PNQ-370:
A Novel Adenosine A_{2A} Receptor Antagonist

PNQ-370 is a novel, **oral Immuno-oncology agent** *for the treatment of multiple cancers across a wide spectrum of patients*

PNQ-370: A_{2A} Adenosine Receptor (A_{2A} AdoR) Antagonist Stage: Preclinical Development

- Most potent and highly selective adenosine A_{2A} receptor antagonist
- Very long receptor occupancy even in the face of high adenosine concentrations
- Efficacy established in Preclinical PoC studies in two cancer models
- Potential Best-in-class compound
- IND ready in 4-6 months
- Long patent life till 2031
- CMC completed, with low cost of goods and easy synthesis

PNQ-370: Potential Therapeutic Value and Clinical Positioning

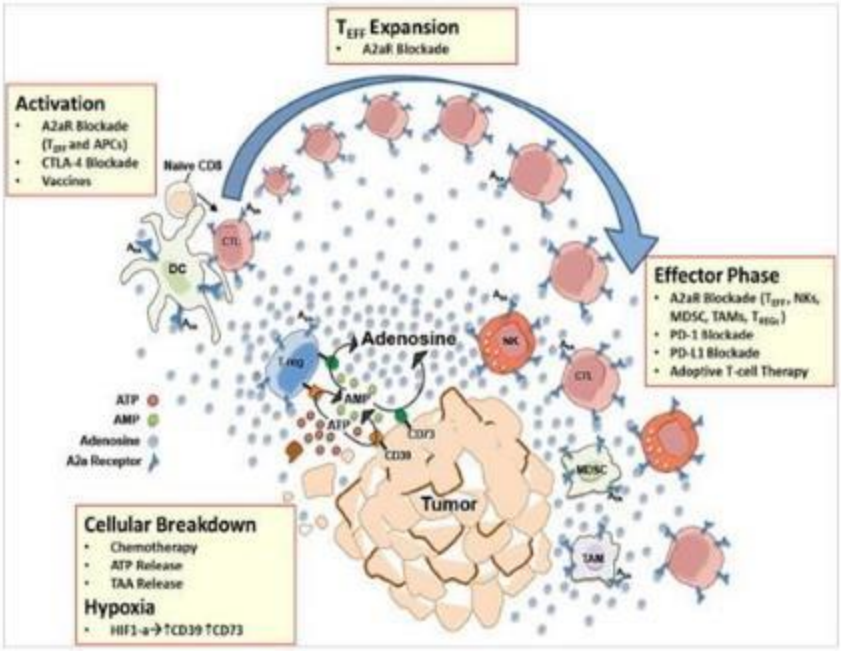
PNQ-370 has the potential to be a critical component in the immuno-oncology regimen to achieve tumor regression in a variety of patients including those with difficult to treat and advanced cancers as well as in immuno-therapy-resistant cancers

Therapeutic Value & Positioning

- Widespread use in multiple cancers
  - **NSCLC :** Likely to be highly effective, given the high exposure of compound in lungs
  - Head and Neck
  - Melanoma
  - Breast
- Effective in treatment naïve as well as refractory , immune resistant patients and patients non-responsive to Anti-PD-1 and CTLA4 treatments
- Potential synergy with check-point inhibitors including :
  - Anti- PD-1, PD-L1
  - CTLA-4, IBB-4

$A_{2A}R$ Blockade : A Therapeutically Relevant MoA for Multiple Cancers

Blockade of A_{2A} receptor down-regulates several anti-inflammatory molecules and immunoregulatory cells leading to improved immune surveillance



A2aR blockade in the tumor microenvironment.

- Substantial evidence for increased Adenosine levels and increased $A_{2A}R$ expression in multiple cancers, including Prostrate and Lung cancers
- CD73 is an independent prognostic factor in prostate cancer
- Increased Adenosine signaling drives immuno-suppression by
  - upregulating the T_{REG} phenotype
  - Suppressing NF-κB and MCDFs signaling in tumor cells
  - Suppressing TCR signaling and immunosurveillance by CD8(+) T cells
  - Reduced cell–cell adhesion
  - Increase of cell scattering/metastasis and angiogenesis, neoplastic transformation and growth

The robust efficacy shown by PNQ-370 in breast and colon cancer models is likely to be seen in other cancers like Lung and Prostrate cancers as well

The PNQ-370 Advantage Over Competition

Potency
- Sub-nanomolar potency for A_{2A}, a high affinity adenosine receptor
- Functional potency of 65 pM

Selectivity over A_1 AdoR
- A_1 engagement known to cause severe CNS side effects
- Excellent selectivity over A_1 AdoR

Target Engagement
- Longest receptor residence time; slowest off-rate amongst competitors
- Extended receptor binding also seen in the presence of high adenosine
- Slow receptor off rate even in the face of high tumor conc. of Adenosine

Efficacy in Oncology and other Models
- Superior efficacy in 2 immuno-therapy resistant animal models
  - 4T1 Syngeneic model of Breast Cancer
  - CT 26 Syngeneic model of colon Cancer
- Robust efficacy in models of Parkinson's and other cognitive disease

Increased compound safety
- >5000 fold safety based on exposure in 28 day rodent toxicity
- NOAEL – 30mg/kg –highest dose tested

PNQ-370 is differentiated from other A_{2A} receptor antagonists on multiple aspects that confer benefits for oncology and other Indications

PNQ-370 Exhibits Picomolar Functional Potency & High Selectivity Over Other Adenosine Subtypes

Receptor Human	Ki (nM)	Selectivity Ratio
A_{2A}	0.065	
A_1	10,000	>10000
A_{2B}	100	>1400
A_3	10,000	>10000

- **Picomolar potency may be critical for effective antagonism** of A_{2A} -a high affinity receptor in presence of very high concentration of adenosine in tumor microenvironment.
- Better selectivity over A_1R than the competitor compounds predicts decreased potential severe CNS based side effect
  - Seizures reported with A_1R antagonist Rollofylline in clinic

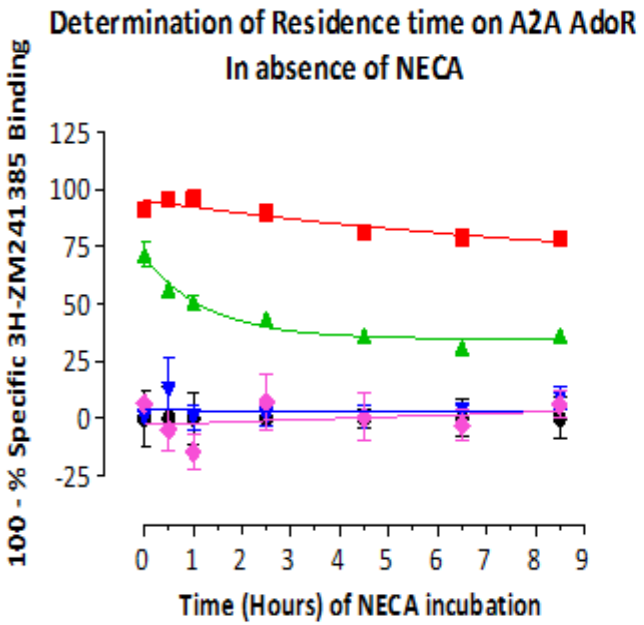
More Potent & Selective Compared to Competition

A_{2A} Antagonist	A_{2A}	A_1	A_{2B}	A_3
	Affinity Ki (nM)	Selectivity over A_{2A} receptor		
PNQ-370	0.68	700	2000	10000
CPI-444	3.52	54	531	693
AZD4635/ HTL1071	1.58	0.1	Not available	Not available
Vipadenant	1.3	48	52	773
Istradefylline	36	79	50	>83
Tozadenant (SYN-115)	5	140	270	314

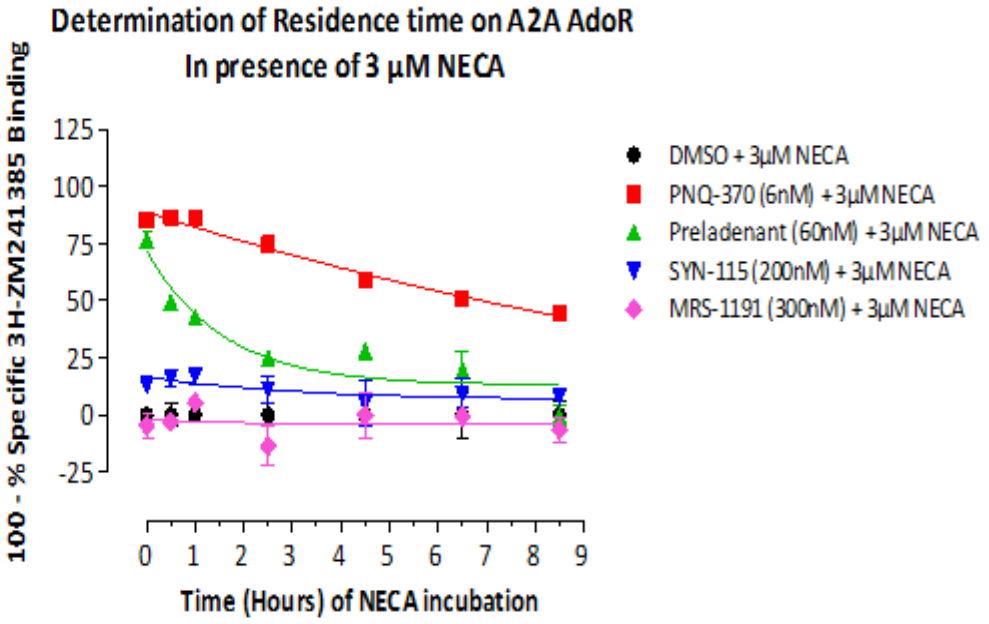
- Potency & selectivity better than competitor compounds – also evident in affinity determination
- PNQ-370 is significantly more selective over A_1R than competitor compounds

Key Differentiator- Binding Off-Rates of PNQ-370

In absence of NECA



In presence of 3µM NECA
~ >100 fold Kd of NECA for $A_{2A}R$



- Slow off rate with potency drives prolonged receptor antagonism even in face of high tumor adenosine levels.

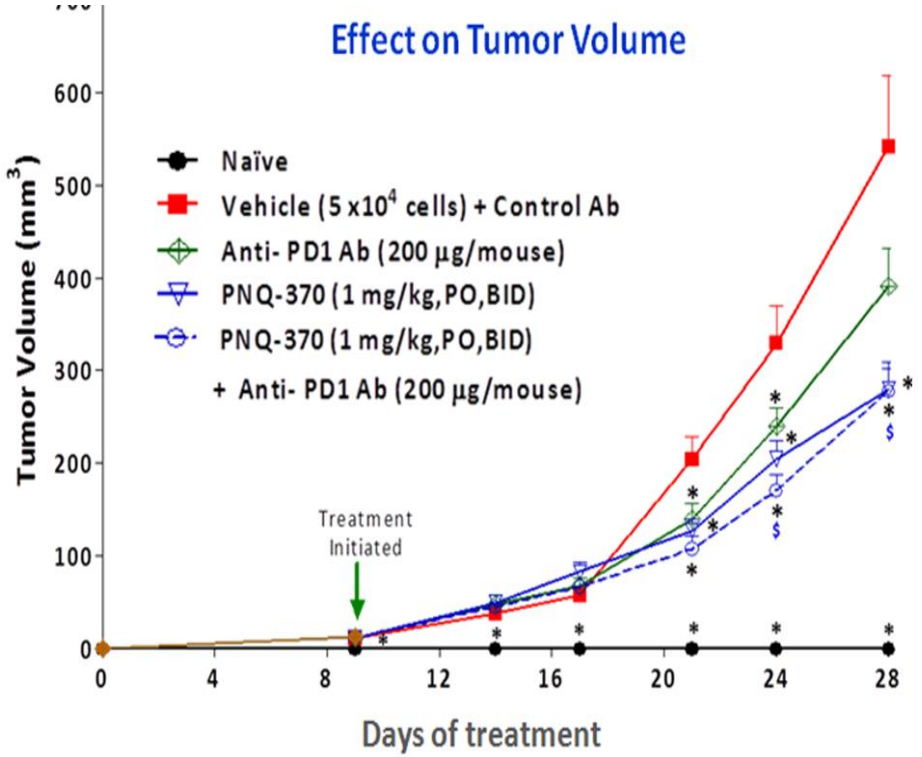
PNQ-370: Excellent Efficacy

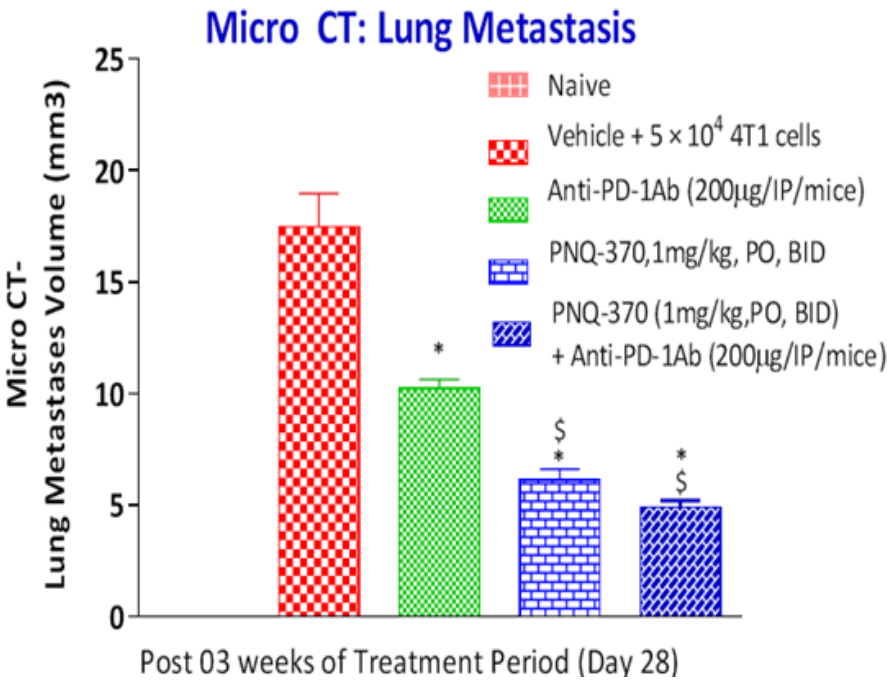
Effect of PNQ -370 was evaluated as a mono-therapy and in combination with anti-PD-1 antibody in two immunotherapy resistant murine models

- **4T1 Syngeneic Breast Cancer Mouse Model**
  - Highly malignant & poorly immunogenic model which resembles advanced breast cancer in humans
  - Refractory to most immune stimulation based therapies
  - Is CD73 positive
  - Highly metastatic

- **CT-26 Syngeneic Colon Cancer Mouse Model**
  - A relatively immunotherapy resistant tumor model
  - Is CD73 positive

PNQ-370 : Effect on Tumor Volume and Lung Metastasis in 4T1 Breast Cancer Model

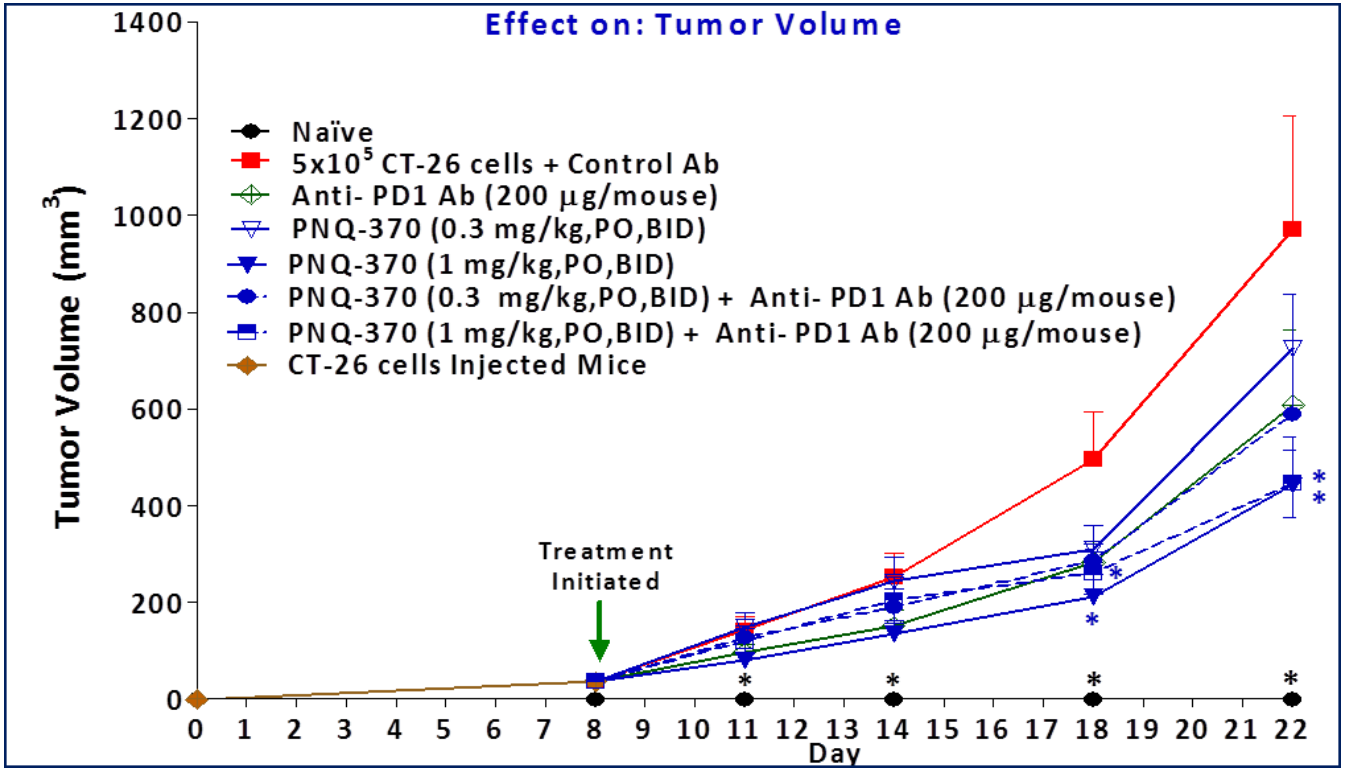




*Data is shown as Mean ± S.E.M.(n=11-12). One-way ANOVA followed by Dunnett's Multiple Comparison Test .*P < 0.05 versus Control Ab + Vehicle ; .$P < 0.05 versus Anti-PD-1, unpaired 't' test*

PNQ-370 (1mg/kg, PO, BID) *per se* exhibited
greater **decrease in Tumor volume** and **greater decrease in Lung Metastasis** than Anti-PD-1

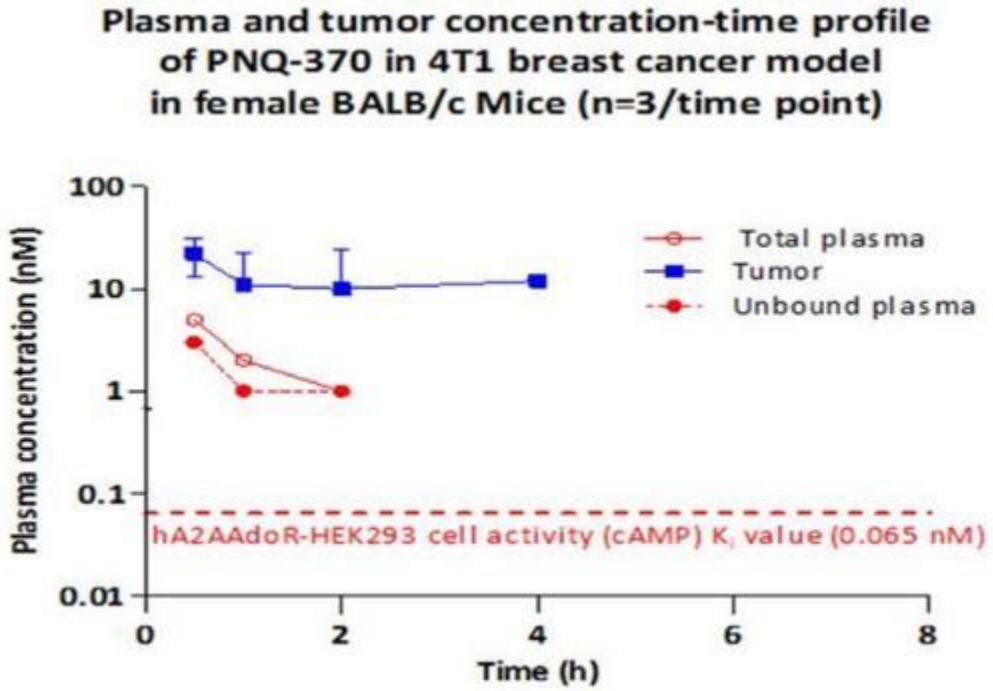
PNQ-370: Tumor Volume in CT26 Colon Cancer Model



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-370 exhibits dose dependent **decrease in Tumor volume** greater than Anti-PD-1

Wide Therapeutic Index



- Plasma (total and unbound) and tumor concentrations of PNQ-370 were well above its K_i value in functional assays at 1mg/kg
- PNQ-370 showed greater safety margin (>5000-fold) in 28-day oral rat toxicity study based on this exposure

PNQ-370: Summary

Preclinical candidate with a clean safety profile

- Drug Matrix Screen
  - High selectivity over diverse targets -No Concerns
- 28 day study in rodents completed
  - NOAEL -30mg/kg in rats (Highest dose tested), Target organ not identified.
  - Safety margin >5000 fold based on exposure in cancer efficacy studies
- Mutagenicity
  - Non-mutagenic
  - No hERG liability
- Canine toxicity planned
- 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
- IND filing possible in 4-6 month

Thank You