PNQ-103-1:
A Novel Adenosine A_{2B} Receptor antagonist – An Oral Immune Modulator for Oncology

PNQ-103-1: A_{2B} Adenosine Receptor (A_{2B} AdoR) Antagonist Stage: Preclinical Development

- PNQ-103 is potent and selective adenosine A_{2B} receptor antagonist
  - PNQ 103-1 is an oral pro-drug of PNQ-103
- Excellent efficacy established in Preclinical PoC studies in 2 cancer models as a stand-alone therapy
- Potential for first -in-class compound, with very sparse competition
- Few months away from IND filing
- Long patent life till 2031

PNQ-103/ 103-1: Potential Therapeutic Value and Clinical Positioning

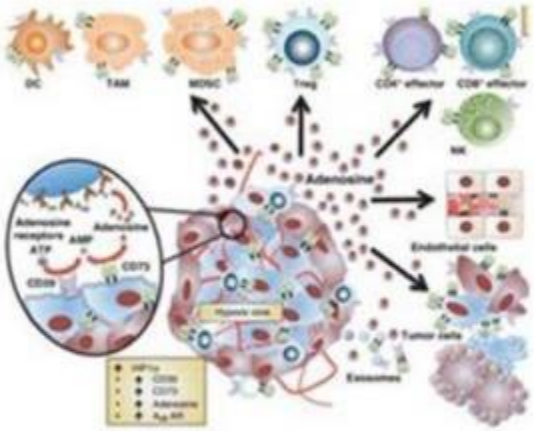
PNQ-103/103-1 is a novel oral immuno-oncology therapy for the treatment of multiple cancers including metastasizing cancers across a wide spectrum of patients, either as a stand-alone or in combination with other Standard of Care therapies

Therapeutic Value & Positioning

- Widespread use in multiple cancers
  - Prostrate
  - Head and Neck
  - Melanoma
- Effective in treatment naïve as well as refractory , immune resistant patients
- Potential synergy with check-point inhibitors including :
  - Anti- PD-1, PD-L1
  - CTLA-4, IBB-4

Adenosine $_{2B}$ Receptor : An Immune- Checkpoint Modulator

A_{2B} receptor antagonism that impacts the Adenosine – hypoxia axis to disrupt signaling leading to increased differentiation and proliferation of tumor cells while down-regulating several anti-inflammatory molecules and immunoregulatory cells



- A_{2B} receptors are ubiquitously expressed on multiple immune cells including T cells, B cells, NK cells , MDSCs and APCs and is involved in adenosine mediated effects in tumor microenvironment.
- A_{2B} receptor is also expressed on several tumors and endothelial cells.
- A_{2B} receptor blockade
  - **directly reduces tumor cell growth**
  - enhances apoptosis,
  - reduces endothelium-derived angiogenesis,
  - reduces neovascularization and metastasis.

PNQ-103: Affinity, Potency & Receptor Subtype Selectivity

Receptor Human	Ki (nM)	Selectivity Ratio
A_{2B}	13	1
A_1	300	23
A_{2A}	1800	138
A_3	> 60,000	> 4000

Receptor Human	Ki (nM)	Selectivity Ratio
A_{2B}	66	1
A_1	>30,000	>400
A_{2A}	>10,000	>150
A_3	>30,000	>400

IL-6 is a target & disease relevant biomarker

Inhibited IL-6 production in **normal human lung fibroblasts** with IC_{50} 47 nM (n=3)

- PNQ-103 is a potent and selective A_{2B} receptor antagonist

PNQ-103-1: Excellent Efficacy

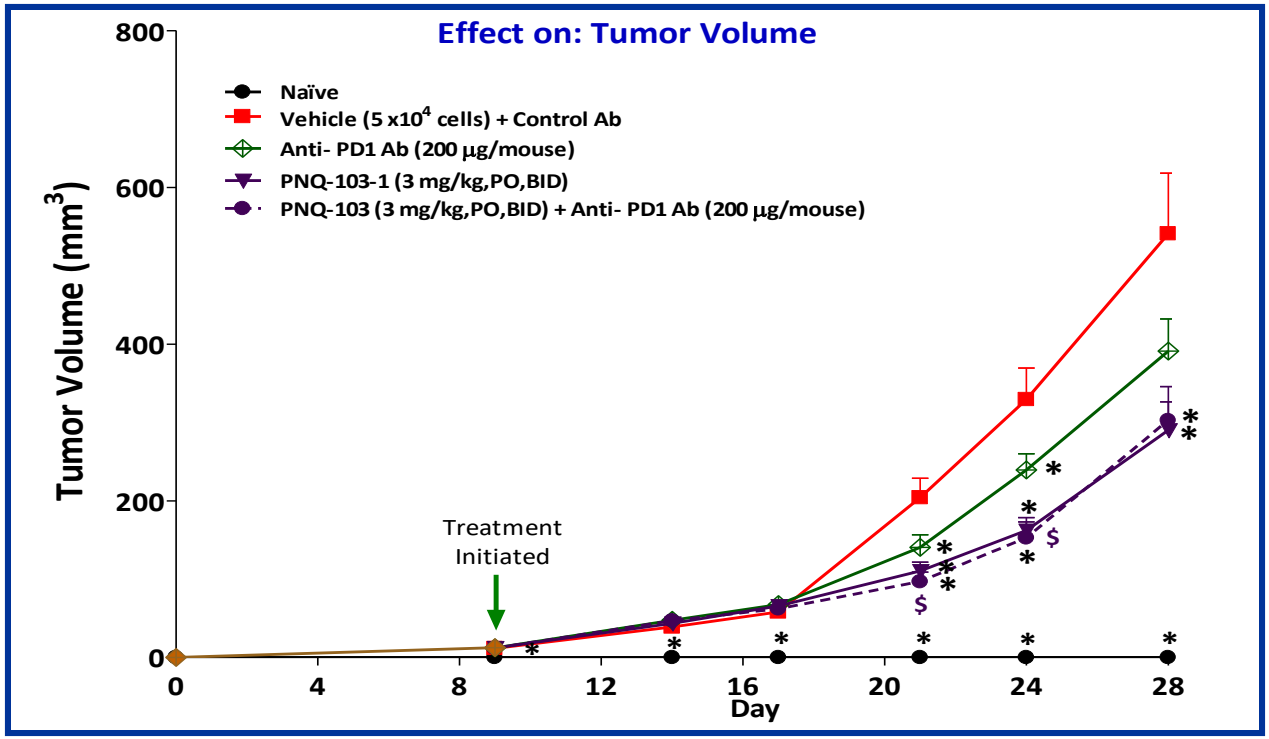
Effect of PNQ -103-1 was evaluated as a mono-therapy and in combination with anti-PD-1 antibody in two murine models

- **4T1 Syngeneic Breast Cancer Mouse Model**
- **CT-26 Syngeneic Colon Cancer Mouse Model**

- PNQ-103-1 demonstrated excellent efficacy as stand alone therapy in two immunotherapy resistant models

- PNQ-103 has shown a beneficial effect on RBC from Sickle Cell patients *in vitro*
- Efficacy has also been demonstrated in preclinical models of
  - Asthma
  - Lung Fibrosis

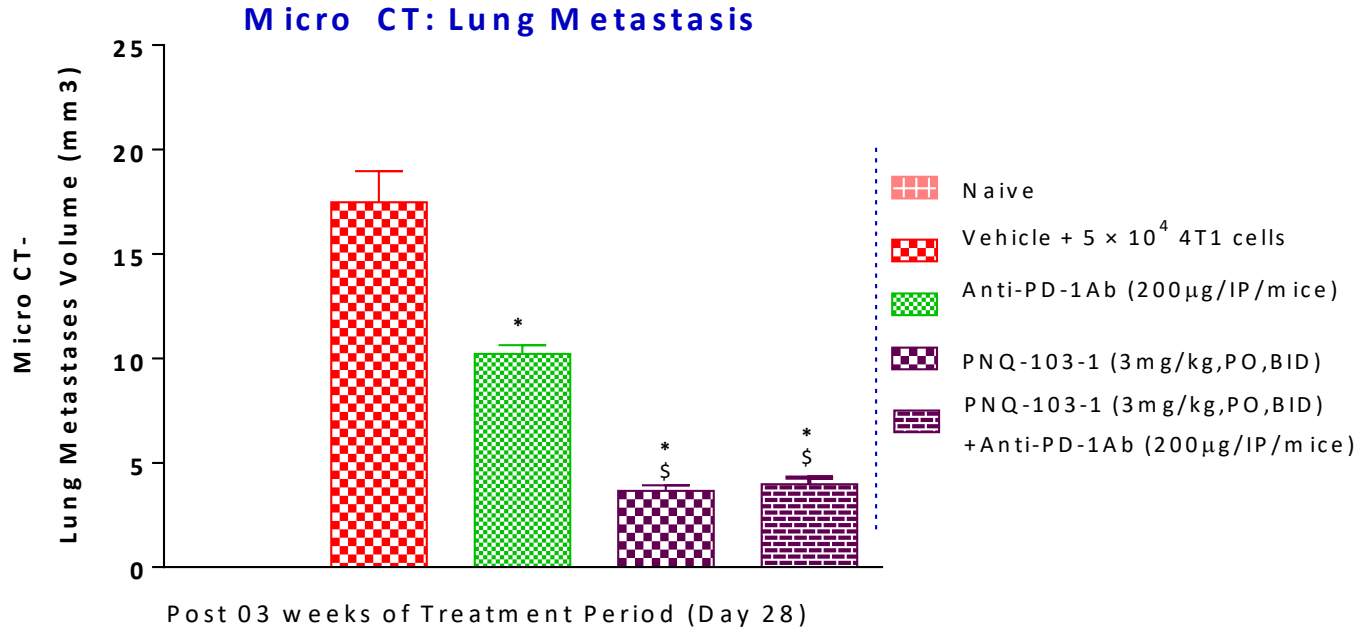
PNQ-103-1: Tumor Volume in 4T1 Breast Cancer Model



*Data is shown as Mean ± S.E.M.(n=11-12). One-way ANOVA followed by Dunnett's Multiple Comparison Test .*P < 0.05 versus Control Ab + Vehicle ; .$P < 0.05 versus Anti-PD-1, unpaired 't' test*

PNQ 103-1 (3mpk, PO, BID) significantly **decreased Tumor volume**
The effect of PNQ 103-1 alone is significantly greater than Anti-PD-1

PNQ-103-1: Lung Metastasis in 4T1 Breast Cancer Model

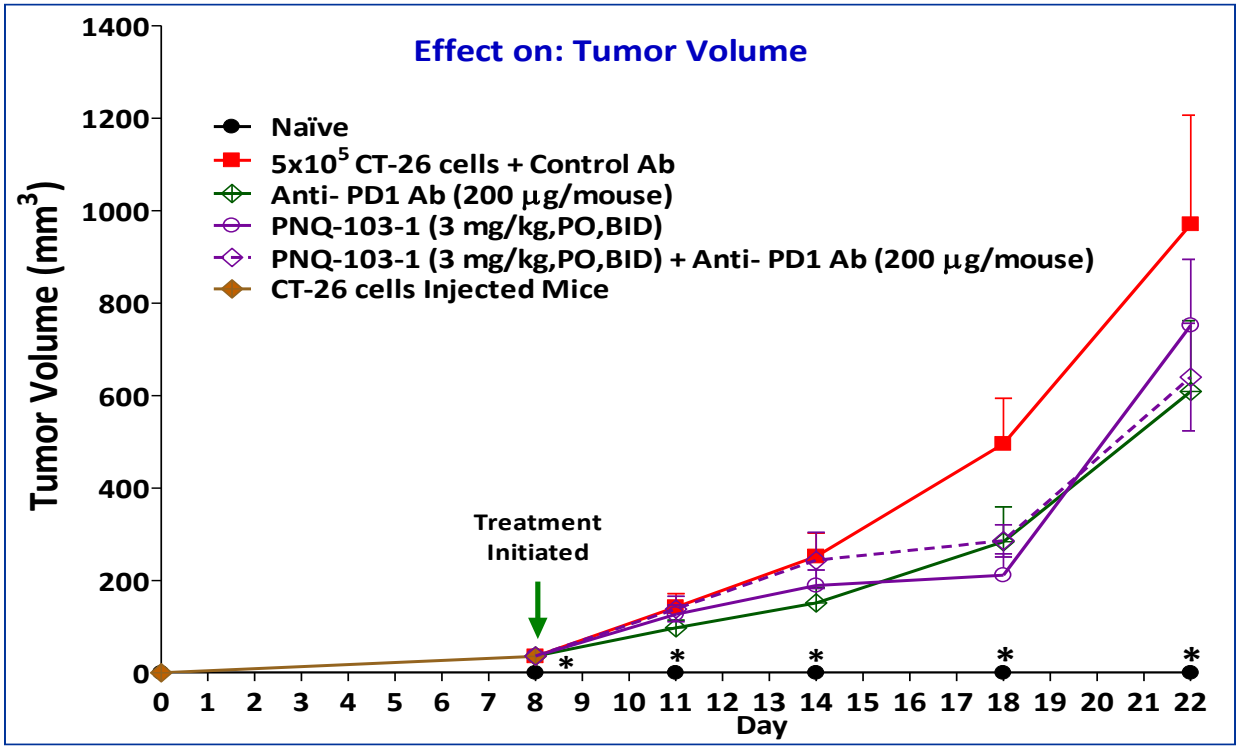


*Data is shown as Mean ± S.E.M.(n=6);One-way ANOVA followed by Dunnett's Multiple Comparison Test.*P < 0.05;*

** Significant different as compared with Vehicle Group ; Significant different as compared with Anti-PD-1 Ab$P < 0.05*

- PNQ-103-1 (3mg/kg, PO, BID) alone significantly **decreased Lung Metastases** greater than Anti-PD-1

PNQ-103-1: Tumor Volume in CT26 Colon Cancer Model



Data is shown as Mean ± S.E.M.(n=10-12).
*One-way ANOVA followed by Dunnett's Multiple Comparison Test .*P < 0.05 versus Control Ab + Vehicle*

- PNQ-103-1 (3mg/kg, PO, BID) alone significantly **decreased tumor volume** comparable to Anti-PD-1

PNQ-103-1: Summary

Clean preclinical safety profile

- Drug Matrix Screen
  - High selectivity over diverse targets -No Concerns
- 14 day exploratory study in rodents completed;
  - NOAEL 100 mg/kg in rats
- Mutagenicity
  - Non-mutagenic
  - No hERG liability
- Long patent life till 2031
  - US and EP patents granted
- CMC
  - Low cost of goods with easy synthesis
  - GMP material easily generated for clinical studies
- Ready For IND filing in 6-8 months

PNQ-103-1 : Other Indications

Model	Doses	Outcomes
Ovalbumin-induced Allergic Asthma Model in BALB/c Mice (inflammation as well as airway hyperreactivity)	1 to 30 mg/kg, BID	▪ Dose-dependent inhibition of total cell count in BALf – PNQ-103 ED_{50} = 5.7 mg/kg, BID – PNQ-103-1 ED_{50} = 3.2 mg/kg, BID ▪ Significant reduction in NECA induced airway hyper-responsiveness ▪ Efficacy comparable to 1 mg/kg Prednisolone
Bleomycin-Induced Lung Fibrosis in C57BL/6J Mice	30 mg/kg, BID	▪ Significant inhibition of airway inflammation (total cell count and IL-6 levels) in BALf ▪ Significant reduction in lung collagen content ▪ Efficacy comparable to 30 mg/kg CVT-6883

Efficacy in SCD

PNQ-103 shows beneficial effects on biomarkers of SCD in normal and SCD human blood

Thank You