A Phase 1, Open-Label, Dose Escalation Study of the Safety and Tolerability of ANK-101 in Advanced Solid Tumors*

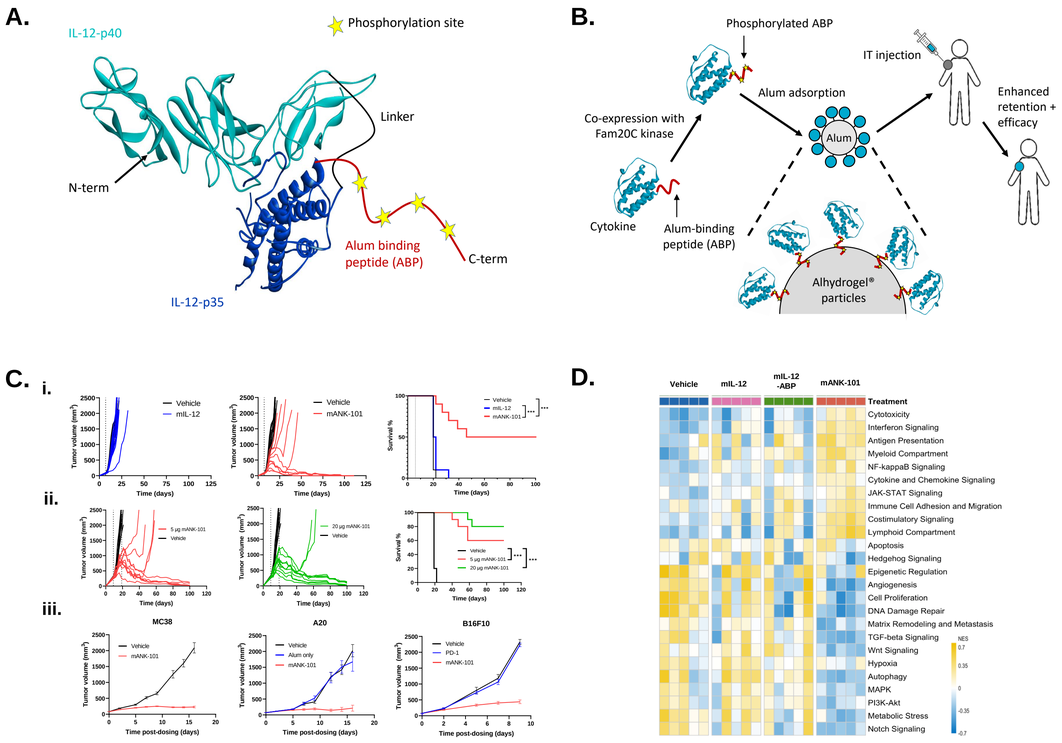
ABSTRACT #TPS2689

Jong Chul Park[1], Marcus Butler[2], Brendan Curti[3], Leisha A. Emens[4], Danielle Pastor[5], Joseph Elassal[4], Howard L Kaufman[4], John M. Kirkwood[6]

[1]Massachusetts General Hospital, Boston, MA; [2]Princess Margaret Cancer Center, Toronto ON, Canada; [3]Providence Portland Medical Center, Portland, OR; [4]Ankyra Therapeutics, Cambridge, MA; [5]National Cancer Institute, Bethesda, MD; [6]University of Pittsburgh, Pittsburgh, PA[4]

Background

Figure 1: Schematic of ANK-101 complex



A. Single-chain human IL-12 with wild-type p40 and p35 sequences was genetically fused at its C-terminus to an alum-binding peptide (ABP) to form IL-12-ABP, and complexed with a 10X mass excess of Alhydrogel® to form ANK-101.

B. Cytokines and other potent immune agonists are genetically fused to a proprietary ABP and co-expressed with Fam20C kinase to phosphorylate the peptide at multiple serine residues. The phosphorylated fusion proteins are mixed with the Alhydrogel® (aluminum hydroxide) to form a spontaneous complex. Cytokine/Alhydrogel® complexes are administered IT where they are locally retained due to their size and charge, leading to a cytokine depot that promotes potent and long-lasting local immune activation.

C. (i) Tumor volume (TV) and survival for BALB/c mice (10/group) bearing ~80 mm^3 CT26 tumors that were administered a single IT injection of vehicle, 5 µg mIL-12, or 5 µg mANK-101. (ii) Tumor growth curves and survival of BALB/c mice bearing ~300 mm^3 CT26 tumors administered two IT doses of vehicle, 5 µg or 20 µg mANK-101 ten days apart. (iii) 5 µg mANK-101 was tested for anti-tumor response in various syngeneic tumor models.

D. C57Bl/6 mice bearing MC38 tumors were administered a single IT injection of vehicle or 5 µg of mANK-101. Tumors were harvested 7 days post-treatment and transcriptional analysis was performed by Nanostring (PanCancer IO 360 panel).

- Cytokines have demonstrated anti-tumor activity in patients with cancer but usually require high doses resulting in significant systemic toxicity
- Human interleukin-12 (IL-12) is composed of a p35 and p40 subunit (Fig. 1A) and exerts its effector function through activation of T and NK cells and induction of interferon-gamma
- Systemic IL-12 promotes potent anti-tumor effects but was associated with serious systemic toxicity in clinical trials
- ANK-101 is a novel anchored IL-12 drug composed of IL-12 linked to aluminum hydroxide (Alhydrogel®) via an alum-binding peptide (ABP) (Fig. 1B)[1]
- ANK-101 allows prolonged retention of IL-12 within the tumor microenvironment without systemic toxicity [2-3]

Objectives

Primary Objectives:

- The safety and tolerability of escalating doses of ANK-101
- To determine the RDE of ANK-101

Secondary Objectives:

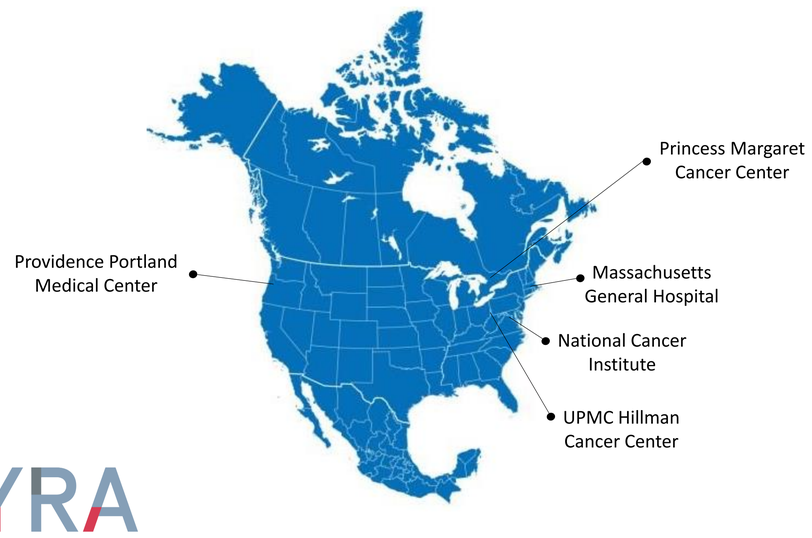
- To evaluate the PK of ANK-101
- To evaluate the immunogenicity (ADA) of ANK-101
- To evaluate the preliminary clinical activity of ANK-101

Exploratory Objectives:

- To determine immune responses and biomarker changes in participants treated with ANK-101
- To assess the QOL while on ANK-101 treatment

Clinical Sites

Figure: 2 Clinical Sites



ANKYRA

* Study protocol has been amended since abstract submission

Study Design

Figure 3: Phase 1 dose-escalation and dose-expansion schema

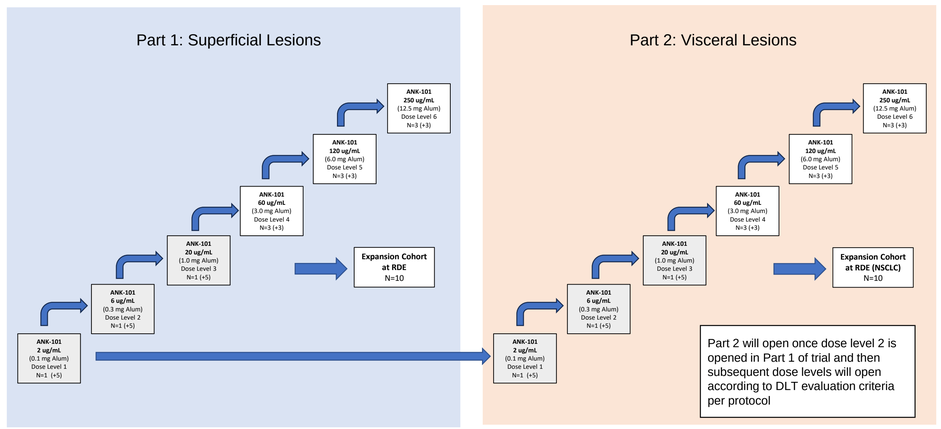
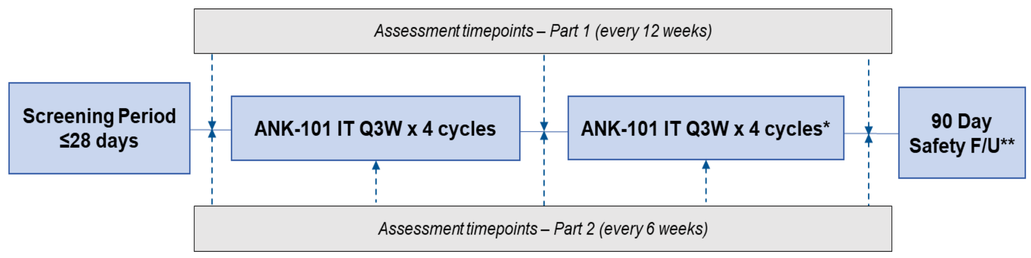


Figure 4: Treatment plan



- The study is comprised of 2 parts: Part 1, superficial tumors, and Part 2, visceral tumors. Both parts have dose-escalation and dose-expansion cohorts (Fig. 3)
- Part 1 will be restricted to superficial lesions and Part 2 will enroll subjects with visceral disease; Part 2 cohorts may begin following the DLT period in Part 1 dosing cohort
- In dose-escalation cohorts in Part1 and Part 2, the accelerated dose-escalation method with a single subject for the first 3 dose levels (DL) will be used followed by the standard 3+3 design for the next 3 DLs
- There will be a 21-day DLT period after the first dose at each cohort
- Subjects will receive four doses every 3 weeks and may repeat an additional four doses in the absence of disease progression or significant toxicity (Fig. 4)
- Imaging will be conducted at baseline and every 3 months
- Blood and tumor biopsies will be collected for PK and immune analyses

Study Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
≥ 18 years of age	Injectable tumors impinging upon major airways or blood vessels
Have histologically or cytologically confirmed advanced solid tumor malignancy. Participants with metastatic disease will be eligible. **Part 1 only:** Tumor(s) must be cutaneous, subcutaneous, soft tissue, or nodal in locations that are visible, palpable, or detectable by ultrasound. **Part 2 only:** Participants must have at least one tumor located in deep viscera able to be accessed by interventional radiologic or endoscopic procedures for injection (e.g., ultrasound or computed tomography [CT] guided). **Part 2 Dose Expansion Cohort only:** Histologically confirmed Stage III or Stage IV NSCLC.	Prior treatment with recombinant interleukin-12 (IL-12). Have received live vaccines within 28 days prior to the start of ANK-101 treatment (C1D1). **Note:** Administration of attenuated vaccines is allowed. Have primary or acquired immunodeficient states (e.g., leukemia, lymphoma). Have had prior organ or hematopoietic stem cell transplantation.
Have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Have known history of hepatitis B virus, known active hepatitis C virus.
Have documented disease progression, be refractory to, or intolerant of existing standard of care (SOC) therapy(ies) known to provide clinical benefit for their condition (including surgical cure) or not be eligible for SOC therapy(ies).	HIV-infected participants with a history of Kaposi sarcoma and/or Multicentric Castleman Disease.
Have adequate renal function defined as creatinine clearance ≥ 50 mL/min as determined by the Cockcroft-Gault equation.	Have active autoimmune disease or medical conditions requiring chronic steroid treatment (i.e., ≥ 20 mg/day prednisone or equivalent).

Study Status

As of May 15, 2024, 5 participants have been enrolled in the study. For additional information clinicaltrials.gov identifier NCT # 06171750

References

1. Agarwal Y, Milling LE, Chang JYH, et a. Intratumorally injected alum-tethered cytokines elicit potent and safer local and systemic anticancer immunity. Nat. Biomed. Eng. 6(2):129-143, 2022. PMID:35013574
2. Wittrup KD, Kaufman HL, Schmidt MM and Irvine DJ. Intratumoral anchored cytokine therapy. Expert Opin. Drug Deliv. 19(6):725-732, 2022. PMID:35638290
3. Battula S, Papastoitsis G, Kaufman HL, Wittrup KD and Schmidt MM. Intratumoral aluminum hydroxide-anchored IL-12 drives potent antitumor activity by remodeling the tumor microenvironment. JCI Insight 8(23):e168224, 2023. PMID:38063196

Acknowledgments

The authors wish to thank the patients and their families who have elected to participate in the clinical trial. We also thank the investigators, co-investigators, and study teams at participating centers. We thank Saran Vardhanabhuti, PhD for statistical support.
All author disclosure forms flied on-line at ASCO.