NKTR-255 + Cetuximab in Patients with Solid Tumors: Interim Safety and Efficacy Results from the Phase 1b Dose-escalation Study

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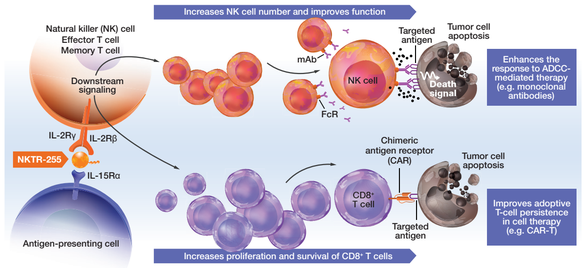
BACKGROUND

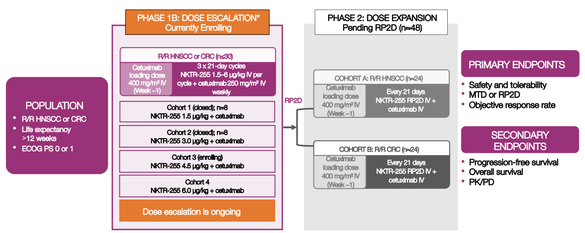
- There is an unmet need for new cancer immunotherapies that can boost the number and function of NK cells to improve clinical outcomes
- NKTR-255 is a polymer-conjugated rhIL-15 agonist that engages the full IL-15 receptor pathway providing sustained PD responses without the need for daily dosing[1]
- In preclinical models, NKTR-255 induced the proliferation and activation of NK cells and promoted the survival and expansion of CD8$^+$ T cells.[1] NKTR-255 also enhanced the antitumor activity of tumor-targeted antibodies with an ADCC mechanism[1,2]
- This phase 1b/2 (NCT04616196)[3] dose-escalation study with expansion cohorts evaluates the safety and antitumor activity of NKTR-255 plus cetuximab in patients with R/R HNSCC and CRC
- **Here we report preliminary data on safety, PK/PD, and efficacy from the dose-escalation portion**

NKTR-255 Engages the IL-15Rα/IL-2Rβγ Complex to Boost NK Cell and CD8$^+$ T-cell Expansion, Proliferation, Activation, Function, and Survival[2]



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

PHASE 1B/2 STUDY DESIGN



NCT04616196. *Dose-escalation rules: Successive cohorts each receive escalating doses of NKTR-255 every 21 days plus a fixed dose of cetuximab weekly to determine the MTD/RP2D. A two-parameter Bayesian logistic regression model was used to guide each dose level and determine the MTD. The MTD will be declared when at least 6 patients have been evaluated at a dose and the posterior probability of targeted toxicity is at least 60% for that dose. Patients who achieve an optimal response (PR or CR), will be given the option to continue NKTR-255 (every 28 days) as maintenance therapy. CR, complete response; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Study Procedures and Assessments (at October 13, 2021)

Safety and Tolerability	PK and PD	Efficacy
• AEs were assessed by CTCAE v5.0 • The safety evaluable population includes all patients who received ≥1 dose of treatment	• PK with concentration–time profiles (data cutoff: June 8, 2021) • PD (data cutoff: July 30, 2021) — Assessment of CD4$^+$ T cells, CD8$^+$ T cells, and NK Cells — Evaluation of inflammatory cytokines — Evaluation of Tregs	• Objective response: assessed by investigator every 9 weeks (±1 week) per RECIST v1.1 • Per protocol, efficacy-evaluable population defined as patients with ≥1 post-baseline, on-treatment radiographic scan

RESULTS

Heavily Pretreated Population Enrolled in Dose Escalation Phase

Patient Demographics and Disease Characteristics

Patients with HNSCC		N=4
Median age, years		59.5
Sex, n (%)	Female Male	0 4 (100)
ECOG PS, n (%)	0 1	2 (50) 2 (50)
Metastatic disease, n (%)		4 (100)
Median (range) number of prior therapies		4 (1–4)
Previous EGFR-targeted therapy, n (%)		1 (25)
Previous CPI, n (%)		3 (75)

Patients with CRC		N=10
Median age, years		59.5
Sex, n (%)	Female Male	2 (20) 8 (80)
ECOG PS, n (%)	0 1	4 (40) 6 (60)
Mutational status, n (%)	*BRAF/RAS* all wild-type *KRAS* or *NRAS* mutation *RAS* wild-type *BRAF* missing	5 (50) 4 (40) 1 (10)
Median (range) number of prior therapies		3 (2–8)
Previous EGFR-targeted therapy, n (%)		4 (40)
Previous CPI, n (%)		3 (30)

Data cutoff: October 13, 2021. CPI, checkpoint inhibitor; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma.

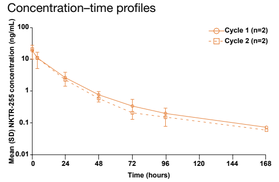
NKTR-255 + Cetuximab was Well Tolerated with no Grade 4/5 TRAEs

Selected TRAEs; n (%)	NKTR-255 dose		Total (N=14)
	1.5 µg/kg (n=7)	3.0 µg/kg (n=7)	
Grade 1 or 2 (≥1 patient)			
Chills	1 (14.3)	1 (14.3)	2 (14.3)
Fatigue	1 (14.3)	2 (28.6)	3 (21.4)
Infusion-related reaction	2 (28.6)	6 (85.7)	8 (57.1)
Nausea	0	2 (28.6)	2 (14.3)
Grade 3 (all)			
Infusion-related reaction/hypoxia*	0	1 (14.3)	1 (7.1)

Data cutoff: October 13, 2021. *This event was considered a NKTR-255-related DLT and resolved within 24 hours. DLT, dose-limiting toxicity; TRAE, treatment-related adverse event.

NKTR-255 Demostrates Extended $T_{½}$ with Minimal Accumulation

Concentration–time profiles



Preliminary PK analyses

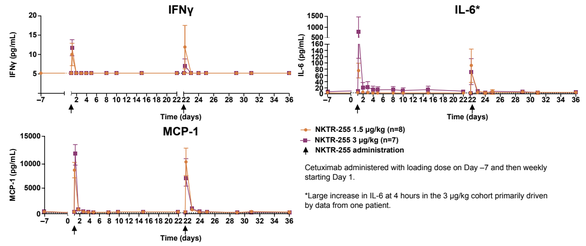
Dose	Cycle	T_{max} (hr)	C_{max} (ng/mL)	AUC_{last} (hr*ng/mL)	$T_{½}$ (hr)	CL (L/hr)
1.5 µg/kg	1 (n=2)	0.58 (0.52, 0.65)	18.4 (8.90)	209 (50.1)	27.8 (33.2)	0.79 (69.9)
	2 (n=2)	0.53 (0.52, 0.53)	21.5 (30.9)	204 (18.4)	20.2 (62.2)	0.70 (41.7)

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.

The mean $T_{½}$ of NKTR-255 (1.5 µg/kg) was 27.8 hours, which is ≈10-fold longer than that reported for rhIL-15,[4] with no or minimal accumulation following repeat dosing.

Data cutoff: June 8, 2021.
A validated method was used to measure plasma concentration of NKTR-255, which was expressed in IL-15 content.
AUC, area under the curve; CL, clearance; C_{max}, peak concentration; IL-15, interleukin-15; PK, pharmacokinetic; $T_{½}$, half-life; T_{max}, time to maximum concentration; SD, standard deviation.

NKTR-255 + Cetuximab Induced Transient Upregulation and Rapid Decline of Inflammatory Cytokines by Day 2–3

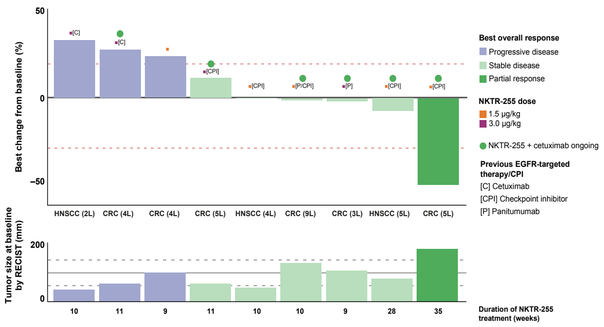


Cetuximab administered with loading dose on Day −7 and then weekly starting Day 1.

*Large increase in IL-6 at 4 hours in the 3 µg/kg cohort primarily driven by data from one patient.

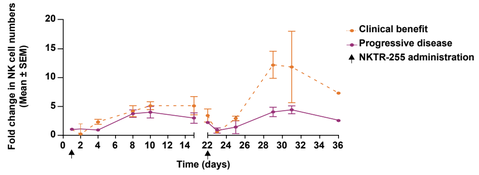
IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein.

NKTR-255 + Cetuximab Shows Evidence of Preliminary Efficacy at Initial Doses



One patient experienced a DLT and was not included in the analysis. 4 patients experienced symptoms consistent with progression and discontinued without protocol specified tumor assessment. CPI, checkpoint inhibitor; C, cetuximab; DLT, dose-limiting toxicity; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; P, panitumumab; RECIST, Response Evaluation Criteria in Solid Tumors.

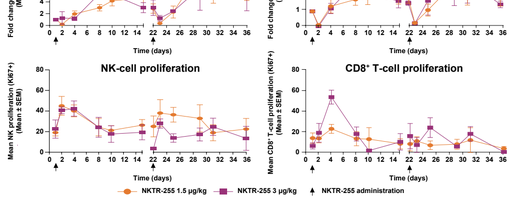
NKTR-255 + Cetuximab Led to Greater Expansion of NK Cells* in Patients with Clinical Benefit Versus Patients with Progressive Disease, Supporting the MOA of NKTR-255



*Data combined for both Cohorts 1 and 2. Cycle 1: clinical benefit n=5, progressive disease n=3. NK, natural killer; SEM, standard error of the mean.

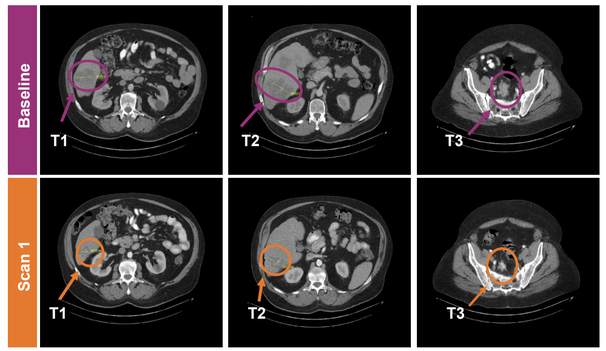
NKTR-255 + Cetuximab Led to Expansion and Increased Proliferative Capacity of NK and CD8$^+$ T Cells

Minimal changes in CD4$^+$ Tregs in blood were observed with NKTR-255 + cetuximab (data not shown)



Cetuximab administered with loading dose on Day −7 (not shown), and then weekly starting Day 1. CD, cluster of differentiation; NK, natural killer; SEM, standard error of the mean.

4L CRC Patient Achieved a Confirmed PR (–51.5%) with NKTR-255 + Cetuximab



	Tumor assessment	Lesion	Baseline	Scan 1 (Week 9)	Scan 2 (Week 18)
Target lesions measurements, mm	T1 – Liver	Right dome liver	61 x 51	38 x 34	22 x 14
	T2 – Liver	Interior right lobe liver	86 x 69	52 x 36	38 x 22
	T3 – Pelvis	Pelvic mass	47 x 42	32 x 25	34 x 23
Non-target lesions	NT01 – Lung	Lung nodule	Present	Present	Present
Sum of diameters, mm (% change from baseline)			194	122 (–37.5)	94 (–51.5)
Overall response (RECIST v1.1)				PR	PR

Prior treatment (best objective response): 1) FOLFOX + nivolumab + bevacizumab (PR, Mar 19 to Nov 19); 2. Aflibercept + FOLFIRI (SD, Feb 2 to Mar 20); 3. Regorafenib (SD, Mar 20 to Jun 20); 4. Trifluridine/tipiracil (progressive disease, Jul 20 to Oct 20). CRC, colorectal cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

CONCLUSIONS

- **The combination of NKTR-255 + cetuximab was well tolerated at NKTR-255 doses of 1.5 and 3.0 µg/kg Q21D and TRAEs were generally low-grade, transient, and easily managed**
- **Early evidence of on-target biological activity was observed: NKTR-255 led to expansion and proliferation of NK and CD8$^+$ T cells**
- **Early evidence of clinical activity was observed with 1 patient achieving a PR and 5 patients experiencing SD in this heavily pre-treated and highly refractory patient population**
- **The MTD/RP2D has not yet been reached and dose escalation of NKTR-255 + cetuximab in patients with R/R HNSCC and CRC is ongoing**

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DISCLOSURES
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ABBREVIATIONS
ADCC, antibody-dependent cellular cytotoxicity; AE, adverse event; C, cetuximab; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CPI, checkpoint inhibitor; CRC, colorectal cancer; CTCAE, Common Terminology Criteria for Adverse Events; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FcR, Fc receptor; HNSCC, head and neck squamous cell carcinoma; IFN, interferon; IL, interleukin; IV, intravenous; mAb, monoclonal antibody; MCP-1, monocyte chemoattractant protein-1; MOA, mechanism of action; MTD, maximum tolerated dose; NK, natural killer; P, panitumumab; PD, pharmacodynamic; PD-1, programmed death-1; PK, pharmacokinetic; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; Q21D, every 21 days; rh, recombinant human; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; TRAE, treatment-related AE; Tregs, regulatory T cells; SEM, standard error of the mean.

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