21d: Every 21 days; RP2D: Recommended Phase 2 dose