ANKYRA

# Anchored IL-12 Drug Conjugate:
## A New Approach to Local Skin Cancer Treatment

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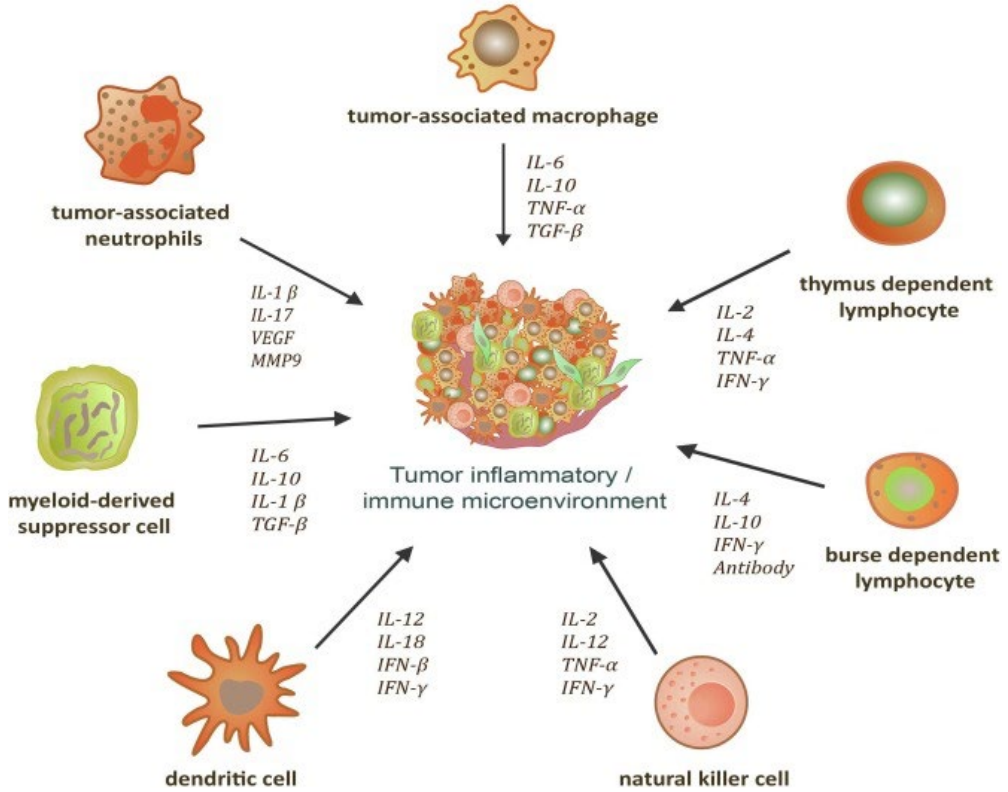
# Disclosures

- I am an employee of Ankyra Therapeutics
- I am on the Board of Directors for Crichton Biosciences
- I serve on advisory boards for Castle Biosciences, Marengo Therapeutics, Tatum Biosciences, and Virogin Therapeutics
- I have received honoraria from the Society for Immunotherapy of Cancer
- I have stock in Replimune, Inc.

# Cytokines regulate immune responses and the TME



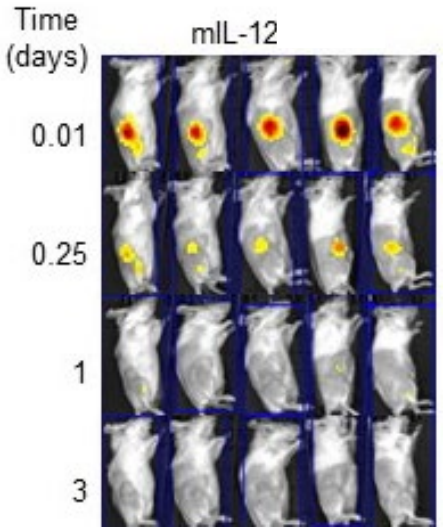

- Cytokines can regulate the type and intensity of immune responses
- Therapeutic cytokines are approved for cancer therapy
- Generally, anti-tumor activity require supra-physiologic doses
- Can be associated with significant toxicity

Li et al. Int Immunopharmacol. 2020

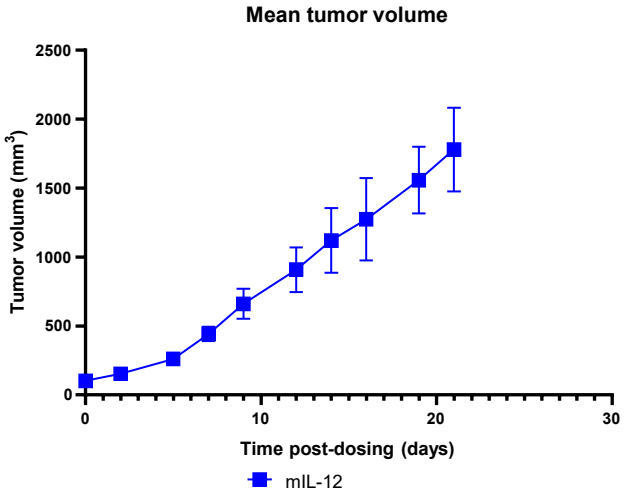
# Local delivery limits toxicity but does not result in durable retention

Rapid clearance limits drug exposure to tumors, which leads to

- Reduced efficacy
- Necessitating frequent administrations
- Increased systemic exposure and potential toxicity

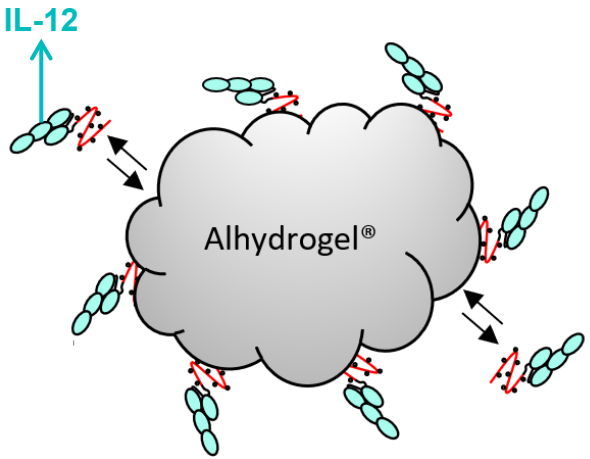



CT26 model, single injection



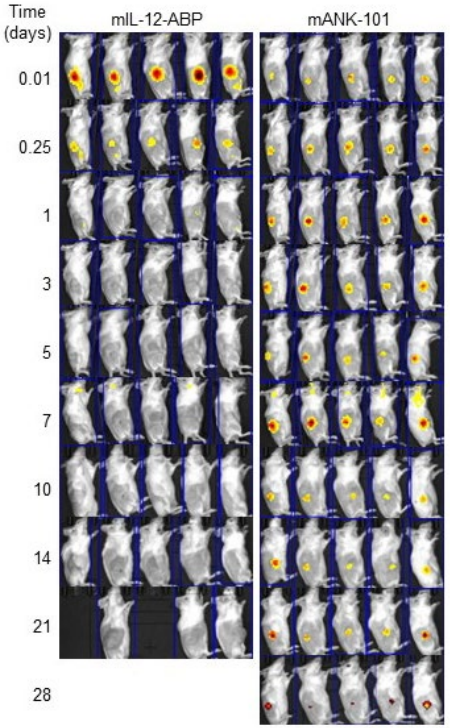

Adapted from Battula S, et. al. *JCI Insight* (2023)

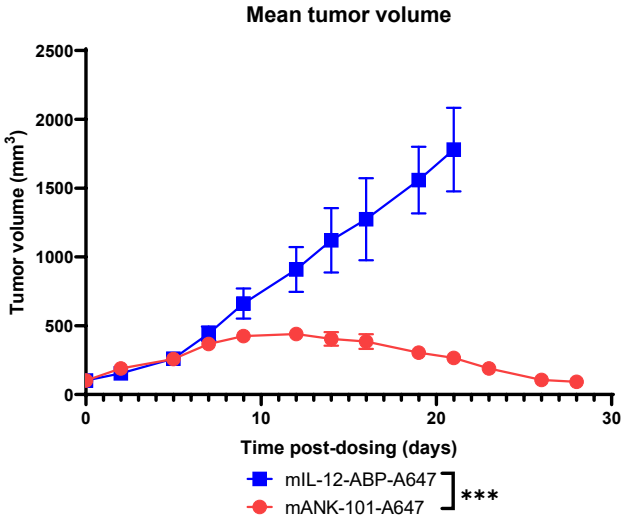
# Lead Drug Candidate: ANK-101 (anchored IL-12)




- ✓ IL-12–ABP bound to aluminum hydroxide (Alhydrogel®) via alum-binding peptide to form a stable complex
- ✓ Retained at the tumor site for several weeks
- ✓ Very slow release of IL-12
- ✓ Shows potent monotherapy therapeutic activity in multiple murine tumor models
- ✓ Has favorable safety profile
- ✓ In phase 1 clinical trial for solid tumors

# mANK-101 remains in the tumor for weeks and induces potent therapeutic activity



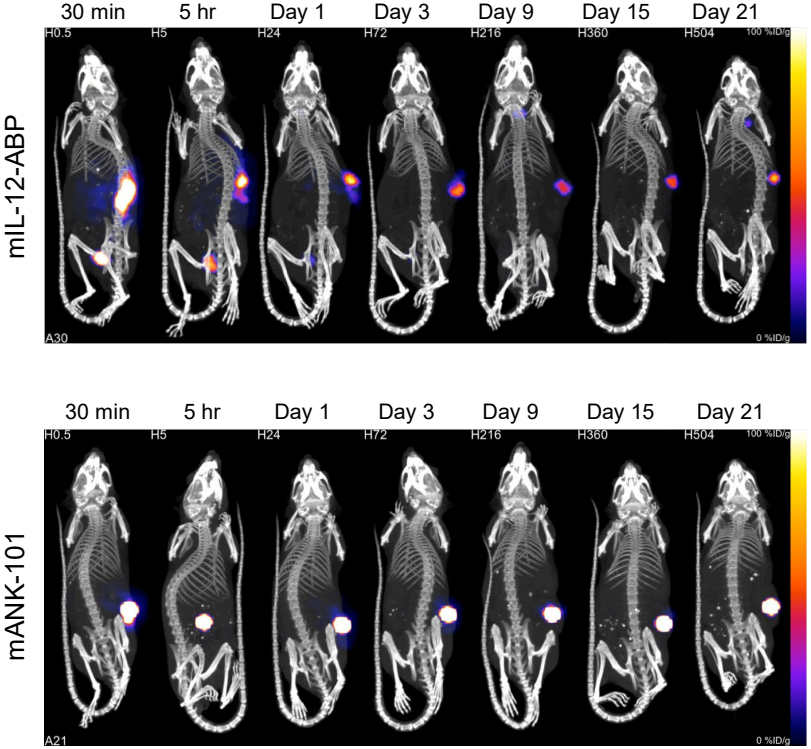



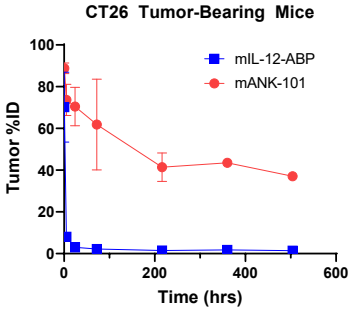

Following single injection, mANK-101 was still detectable at study completion on day 28

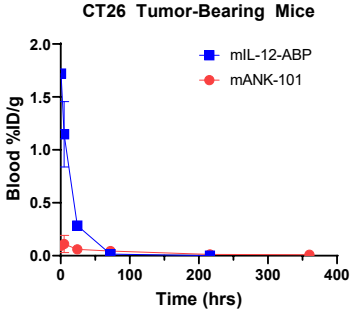
Extended retention significantly enhanced antitumor efficacy without toxicity

Established CT26 colorectal cancer model

# mANK-101 retained at injection site for at least 21 days

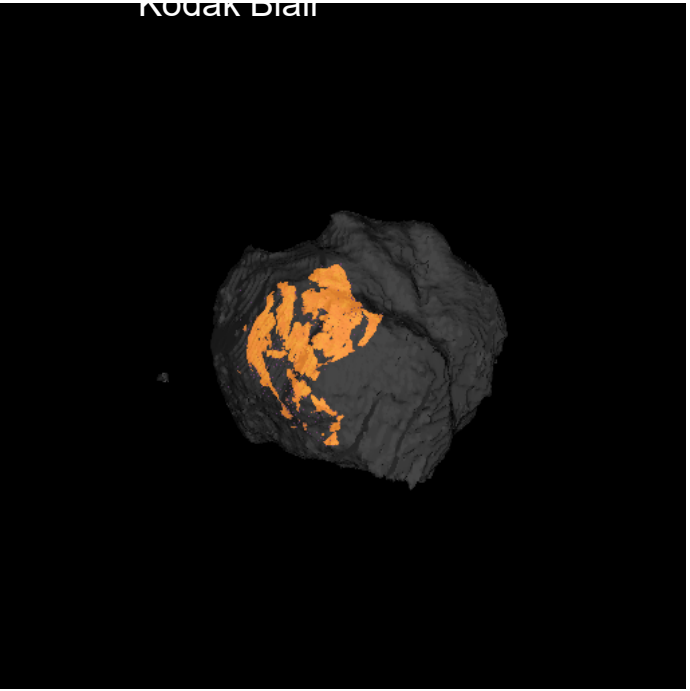


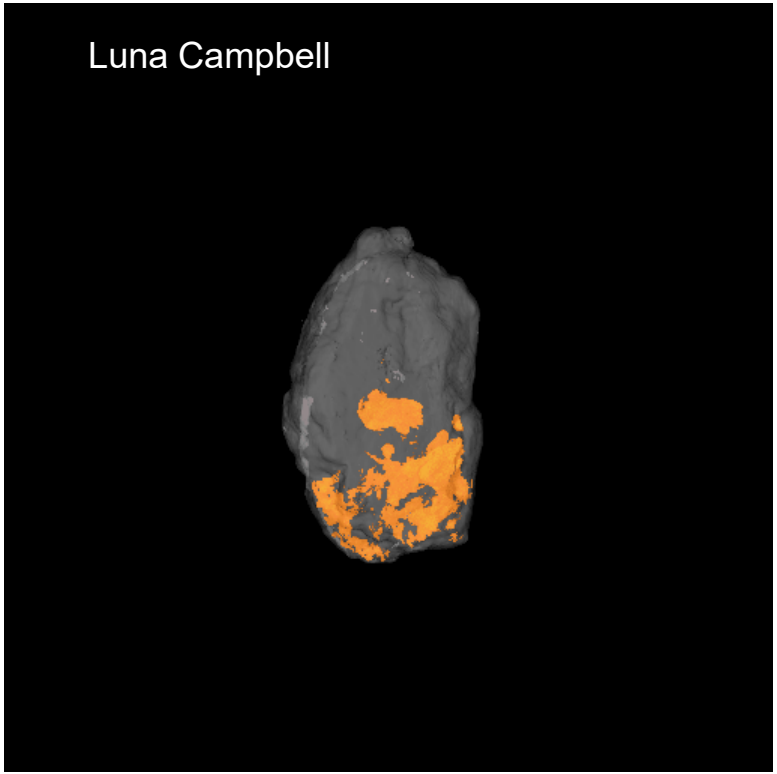




SPEC/CT images after single IT administration of $^{125}$I-labeled mIL-12-ABP and mANK-101

# Drug biodistribution in established canine tumors

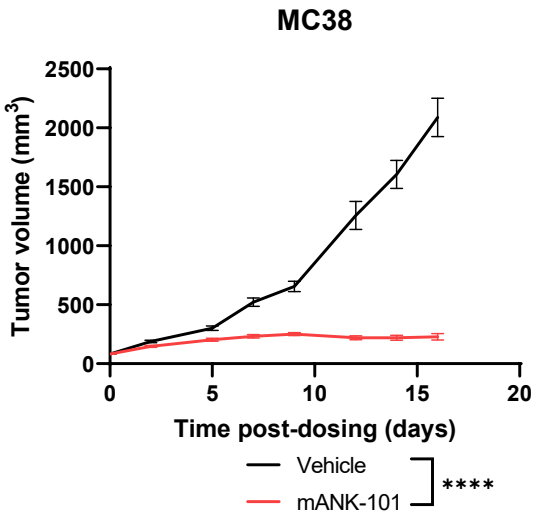


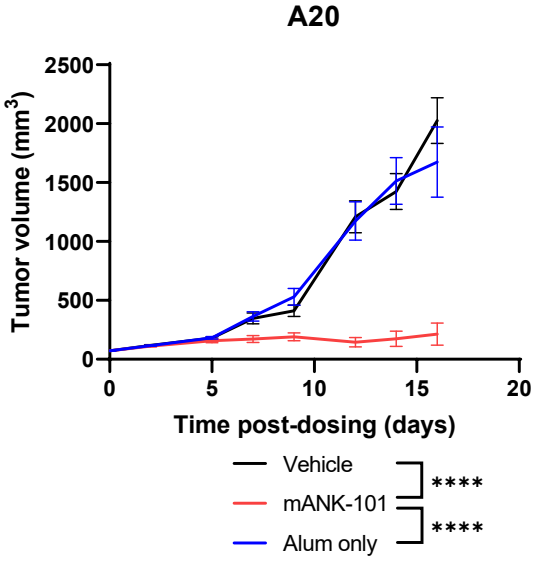


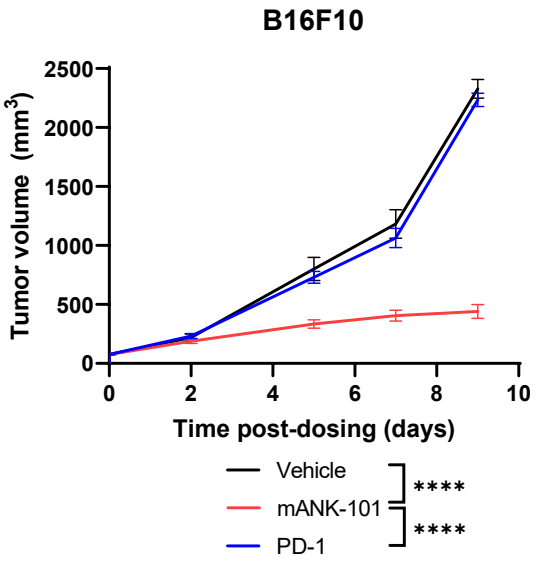
# mANK-101 induces therapeutic activity

Highly immunogenic

Poorly immunogenic



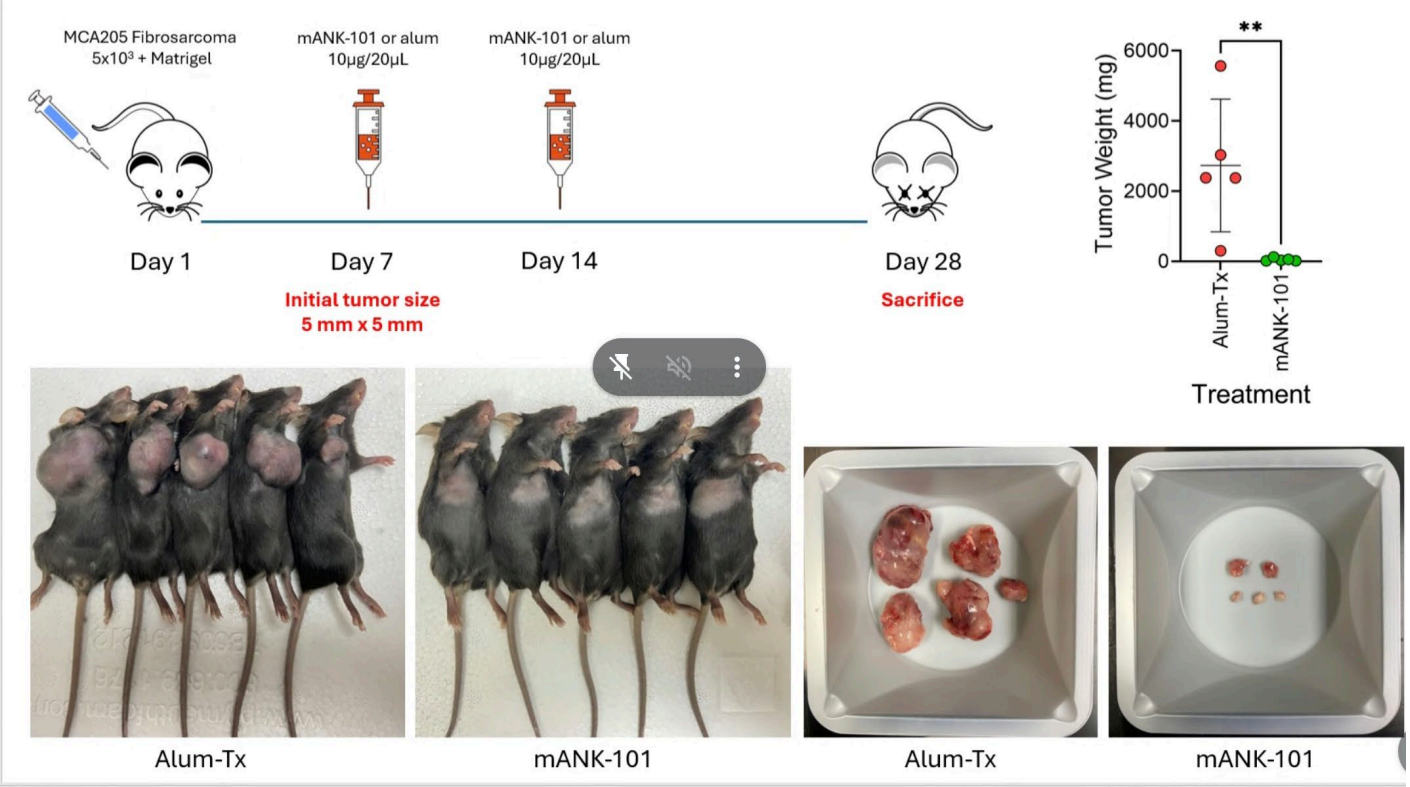




Single IT injection in MC38 model

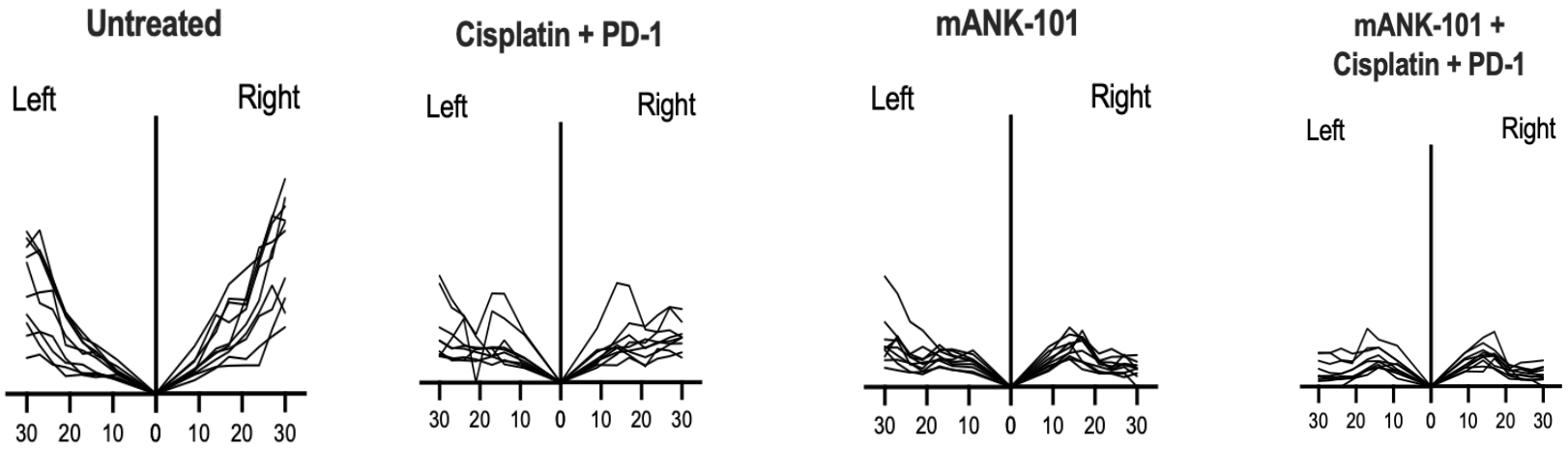
Two IT injections (2nd on D7) in A20 & B16F10 models

# mANK-101 induces regression against murine sarcoma



# mANK-101 has abscopal activity and synergizes with α-PD-1 and chemotherapy

mANK-101, alone or in combination induces abscopal responses




Left = Non-injected; Right = Injected

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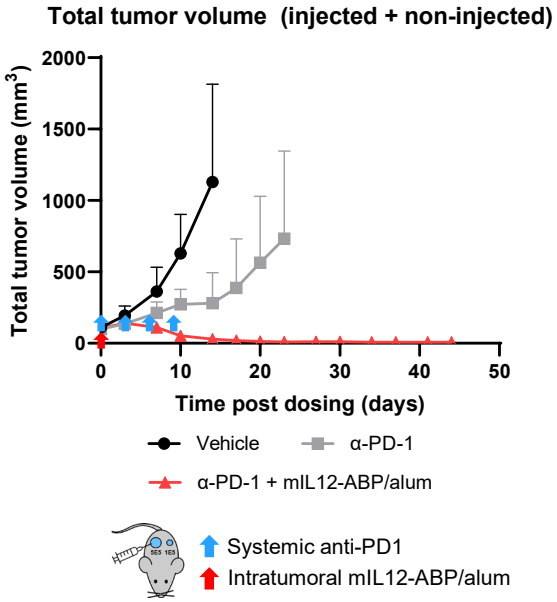
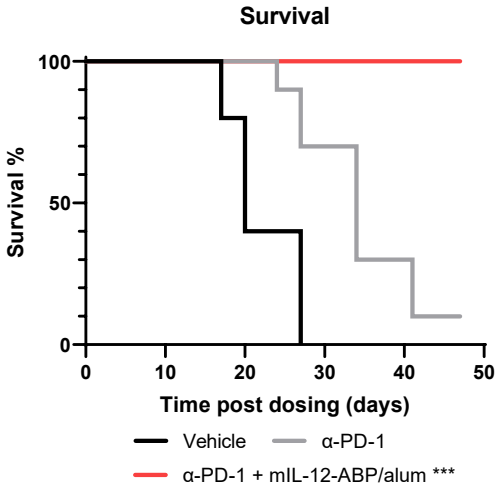
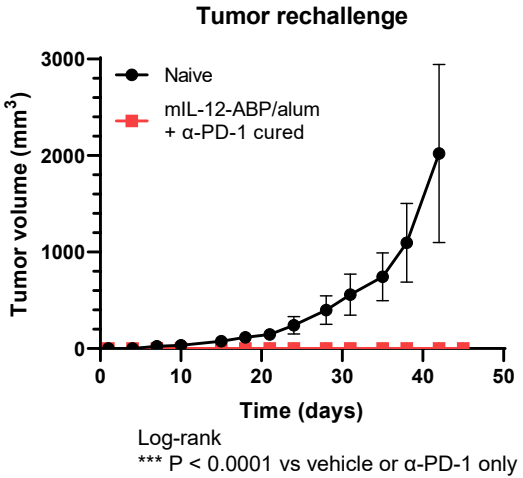
# mANK-101 promotes survival and immunological memory



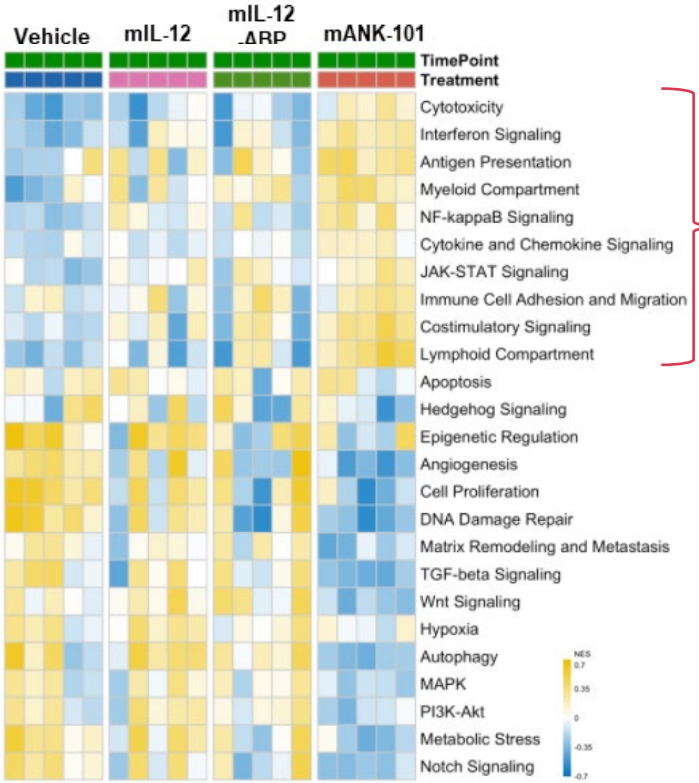

Single IT injection in MC38 model



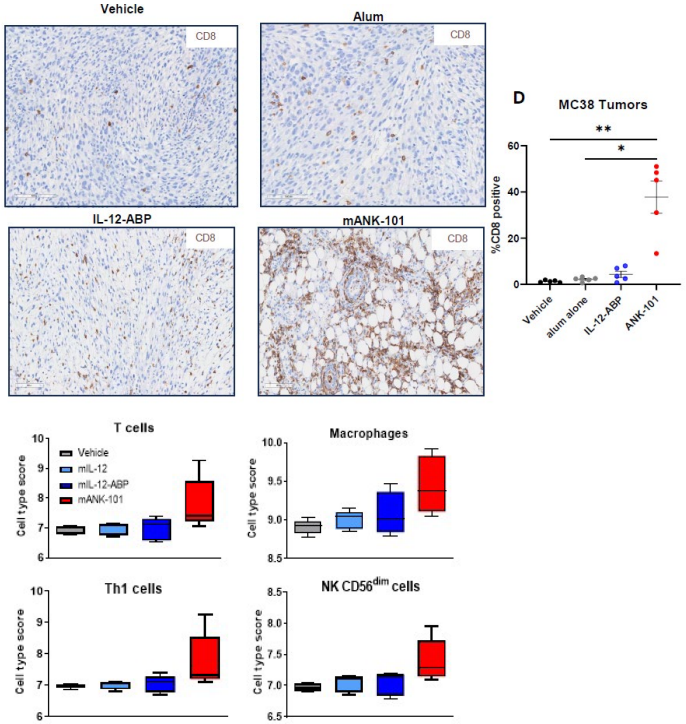

Log-rank
*** P < 0.0001 vs vehicle or α-PD-1 only

# mANK-101 remodels the tumor microenvironment and promotes immune cell recruitment and activation



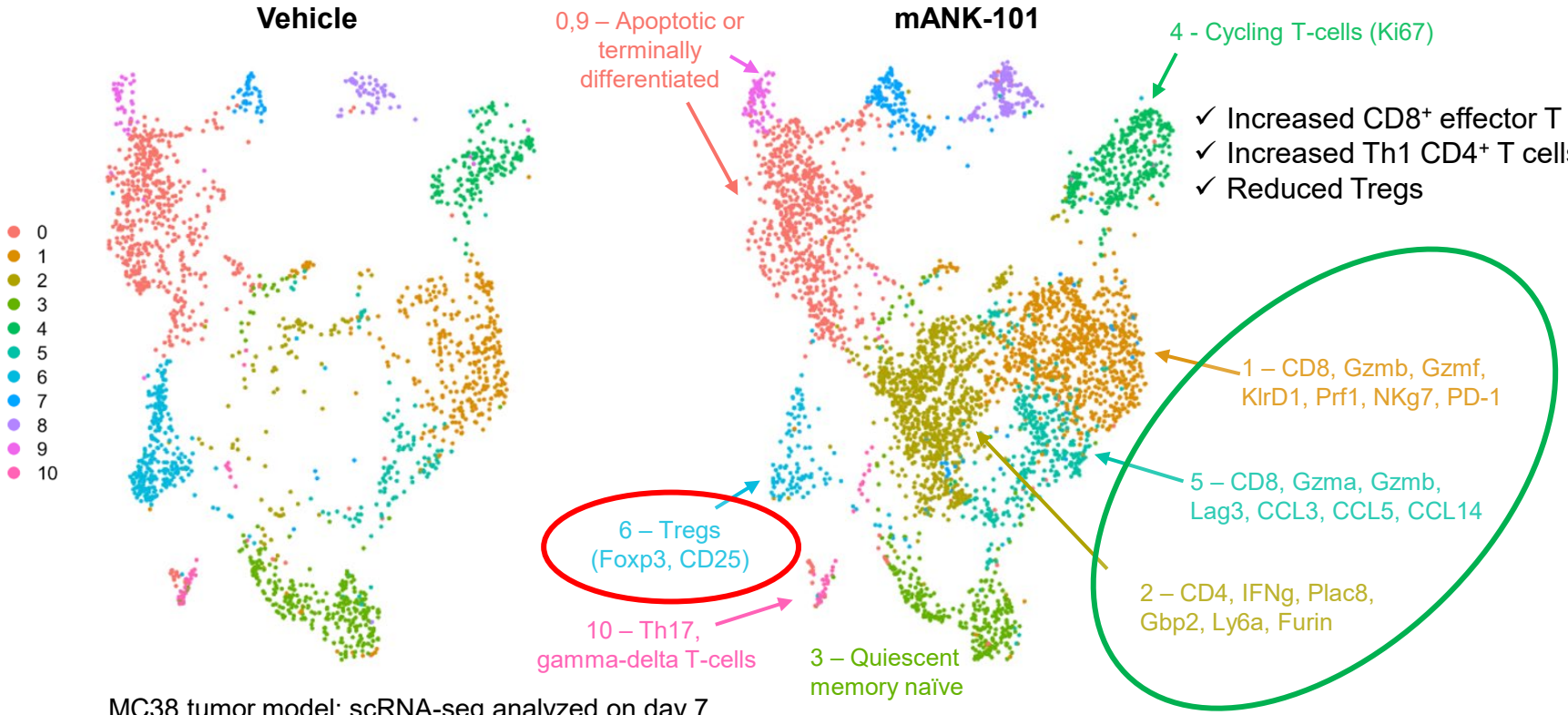

7 days post-treatment:

- Upregulation of genes associated with immune cell activation and cytotoxicity
- Consistent with increased infiltration of T cells, macrophages, and NK cells



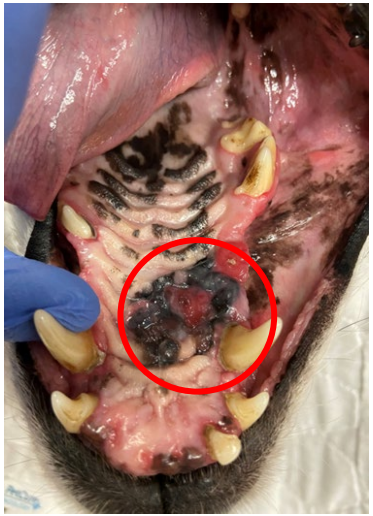

MC38 model

# mANK-101 remodels the tumor microenvironment

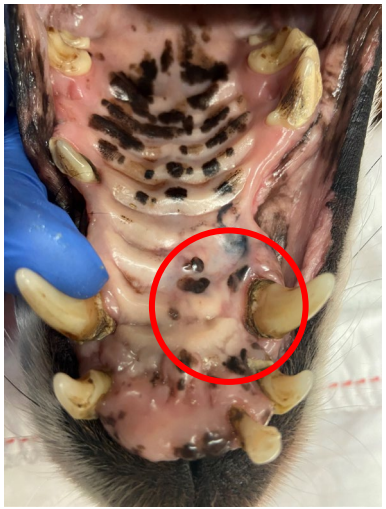



MC38 tumor model; scRNA-seq analyzed on day 7

# Anchored immunotherapy demonstrates therapeutic benefit in dogs

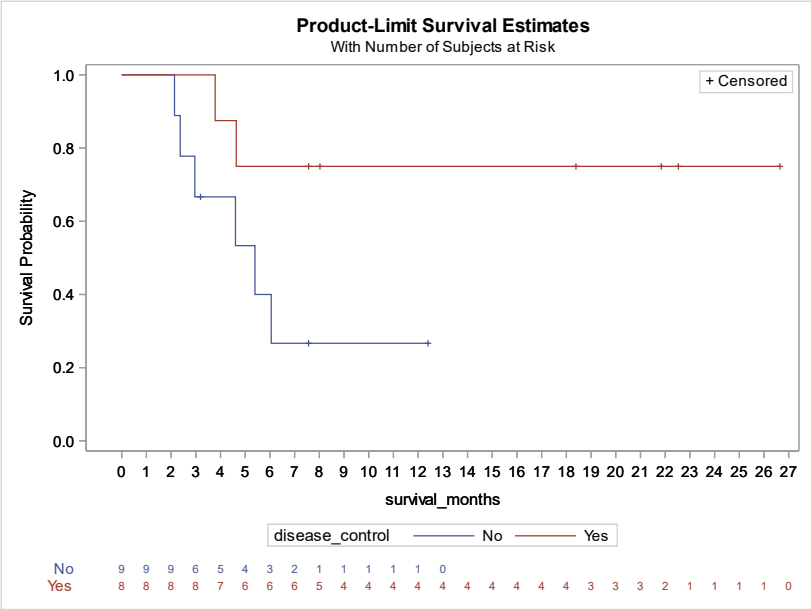


*Day 1, Pre-injection*



*Day 336, Follow-up*

Overall survival after treatment by best response comparing Disease Control Rate vs Progressive Disease

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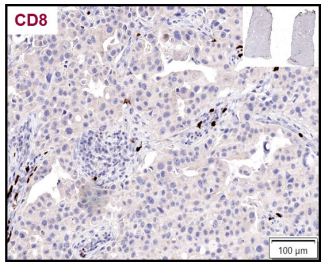
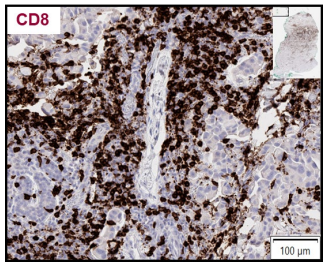
# Biological activity after a single dose of ANK-101

## Increased Immune Cell Infiltration

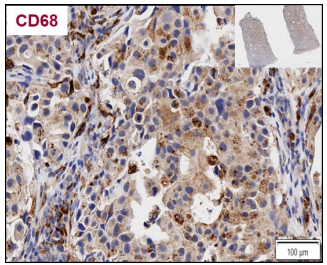
**D1 (Baseline)** **D21 (Post-Treatment)**

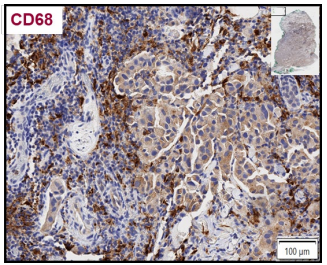
CD8+ T-cells



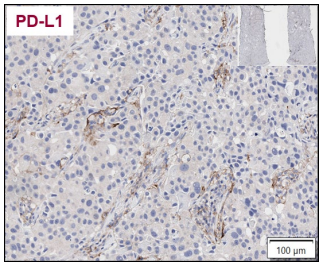

Macrophage

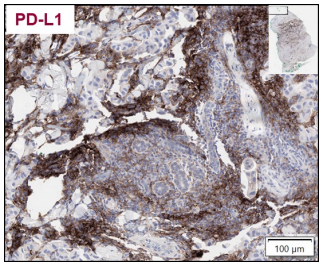



## Increased PD-L1 Expression

**D1 (Baseline)** **D21 (Post-Treatment)**

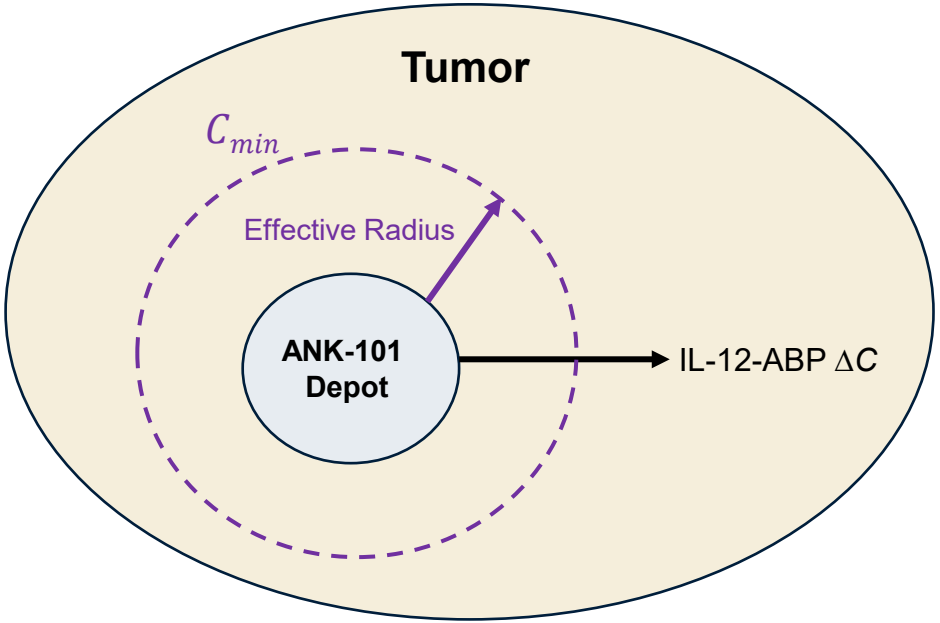


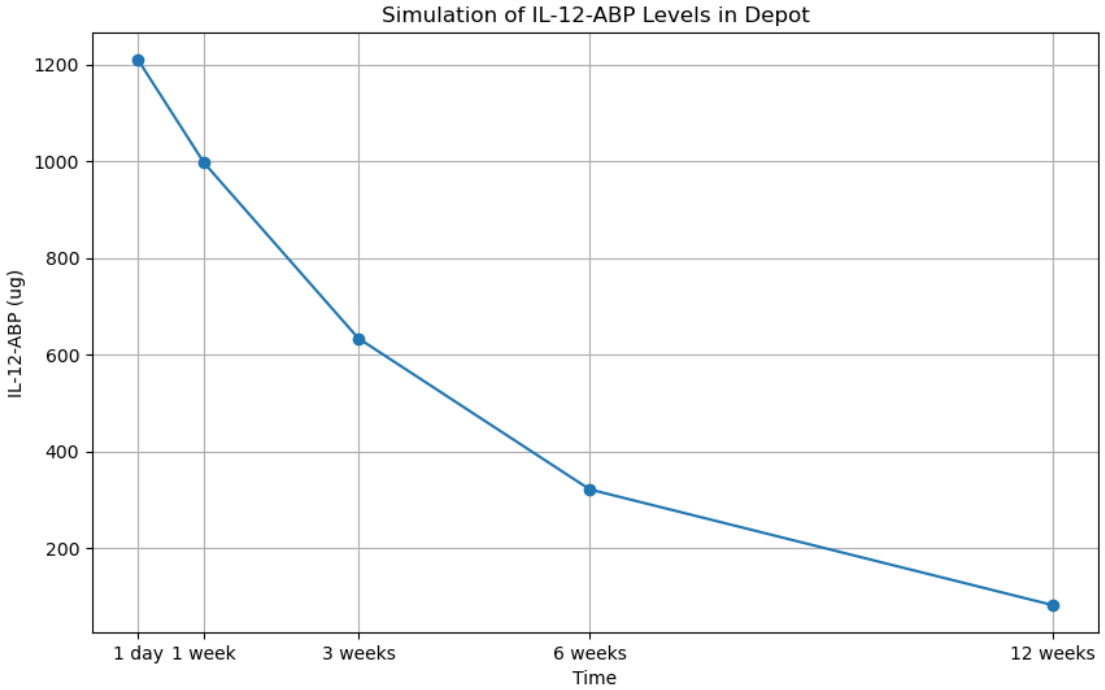

| | |
|---|---|
| Subject ID: | ANK001-104-301 (74 yrs, Female, White) |
| Dose Cohort: | 3 (20 µg/mL) |
| Diagnosis: | Bladder Cancer |
| Body Site: | Skin Abdomen |
| Prior Therapies: | BCG, Cisplatin/Gemzar, Herceptin, Atezolizumab, Enfortumab Vedotin, Nivolumab |

# Diffusion-Limited Drug Release Model of ANK-101

The **Diffusion-Limited Drug Release Model** is designed to predict the diffusion kinetics of IL-12-ABP through tumor tissue. This simple model can be used to predict the radius of effective drug concentration surrounding the depot and the amount of drug remaining in the depot over time.

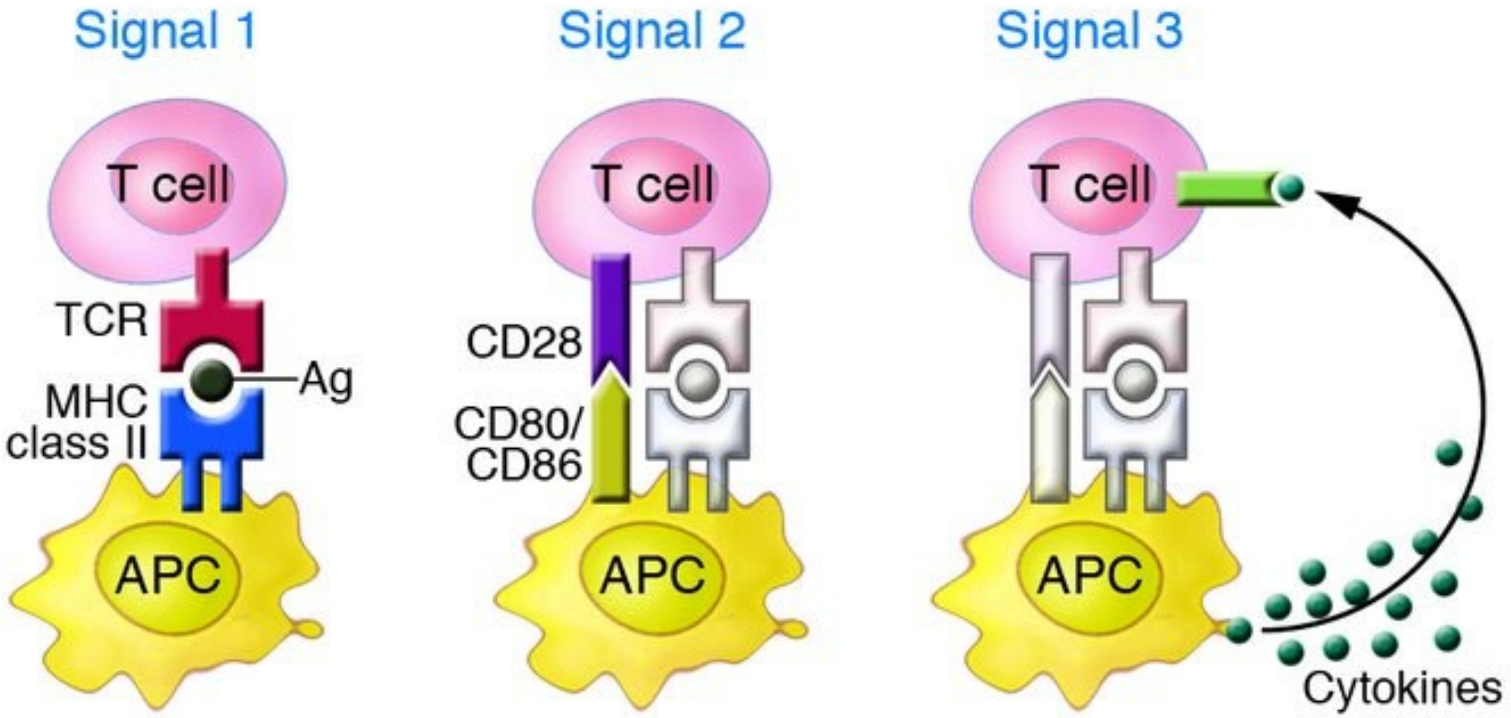


# Simulation of drug amounts remaining in the depot




- Model predicts approximately 50% of drug remaining at 3 weeks, which aligns well with our empiric observations in mice where ~40% of dose remained at 3 weeks by SPECT/CT imaging

# T cell activation

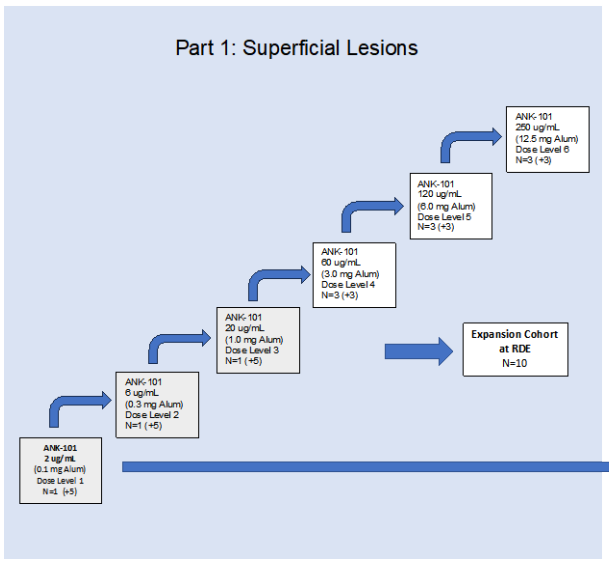


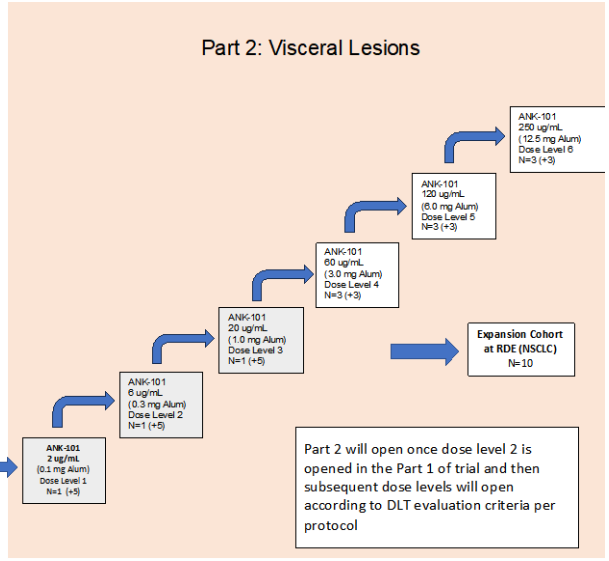

Gutcher and Becher, JCI 2007

# Overview of FIH Trial

Monotherapy

Combo (ANK-101+PD-(L)1)




**CSCC in patients who have failed PD-1**

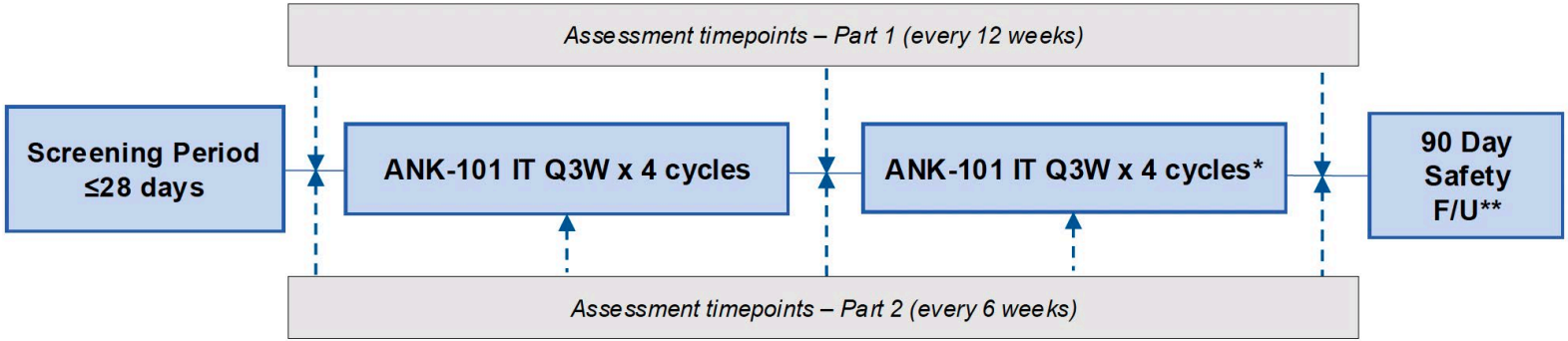
ANK-101 @ RDE + cemiplimab

N=15

**Notes:**

- Part 1 to include backfill of two doses of interest to total of 10 pts each (Cohort 5 + one other Cohort to be determined after dose-escalation complete)
- Part 3 CSCC combo cohort is part of drug supply deal with Regeneron

# ANK-101 Phase 1 Study Schema




*if there is no significant clinical deterioration as determined by the Investigator, or unacceptable toxicity at Week 12, participants may receive four more cycles provided they continue to meet eligibility criteria

**The 90-day Safety Follow Up/EOS visit is to occur either by phone or in clinic 90 days from the last dose of ANK101. If the visit occurs in-clinic, then all assessments should be performed. If this visit is by phone, then only AEs and concomitant medications will be collected.

# ANK-101 Is Well-Tolerated Through Six Dose Cohorts

- Treatment-emergent AEs ***related to study drug*** seen in 14 patients across both Parts 1 and 2
  - All ≤ Grade 2 in severity
  - Myalgia and chills most commonly seen (N=10 episodes, each)
  - Five instances of G1 CRS in 3 patients (all in Part 1 and treated at 120 ug/mL)
    - Based on fever
    - Recorded all at one site
  - ***No overlapping toxicities with known safety profile of anti-PD1 antibodies***

- SAEs reported in three patients (all not related to drug):
  - Soft tissue infection, choledocholithiasis, procedure-related mild pneumothorax

- Seeing signs of clinical activity at low dose levels
  - Two patients now have reached end of dosing schedule with at least SD
  - Disease control rate in Part 1 of 67% in a heavily treated population
  - Evidence of pathologic responses in some patients

# Acknowledgments


- **Patients and families** on our clinical trials

- Our clinical investigators:
  - **Marcus Butler**, MD, Univ. of Toronto
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  - **John Kirkwood**, MD, Univ. of Pittsburgh
  - **Jong Park**, MD, Mass General Hosp.

- **Tim Fan**, DVM, PhD, University of Illinois

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  - **James Gulley**, MD, PhD

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  - **Julia Stephanus**
  - **Ira Gordon**, DVM

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