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 NKTR-255 is an investigational IL-15R α -dependent, polymer-conjugated, recombinant human IL-15 agonist designed to provide sustained pharmacodynamic (PD) responses without the need for daily dosing. NKTR-255 engages all IL-15 receptor binding complexes to expand, proliferate and activate natural killer (NK) and CD8+ T-cells. This Phase 1b/2 trial (NCT04616196) evaluates NKTR-255 +cetuximab in highly refractory patients with head-and-neck squamous cell carcinoma (HNSCC) or colorectal cancer (CRC).

Methods Successive cohorts received escalating doses of NKTR-255 (q3w) +cetuximab (250mg/m² sup >2</sup> weekly), 1 week after a loading dose of cetuximab alone. Safety (CTCAEv5.0; MTD/recommended Phase 2 dose [RP2D]) and efficacy (RECISTv1.1) were measured. PK/PD analyses were conducted, including assessment by flow cytometry/plasma cytokine analysis. Fold-change was calculated as treatment over baseline for NKTR-255 (baseline=1).

Results As of August 15, 2021, 12 patients had received ≥ 1 dose of NKTR-255+cetuximab; (37–70 years; 92% male; HNSCC n=4, CRC n=8; NKTR-255 1.5 μ g/kg n=7, NKTR-255 3.0 μ g/kg n=5). Patients had received a median 3.5 lines of prior therapy for metastatic disease. 11 patients had no response to the most recent prior therapy. Of the 12 patients, seven remain on treatment, with five not yet reaching first scan. RP2D has not yet been reached; dose escalation is ongoing.

10 patients experienced an AE; one G5 AE occurred (due to progression). Seven patients reported NKTR-255-related AEs (all G1-2, except one G3 [which resolved in 24 hours]). Any-cause AEs in $\geq 20\%$ were acneiform dermatitis, fatigue, and infusion-related reaction.

Treatment-induced transient changes in inflammatory cytokines, including IFN γ , MCP-1 and IL-6, at 1.5 μ g/kg (n=3) peaked 4 hours post-infusion and resolved by 24–48 hours. Mean T_{1/2} of NKTR-255 (1.5 μ g/kg dose, first cycle) was 27.8 hours.

Dose-dependent expansion of NK and CD8+ T-cells was observed in peripheral blood. For NK cells, mean peak fold-change was ~4-fold and ~6-fold, and for CD8+ T-cells was ~2-fold and ~3-fold (1.5 μ g/kg and 3 μ g/kg dose levels, respectively). NK and CD8+ T-cells demonstrated increased Ki67+ proliferative ability.

As of August 15, four patients in the 1.5 μ g/kg NKTR-255 dose cohort were response-evaluable: one CRC patient (4 prior metastatic treatment lines) reported a confirmed PR (~52%) after 3 cycles; two HNSCC patients reported SD.

Conclusions NKTR-255 was biologically active and led to expansion and proliferation of NK and CD8+ T-cells. Early dose-escalation data suggest that NKTR-255+cetuximab is safe and tolerable with preliminary anti-tumor activity. Updated data will be presented. NKTR-255, alone and in combination with daratumumab and rituximab, is also being evaluated in liquid tumors.

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Trial Registration NCT04616196

Ethics Approval The study was approved by site IRBs.

Consent N/A

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