A Phase 1b/2, open-label, multicenter, dose-escalation and dose-expansion study of NKTR-255 plus cetuximab as a salvage regimen in patients with solid tumors

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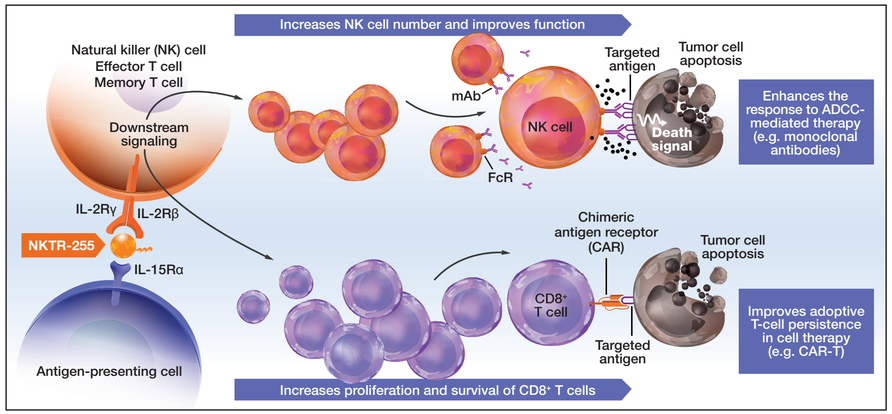
BACKGROUND

- There is an unmet need for new therapies that can boost NK cell number and function, with the purpose of aiding current approved therapies for HNSCC and CRC[1]
- NKTR-255 is a polymer-conjugated rhIL-15 agonist, which provides sustained PD responses without the need for daily dosing **(Figure 1)**[2]
- In preclinical models, NKTR-255:
  - Induced proliferation and activation of NK cells[2]
  - Promoted survival and expansion of CD8+ T cells[2]
  - Induced NK cells with the potential for greater antitumor activity compared with IL-15 superagonists[3]
  - Enhanced antitumor activity of tumor-targeted antibodies with an ADCC mechanism[2]

Figure 1. NKTR-255 engages with the IL-15Rα/IL-2Rβγ receptor complex to boost NK cell number and CD8+ T-cell expansion, proliferation, activation, function, and survival[2]



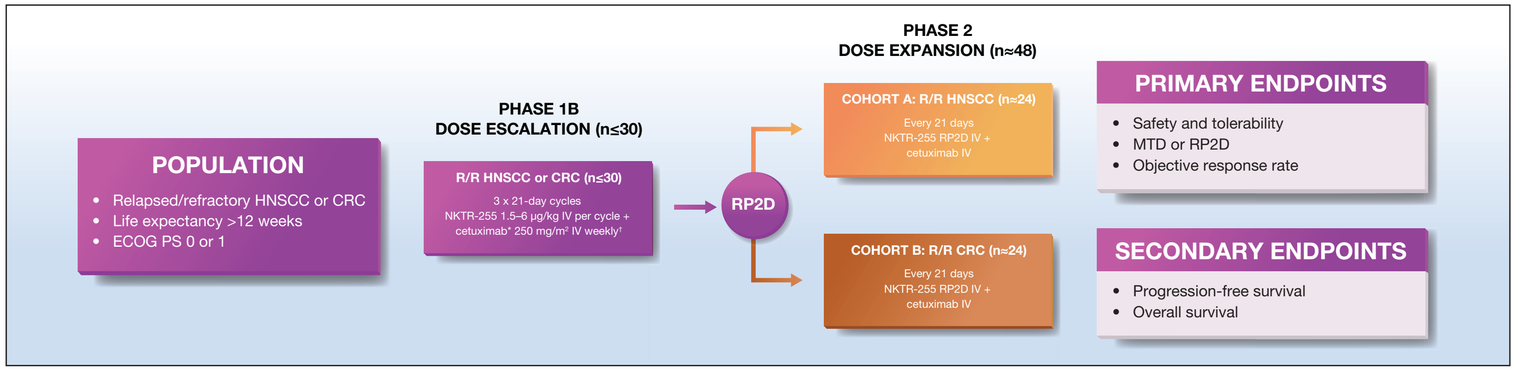
ADCC, antibody-dependent cellular cytotoxicity; CAR, chimeric antigen receptor; CAR-T, CAR T-cell therapy; CD, cluster of differentiation; FcR, Fc receptor; IL-2R, interleukin-2 receptor; IL-15R, interleukin-15 receptor; MAb, monoclonal antibody; NK cell, natural killer cell.

STUDY

Design

- A phase 1b/2 (NCT04616196) multicenter, open-label, dose-escalation, and dose-expansion study to evaluate the safety and antitumor activity of NKTR-255 plus cetuximab in patients with metastatic R/R HNSCC or CRC **(Figure 2)**
- In the dose-escalation phase, ≤30 patients will receive NKTR-255 every 21 days plus cetuximab weekly
  - Until the MTD and/or RP2D is determined, successive cohorts of 2–4 patients will receive ascending doses of NKTR-255
  - Patients who achieve optimal (partial or complete) response will be given the choice to continue NKTR-255 as maintenance therapy every 28 days
- In the dose-expansion phase, ≈48 patients from the R/R HNSCC and CRC cohorts will receive the RP2D of NKTR-255 plus cetuximab every 21 days
  - Patients will be treated until disease progression or unacceptable toxicity

Figure 2. Phase 1b/2 dose-escalation and dose-expansion study design of NKTR-255 plus cetuximab in patients with R/R HNSCC and CRC



*On day –7, cetuximab 400 mg/m² IV will be given as a loading dose.

†Patients who achieve optimal (partial or complete) response, will be given the option to continue NKTR-255 (every 28 days) as maintenance therapy.

CRC, colorectal cancer; IV, intravenous; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; R/R HNSCC, relapsed/refractory head and neck squamous cell carcinoma.

Eligibility criteria

Key inclusion criteria

- ≥18 years of age
- Locally advanced or metastatic HNSCC or CRC, not amenable to curative therapy, with measurable disease per RECIST v1.1
- Life expectancy >12 weeks as determined by the Investigator
- ECOG PS 0 or 1
- No prior cetuximab or other EGFR-targeted therapy (phase 2 only)*

HNSCC	CRC
Disease progression on 1L/2L platinum-based chemotherapy or anti-PD-(L)1 checkpoint inhibitor	Confirmed *KRAS* wild-type EGFR+ tumor for phase 2 enrollment
Prior treatment with checkpoint inhibitor occurred ≥4 weeks before enrollment	Received or intolerant to ≥2 prior cancer treatments in the metastatic setting
Ineligible for platinum-based chemotherapy or chemoradiation due to decline in renal function and/or intolerance	Patients with microsatellite instability-high or deficient mismatch repair tumors must have received checkpoint inhibitors

*Unless cetuximab was given as part of a primary treatment approach, with no progressive disease for at least 4 months following the end of prior cetuximab treatment.

Key exclusion criteria

- Prior treatment with an investigational agent/device or anti-cancer treatment ≤28 days before study treatment
- Active, known, or suspected autoimmune disease that requires systemic treatment ≤3 months from enrolment or requires systemic corticosteroids or immunosuppressants*
- Surgery/radiotherapy or approved tyrosine kinase inhibitors ≤14 days before study treatment†
- Prior treatment with IL-2 or IL-15 at anytime, or systemic interferon alpha ≤6 months before enrollment
- Contraindication to, or unable to receive cetuximab, including those with prior Grade 4 infusion-related reactions
- HNSCC patients requiring anticoagulation therapy
- Prior treatment with warfarin for CRC patients ≤14 days before study treatment

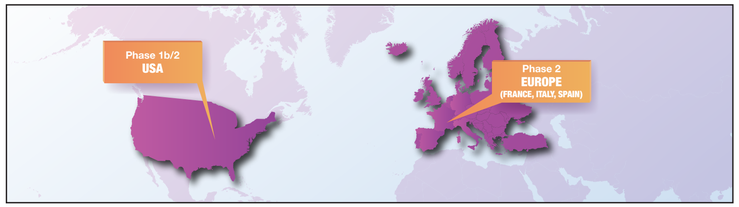
*Exceptions include any patient on ≤10 mg prednisone or equivalent, patients with vitiligo, hypothyroidism stable on hormone replacement, Type I diabetes, Graves' disease, Hashimoto's disease, alopecia areata, eczema, psoriasis, or with Medical Monitor approval.

†Patients receiving sunitinib, sorafenib, vemurafenib, dabrafenib, or cobimetinib ≤14 days before administration of the first dose of study drug(s) will be excluded.

Status

- This study is currently enrolling in the USA and plans to open in Europe for phase 2 **(Figure 3)**
- Enrollment is complete for the NKTR-255 1.5 and 3.0 µg/kg dose levels
- Please visit ClinicalTrials.gov and search for NCT04616196 to find out the latest information on this study

Figure 3. Locations of active or planned clinical trial sites



ABBREVIATIONS

1L, first-line therapy; 2L, second-line therapy; ADCC, antibody-dependent cellular cytotoxicity; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; IL, interleukin; IV, intravenous; MTD, maximum tolerated dose; NK, natural killer; PD, pharmacodynamic; RECIST, Response Evaluation Criteria in Solid Tumors; rh, recombinant human; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

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The study was approved by the institutional review board of each participating site and informed consent is obtained from all patients.

DISCLOSURES

M. Atlan has served as an advisor to GlaxoSmithKline and Shattuck Labs, and has received institutional funding for research from Adaptimmune Therapeutics, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Jounce Therapeutics, Lilly, Merck, Nektar Therapeutics, Novartis, and Shattuck Labs.

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