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

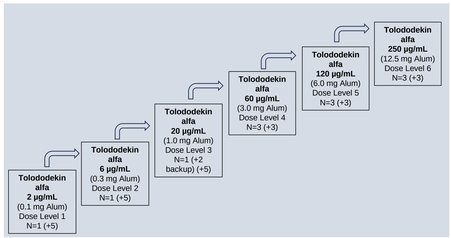


Figure 1: ANK-101 Phase 1 dose escalation study design
DLT = dose-limiting toxicity; N = number; RDE = recommended dose for expansion (same as RP2D) : Additional three patients enrolled into Cohort 3 (20 µg/mL dose level)

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

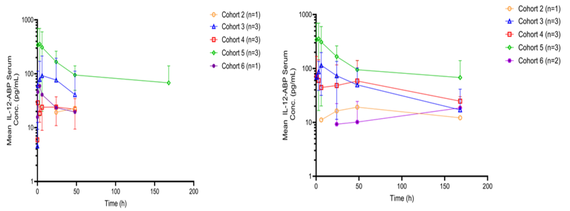


Figure 2: Serial serum samples were collected, and the mean plasma concentration (±SD) of IL-12-ABP was measured over time following Cycle 1 (left) and Cycle 2 (right). Overall, systemic levels of IL-12-ABP remained generally low, although a dose-dependent trend in exposure was observed at higher dosing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

ANK-101 Phase 1 Pharmacodynamics

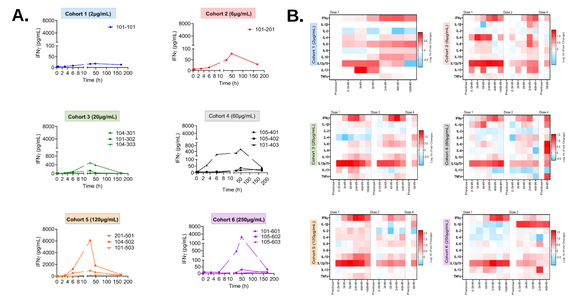


Figure 3: (A) systemic IFN-γ levels following Cycle 1 dosing. A transient and low systemic exposure of IFN-γ with a peak at 48 hours after dosing was observed. **(B)** Heatmaps summarizing the systemic levels of a panel of cytokines following treatment with repeated doses of tolododekin alfa. Systemic 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

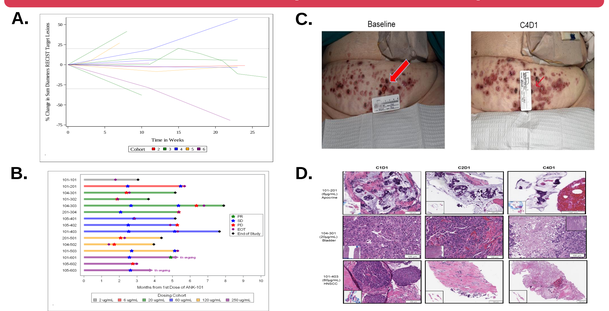


Figure 4: (A) spider plot representing of % change in sum diameters per RECIST in target lesions across all evaluable dosing cohorts (n=11 subjects). (B) Swimmer plot for individual patients across dosing cohorts (n=15 subjects). (C) Photograph of metastatic bladder cancer patient before (left) and after 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

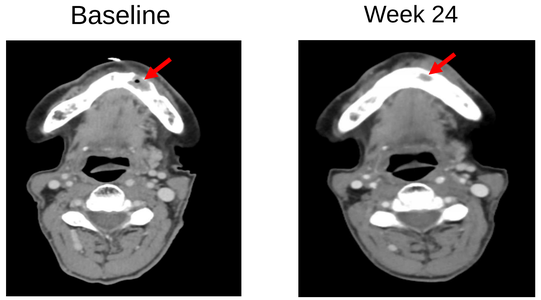


Figure 5: 79F HNSCC (tongue) Target lesion: -69.3%

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

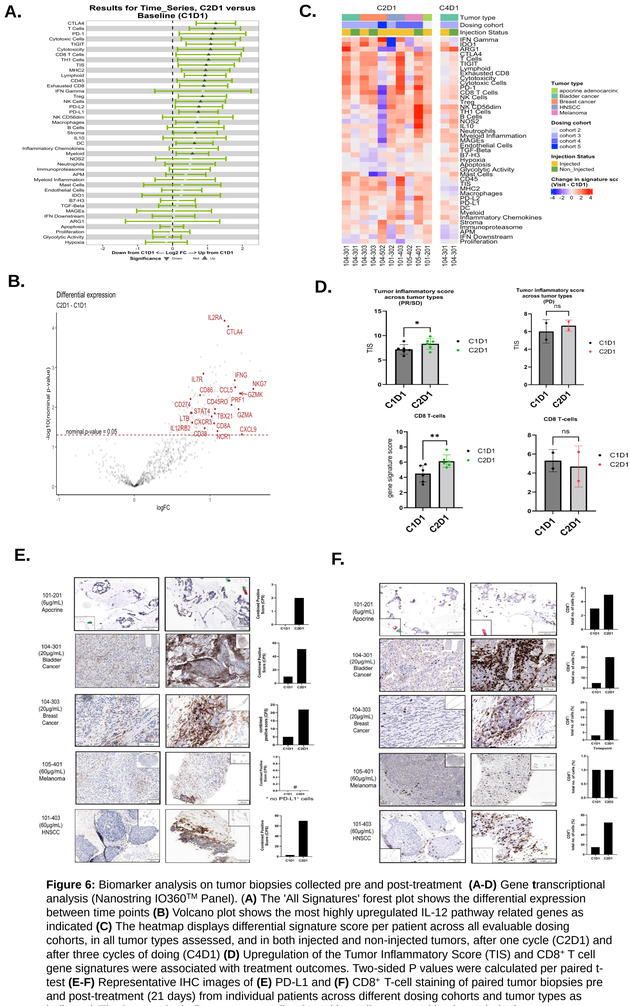


Figure 6: Biomarker analysis on tumor biopsies collected pre and post-treatment **(A-D)** Gene transcriptional analysis (Nanostring IO360™ Panel). **(A)** The 'All Signatures' forest plot shows the differential expression between time points **(B)** Volcano plot shows the most highly upregulated IL-12 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 dosing (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)** PD-L1 and **(F)** CD8⁺ T-cell 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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