The ADENOSINE AXIS

AB680 is a low-molecular weight, reversible, and selective, inhibitor of the ectonucleoside transporter CD73, which blocks the key enzyme responsible for the conversion of extracellular AMP into adenosine. Comparing 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 depletion, and shut down adenosine-driven mechanisms of tumor growth and metastasis. These changes have the potential net effect of changing from a pro-tumor immune response and acting as an important mediator of tumor cell death.

AB680 REDUCES ADENOSINE-MEDIATED HUMAN IMMUNE SUPPRESSION

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 CD3+ cells resulting in normal T cell proliferation and cytokine production.

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

Marine 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 intraocular effector T cells (CD4+ and CD8+) and decrease in immune suppressor cells (Tregs, MDSCs). Pharmacologically, AB680 therapy activates anti-tumor immunity.

RATIONALITY 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 3, with pancreatic cancer expressing one of the highest levels. Multiple oncogenes mutations are strongly associated with CD73 expression, most notably KRAS mutations. In vitro, over 95% of KRAS mutation frequency is making it one of the most RAS-addicted of all cancers (Ahok et al. SCTR 2019 Abstract P379).

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 dosing patients (Ahok et al. SCTR 2019 Abstract P379).

STUDY OVERVIEW

ARC-8 is a PHASE 1/1b EVALUATING AB680 + GEMCITABINE/NAB-Paclitaxel + ZIMBIERELMAB (ANTI-PD-1) IN FIRST LINE mPDAC

- In the dose-escalation phase 1b portion, increasing dose levels of AB680 were administered every 2 weeks (Q2W) in combination with Zim (240 mg-Q2W) and NP/Gem (1000 mg-x2 + NP 125 mg-x4 on days 1, 8, 15 of each 28-day cycle). Up to 30 participants may be evaluated in phase 1b dose-escalation.

- In the dose-expansion phase 1b portion, AB680 will be administered at the recommended dose for expansion in combination with Zin and NP/Gem in up to 48 participants.

AB680 is the first clinical-stage small molecule CD73 inhibitor. It is highly potent, pharmacologically active, and had a favorable safety profile in healthy volunteer dose escalation studies.

This trial will enroll at present mPDAC institutions including: Sarah Cannon Research Institute, Columbia University, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, University of Pittsburgh, Yale University, University of Pittsburgh, University of Delaware, Thomas Jefferson University, University of 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 PH-1b study will be the first to target the adenosine axis using AB680 in Zin in 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. Thanks to Metin Kanatas, Email: mkanatas@arcusbio.com

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