# Results of a first-in-human Phase 1 trial of anchored IL-12 drug conjugate (ANK-101)

ABSTRACT # CT039

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## Introduction

- Systemic delivery of IL-12 is limited by significant toxicity
- To provide the therapeutic window, IL-12 was linked to aluminum hydroxide (designated ANK-101)
- A Phase I clinical trial was conducted to determine safety, PK, and biologic activity in patients with advanced solid accessible (Part 1) or visceral tumors (Part 2)
- Herein, we report Part 1 results

## Methods

- The study is an open-label Phase 1 multi-center trial with the primary objective of defining the safety and tolerability of ANK-101
- Adult patients with histologically or cytologically confirmed advanced solid tumors that had documented disease progression or were refractory to existing standard of care were eligible for enrollment
- A modified 3+3 dose escalation design was utilized using six independent cohorts with tolododekin alfa concentration escalation across six doses (see Fig. 1 below)
- Tolododekin alfa was delivered by intratumoral injection every 3 weeks for up to eight cycles
- Safety was analyzed by CTCAEv5 and response by RECIST v1.1
- PK, PD, and ADA assessments were done for the first two cycles
- Whole blood was used for peripheral immune cell analysis by FACS
- Serial tumor biopsies were obtained for IHC and Nanostring® analysis

## ANK-101 Dose Escalation Study Design

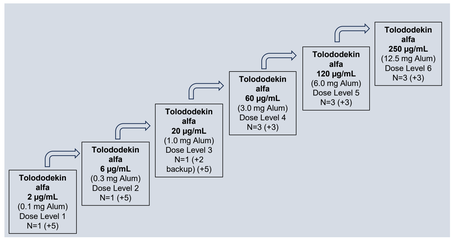



**Figure 1:** ANK-101 Phase 1 dose escalation study design
DLT = dose-limiting toxicity; N = number; RDE = recommended dose for expansion (same as RP2D) : Additional three patients enrolled into Cohort 3 (20 µg/mL dose level)

## ANK-101 Phase 1 Demographics

| | N=15 |
|---|---|
| **Age (years)** | |
| Median (min, max) | 68.0 (36, 79) |
| **Sex** | |
| Female | 9 (60.0) |
| Male | 6 (40.0) |
| **Race [n (%)]** | |
| White | 12 (80.0) |
| Not reported | 3 (20.0) |
| **Ethnicity** | |
| Not Hispanic or Latino | 14 (93.3) |
| Not Reported | 1 (6.7) |
| **Baseline ECOG [n (%)]** | |
| 0 | 9 (60.0) |
| 1 | 6 (40.0) |
| **Solid Tumor Type [n, (%)]** | |
| Melanoma | 7 (46.7) |
| Head and Neck | 4 (26.7) |
| Breast Cancer | 2 (13.3) |
| Bladder Cancer | 1 (6.7) |
| Cutaneous Squamous Cell Carcinoma | 0 |
| Other Cancer Type | 1 (6.7) |
| **Prior Systemic Therapies [n, (%)]** | |
| ≤ 3 | 4 (26.7) |
| > 3 | 11 (73.3) |
| **Prior IO Therapies [n, (%)]** | |
| Yes | 13 (86.7) |
| No | 2 (13.3) |
| **Number of doses administered** | |
| Median (min, max) | 4 (1, 8) |
| **Number of tumor injected per patient** | |
| Median (min, max) | 1 (1, 6) |
| **Number of volume (mL) used per patient** | |
| Median (min, max) | 11 (2, 43) |

**Table 1:** ANK-101 Phase 1 dose escalation study design

## ANK-101 Phase 1 Pharmacokinetics

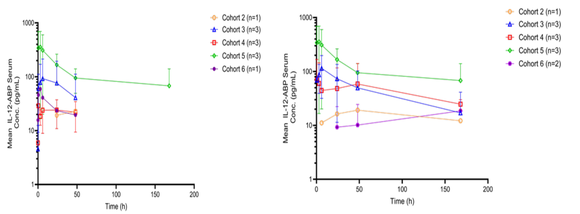



**Figure 2:** Serial serum samples were collected, and the mean plasma concentration (±SD) of IL-12-ABP was measured over time following Cycle 1 (left) and Cycle 2 (right). Overall, systemic levels of IL-12-ABP remained generally low, although a dose-dependent trend in exposure was observed at higher dosing cohorts.

## ANK-101 Phase 1 Pharmacodynamics

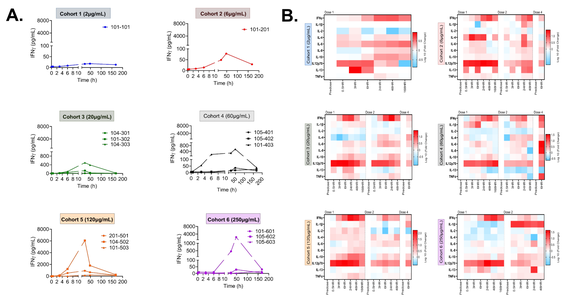



**Figure 3: (A)** systemic IFN-γ levels following Cycle 1 dosing. A transient and low systemic exposure of IFN-γ with a peak at 48 hours after dosing was observed. **(B)** Heatmaps summarizing the systemic levels of a panel of cytokines following treatment with repeated doses of tolododekin alfa. Systemic levels of IL-12 were lower than would be expected from the total dose of IL-12 administered. Despite low serum IL-12 levels there were measurable changes in other cytokines associated with anti-tumor response, especially IFNγ.

## ANK-101 Summary of Clinical Activity

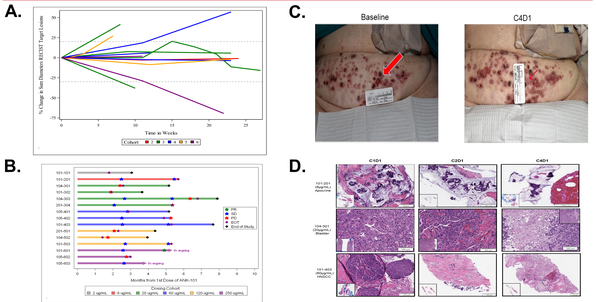



**Figure 4:** (A) spider plot representing of % change in sum diameters per RECIST in target lesions across all evaluable dosing cohorts (n=11 subjects). (B) Swimmer plot for individual patients across dosing cohorts (n=15 subjects). (C) Photograph of metastatic bladder cancer patient before (left) and after four cycles (right); arrow indicates injected lesion and regression seen in injected and satellite lesions after injection. (D) Representative H&E images from individual patients pre-and post-treatment with tolododekin alfa at indicated times show decreased tumor cellularity and increased necrosis.

## Subject 101-601 With Objective PR After 8 Cycles of ANK-101

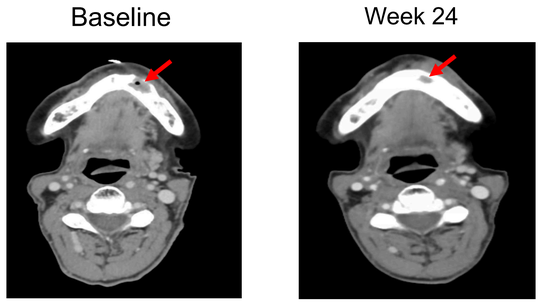



**Figure 5**: 79F HNSCC (tongue) Target lesion: -69.3%

## ANK-101 Related Adverse Events

| | Cohort 1 2 µg/mL (N=1) | Cohort 2 6 µg/mL (N=1) | Cohort 3 20 µg/mL (N=4) | Cohort 4 60 µg/mL (N=3) | Cohort 5 120 µg/mL (N=3) | Cohort 6 250 µg/mL (N=3) | Highest Grade | Total (N=15) |
|---|---|---|---|---|---|---|---|---|
| **Preferred Term** | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | | n (%) |
| Any study treatment related AE | 0 | 0 | 3 (75.0) | 1 (33.3) | 2 (66.7) | 2 (66.7) | 2 | 8 (53.3) |
| Fatigue | 0 | 0 | 0 | 1 (33.3) | 1 (33.3) | 0 | 2 | 2 (13.3) |
| Myalgia | 0 | 0 | 1 (25.0) | 0 | 1 (33.3) | 0 | 2 | 2 (13.3) |
| Abdominal distension | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Abdominal pain | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Arthralgia | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 2 | 1 (6.7) |
| Chills | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Conjunctivitis | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 2 | 1 (6.7) |
| Cough | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Cytokine release syndrome | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 1 | 1 (6.7) |
| Diarrhea | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Dry mouth | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Face oedema | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 2 | 1 (6.7) |
| Influenza like illness | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 2 | 1 (6.7) |
| Injection site pain | 0 | 0 | 0 | 0 | 0 | 1 (33.3) | 2 | 1 (6.7) |
| Malaise | 0 | 0 | 0 | 0 | 1 (33.3) | 0 | 1 | 1 (6.7) |
| Mucosal inflammation | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Nasal congestion | 0 | 0 | 0 | 0 | 0 | 1 (33.3) | 1 | 1 (6.7) |
| Pruritus | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Pyrexia | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |
| Vomiting | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 1 | 1 (6.7) |

**Table 2:** All related treatment emergent adverse events

## Conclusions

- Local ANK-101 monotherapy was well-tolerated at doses up to 250 µg/mL with no DLTs or Grade 3 or greater treatment-related TEAEs
- Highly efficient tumor retention with low systemic IL-12-ABP
- ANK-101 induced CD8⁺ T cell recruitment, PD-L1 expression, and inflammatory gene signatures consistent with biologic IL-12 activity
- Initial results suggest clinical activity with two partial responses and disease control rate of 80% in a heavily pre-treated and diverse patient population

## ANK-101 Tumor Tissue Biomarker Analysis

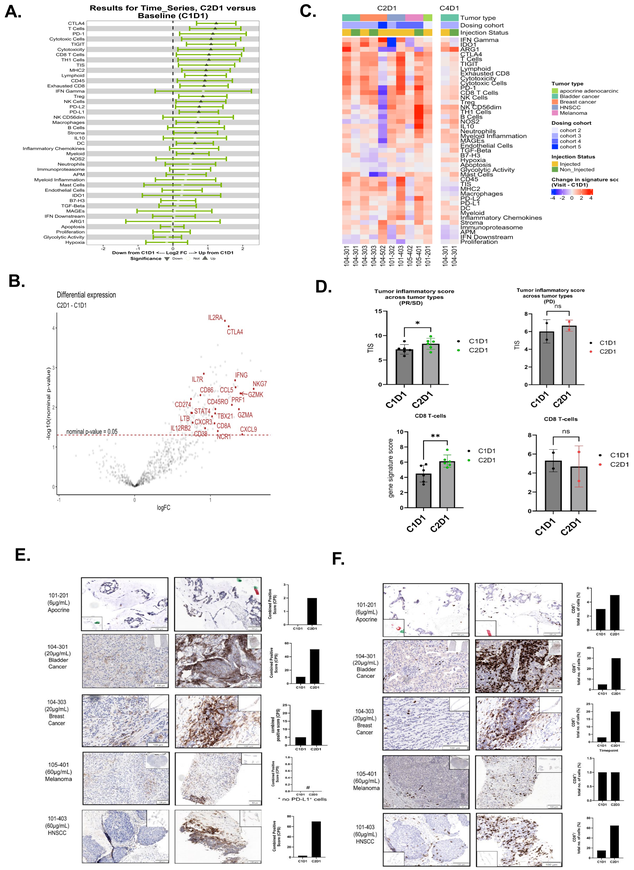



**Figure 6:** Biomarker analysis on tumor biopsies collected pre and post-treatment **(A-D)** Gene transcriptional analysis (Nanostring IO360™ Panel). **(A)** The 'All Signatures' forest plot shows the differential expression between time points **(B)** Volcano plot shows the most highly upregulated IL-12 pathway related genes as indicated **(C)** The heatmap displays differential signature score per patient across all evaluable dosing cohorts, in all tumor types assessed, and in both injected and non-injected tumors, after one cycle (C2D1) and after three cycles of doing (C4D1) **(D)** Upregulation of the Tumor Inflammatory Score (TIS) and CD8⁺ T cell gene signatures were associated with treatment outcomes. Two-sided P values were calculated per paired t-test **(E-F)** Representative IHC images of **(E)** CD8⁺ and **(F)** PD-L1 staining of paired tumor biopsies pre and post-treatment (21 days) from individual patients across different dosing cohorts and tumor types as indicated. The bar graphs indicate corresponding %positive cells as scored by the pathologist.

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