A Phase 1 Study to Evaluate the Safety and Tolerability of AB680 Combination Therapy in Participants with Gastrointestinal Malignancies (ARC-8)

J. Bendell[1], G. Manji[2], S. Pant[3], K. Krishnan[4], J. Colabella[4], W. Berry[4], M. Paoloni[4], W. Grossman[4] and E.M. O'Reilly[5]

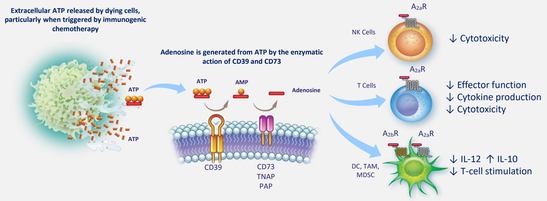
[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [2]Columbia University, New York, NY; [3]MD Anderson Cancer Center, Houston, TX; [4]Arcus Biosciences, Inc., Hayward, CA; [5]Memorial Sloan Kettering Cancer Center, New York, NY

Abstract TPS788

THE ADENOSINE AXIS

The tumor microenvironment contains high levels of immunosuppressive adenosine, which binds to and activates the A_{2a} ($A_{2a}R$) and A_{2b} receptors ($A_{2b}R$) on immune cells, leading to an ineffective anti-tumor response (**Figure 1**). CD73 enzyme and tissue non-specific alkaline phosphatase (TNAP) are primarily responsible for the conversion of extracellular adenosine mono-phosphate (AMP) to adenosine.

Figure 1. Adenosine Pathway Plays a Critical Role in Immunosuppression



AB680 is a low-molecular-weight, reversible, and selective, inhibitor of the ectonucleotidase CD73, which blocks the key enzyme responsible for the conversion of extracellular AMP into adenosine. Dampening the adenosine axis within the tumor microenvironment is designed to shield activated immune cells ($CD8^+$ T cells and NK cells), inhibit adenosine-mediated myeloid cell dysfunction, and shut down adenosine-driven mechanisms of tumor growth and metastasis. These changes have the potential net effect of changing from a pro- to anti-tumor immune response and acting as an important mediator of tumor cell death.

PROPERTIES OF AB680

FIRST SMALL-MOLECULE CD73 INHIBITOR TO ENTER CLINICAL DEVELOPMENT

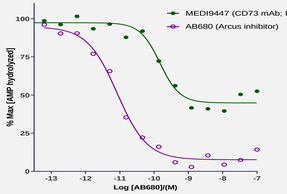
As the first small molecule CD73 inhibitor, AB680 offers potential advantages over anti-CD73 antibodies in development including:

Figure 2. AB680 Potently Inhibits CD73 Enzymatic Activity

- Greater inhibition of CD73 enzymatic activity (soluble & cell-bound)
- Deeper tumor penetration

AB680 has unique small-molecule properties that make it a strong clinical candidate:

- Extraordinarily potent: IC_{50} = 0.008 nM (T cells)
- Low clearance, long half-life molecule



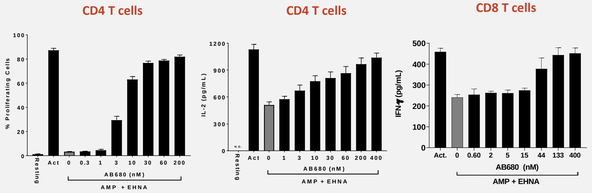
[a] MEDI9447 synthesized by Arcus based on the following publication and patent application: Hay et al., OncoImmunology (2016) 5, e1208875; Patent Appl. US 2016/0129108.

Although the properties of the intravenous formulation are promising for future clinical development, an oral formulation of AB680 has also completed IND-enabling studies.

PRECLINICAL DATA

AB680 REDUCES ADENOSINE-MEDIATED HUMAN IMMUNE SUPPRESSION

Figure 3. AB680 Treatment Promotes CD4 and CD8 T cell Activation

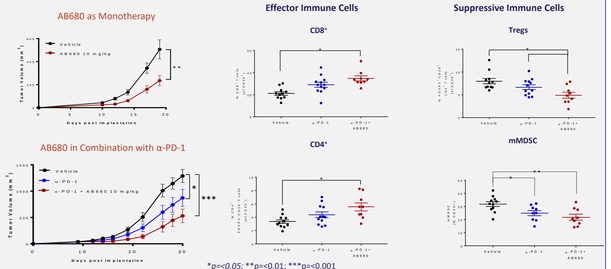


The activation of human T cells, both CD4+ and CD8+, was suppressed by addition of the adenosine precursor AMP. AB680 inhibited the conversion of AMP to adenosine by CD73 expressed on these cells resulting in normal T cell proliferation and cytokine production.

AB680 + ANTI-PD-1 COMBINATION TREATMENT PROMOTES TUMOR CONTROL AND IMMUNE ENGAGEMENT

Murine B16F10 melanoma models have shown inhibition of tumor growth after treatment with AB680. This growth inhibition was further reduced with combination treatment of AB680 and anti-PD-1. In preclinical models, AB680 monotherapy and AB680 combination treatment with anti-PD-1 leads to an increase in intratumoral effector T cells (CD4+ and CD8+) and a decrease in immune suppressor cells (Tregs and MDSCs). Preclinically, AB680 therapy activates anti-tumor immunity.

Figure 4. AB680 & Anti-PD-1 Result in Greater Tumor Control, Enhances Effector and Reduces Suppressive Immune Cells



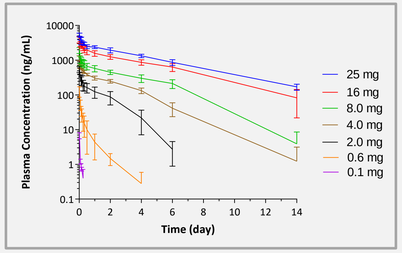
AB680 has been shown to selectively prevent the generation of adenosine from AMP and reverse the immunosuppressive effects caused by high concentrations of AMP/adenosine, without causing any immune activation effects on its own.

ENTRY INTO CLINIC

AB680 DISPLAYS EXCELLENT PK PROFILE IN HEALTHY HUMAN VOLUNTEERS CONSISTENT WITH Q2W DOSING

A dose-escalation study of AB680 administered in single and multiple doses of 0.1 mg to 25 mg was conducted in healthy volunteers. This study was designed to evaluate the safety, tolerability, PK profile, and potential pharmacodynamic effects of AB680.

Figure 5. AB680 Pharmacokinetics are Dose Proportional in Healthy Volunteers



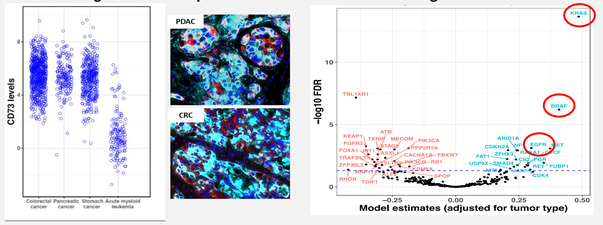
AB680 was well tolerated in healthy volunteers and was found to be dose proportional at higher doses. Twenty-five milligrams (25 mg), the highest dose evaluated, was moved forward as the first dosing cohort in oncology patients (Ashok et. al., SITC 2019 Abstract P379).

RATIONALE IN PANCREATIC CANCER

PANCREATIC DUCTAL ADENOCARCINOMA EXPRESSES HIGH LEVELS OF CD73 THAT IS STRONGLY CORRELATED WITH KRAS MUTATION

CD73 expression across multiple tumor types is shown in **Figure 6**, with pancreatic cancer expressing one of the highest levels. Multiple oncogene mutations are strongly associated with CD73 expression, most notably KRAS. Pancreatic cancer has over 90% KRAS mutation frequency, making it one of the most RAS-addicted of all cancers (Ashok et. al., SITC 2019 Abstract P379).

Figure 6. CD73 Expression and Correlation with Oncogenic Mutations

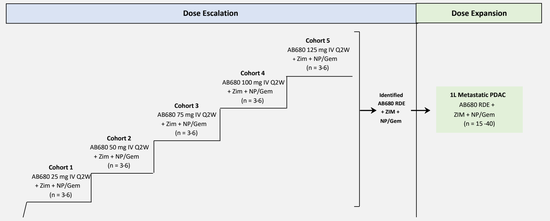


High expression of CD73 and its correlation with KRAS mutation, makes the inhibition of the adenosine axis a promising target in metastatic pancreatic ductal adenocarcinoma (mPDAC).

STUDY OVERVIEW

ARC-8 IS A PHASE 1/1B EVALUATING AB680 + GEMCITABINE/NAB-PACLITAXEL + ZIMBERELIMAB (ANTI-PD-1) IN FIRST LINE mPDAC

- ARC-8 is a Phase 1/1b, open-label, dose-escalation, and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical activity of AB680 in combination with Zimberelimab (Zim; anti-PD-1 antibody) and standard chemotherapy (nab-paclitaxel [NP] and gemcitabine [Gem]) in participants with first line (1L) mPDAC.
- In the dose-escalation Ph1 portion, increasing dose levels of AB680 are administered every 2 weeks (Q2W) in combination with Zim (240 mg Q2W) and NP/Gem (Gem 1000 mg/m2 + NP 125 mg/m2 IV on Days 1, 8, and 15 of each 28-day cycle). Up to 30 participants may be evaluated in Ph1 dose-escalation.
- In the dose-expansion Ph1b portion, AB680 will be administered at the recommended dose for expansion in combination with Zim and NP/Gem in up to 40 participants.



- Safety assessments include the incidence of adverse events (AEs) and dose-limiting toxicities (DLTs) graded according to NCI CTCAE 5.0.
- Antitumor activity is determined per RECIST v1.1 and will determine futility assessments in dose expansion.
- Tumor and peripheral blood samples are collected to describe the PK profile, assess the PD effects, and characterize the biomarker status of AB680 in combination.

This trial will enroll at preeminent mPDAC institutions including: Sarah Cannon Research Institute, Columbia University, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Washington University, Yale University, University of Pittsburgh, University of Oklahoma, Thomas Jefferson, New York University, and University California-Los Angeles.

CONCLUSIONS

- AB680 is the first clinical-stage small-molecule CD73 inhibitor. It is highly potent, pharmacodynamically active, and had a favorable safety profile in healthy volunteer dose escalation studies.
- This Ph1/1b study will be the first to target the adenosine axis using AB680 in 1L mPDAC in combination with standard of care chemotherapy (NP/Gem) and a PD-1 antibody (Zim).

ACKNOWLEDGEMENTS

We thank the Principal Investigators, site staff, and study participants for their efforts on behalf of this study. *Contact: Melissa Paoloni, Email: mpaoloni@arcusbio.com*