A Phase 1b/2, Open-Label, Platform Study Evaluating the Efficacy and Safety of AB928-Based Treatment Combinations in Participants with Metastatic Castrate Resistant Prostate Cancer (ARC-6)

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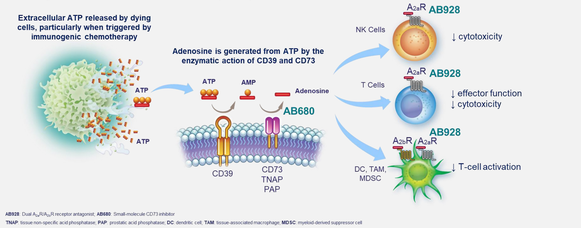
THE ADENOSINE AXIS

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. In certain tumor types, other enzymes, such as prostatic acid phosphatase (PAP) in prostate cancer, can also efficiently convert AMP to adenosine.

Figure 1. Adenosine Pathway Plays a Critical Role in Immunosuppression



AB928: Dual $A_{2a}R/A_{2b}R$ receptor antagonist; **AB680**: Small-molecule CD73 inhibitor
TNAP: tissue non-specific acid phosphatase; **PAP**: prostatic acid phosphatase; **DC**: dendritic cell; **TAM**: tissue-associated macrophage; **MDSC**: myeloid-derived suppressor cell

AB928 is a dual antagonist of adenosine receptors $A_{2a}R$ and $A_{2b}R$ 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. Preclinically, combining AB928 with either chemotherapy or anti-PD-1 resulted in greater tumor growth control, suggesting that AB928 may have additive activity when paired with either of these types of agents in cancer patients.

INITIAL AB928 STUDIES

AB928 REPRESENTS A POTENTIALLY BEST-IN-CLASS ADENOSINE RECEPTOR ANTAGONIST

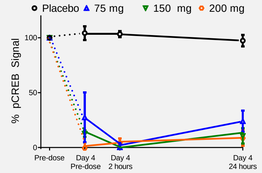
AB928 is the first adenosine receptor antagonist to enter clinical development that:

- Inhibits both $A_{2a}R$ (1.4 nM) and $A_{2b}R$ (2 nM) receptors
- Potency in whole blood, 87 nM, against maximal adenosine receptor activation

Multiple advantages over other $A_{2a}R$ specific antagonists in development include:

- Minimal shift in potency shift from non-specific protein binding
- Excellent drug properties (e.g. PK, tumor penetration)

Figure 1. AB928 Exhibits "24/7" Target Coverage



DiRenzo et al., 2019

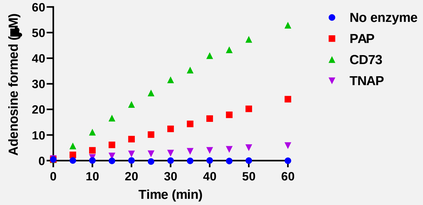
AB928 is highly potent, pharmacodynamically active, and has been well tolerated in four dose escalation studies in combination with chemo/immunotherapy. Phase 1 dose-escalation established 150 mg once daily (QD) as the recommended dose for combination and confirmed receptor coverage in oncology patients. In these early studies, AB928 in combination with chemotherapy and/or anti-PD-1 therapy demonstrated evidence of clinical benefit, including tumor responses and disease stabilization > 6 months in heavily pretreated patients across multiple solid tumor disease indications.

BIOLOGY IN PROSTATE CANCER

PROSTATIC ACID PHOSPHATASE (PAP) CREATES AN ADENOSINE-RICH TUMOR MICROENVIRONMENT IN PROSTATE CANCER

Figure 2. PAP Efficiently Generates Adenosine

PAP, produced nearly ubiquitously in prostate cancer, converts extracellular AMP to adenosine and inorganic phosphate. Increased levels of PAP are found in men with prostatic cancer, especially those with metastatic disease. Prostate cancer may be unique in its reliance on PAP to produce adenosine.



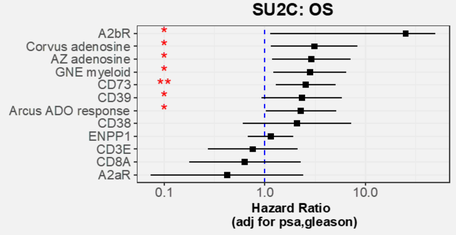
Assays conducted with 1 mM AMP and 1 nM enzyme concentration at pH 7.4

Recent clinical data demonstrated early activity of adenosine pathway inhibition in metastatic castration-resistant prostate cancer (mCRPC) supporting further development in this indication (Bendell et al., 2019).

$A_{2b}R$ EXPRESSION CORRELATES WITH UNFAVORABLE SURVIVAL IN METASTATIC PROSTATE CANCER

The biology of $A_{2b}R$ continues to be elucidated; however, its importance in myeloid rich or unique tumor types is becoming increasing evident. In mCRPC, adenosine axis expression and myeloid signatures were negatively correlated with overall survival, with $A_{2b}R$ being one of the most prognostic genes evaluated.

Figure 3. Adenosine and Myeloid Signatures are Significantly Associated with Poor OS in mCRPC



Stand-Up-2-Cancer (SU2C) data set denoting the prognosis of gene sets via hazard ratio (Abida et al., 2019). Stars indicate statistical significance (*=p< 0.1, **=p< 0.01).

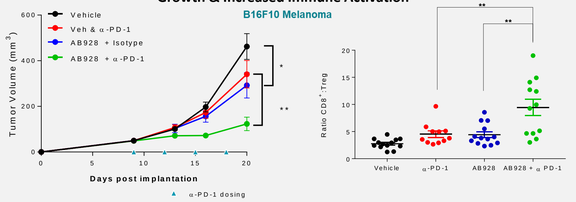
As the only dual adenosine receptor antagonist, AB928 may have distinctive potential to co-opt the adenosine-rich and A_{2b} driven biology in mCRPC.

RATIONALE FOR mCRPC COMBINATIONS

ADENOSINE INHIBITION ENHANCES PD-1 ACTIVITY IN TUMOR MODELS

Treatment with AB928 or AB680 (small molecule CD73 inhibitor) in combination with anti-PD-1 has displayed inhibition of tumor growth in multiple murine tumor models. In preclinical models, AB928 or AB680 plus anti-PD-1 leads to an increase in intratumoral CD8+ T cells and a decrease in immune suppressor cells (Tregs).

Figure 4. Combination of AB928 with anti-PD-1 Results in Significant Reduction in Tumor Growth & Increased Immune Activation



ANDROGEN DEPRIVATION THERAPY SENSITIZES PROSTATE CANCER CELLS TO T CELL KILLING

Ardiani et al. (2014) showed an increased sensitivity of prostate carcinoma cells treated with enzalutamide towards T cell killing. This effect is retained in cells that over-express the androgen receptor, an important mechanism of resistance to anti-hormonal therapy. This suggests that enzalutamide in combination with immunotherapy may improve response in patients with resistance to androgen deprivation.

TUMOR INFLAMMATION INDUCED BY CERTAIN CHEMOTHERAPIES IS AN IMPORTANT COMPONENT OF ANTITUMOR ACTIVITY

The induction of immunogenic cell death (ICD) by certain chemotherapeutics has been the hallmark of combinatory approaches with immunotherapeutics in the clinic. Data by Hodge et al. (2013) suggested that docetaxel as an immunogenic modulator can enhance cancer cell killing without inducing ICD. This may increase its effectiveness in combinations with immunotherapy.

EARLY EVALUATION OF AB928 IN mCRPC

ARC-5 (NCT03629756) is a phase 1/1b study evaluating AB928 and zimberelimab (anti-PD-1 antibody) in mCRPC. Eligible participants have progressed on androgen inhibition and taxane chemotherapy, are ECOG 0-1, and PD-1/PD-L1 treatment naive. The primary endpoint is tolerability, with secondary endpoints of PK, PD, and clinical activity. This trial is presently enrolling and is the backbone regimen for continued development of AB928 in this indication.

Novel therapy development is greatly needed in mCRPC, where initial treatment with anti-PD-1/PD-L1 treatment has been unrewarding. However, the addition of checkpoint inhibition to reinvigorate potential pre-existing immunity makes it a good backbone for combination immunotherapy approaches. Because adenosine is highly immunosuppressive, chemo/immunotherapy may be less effective in adenosine-rich tumors such as mCRPC. Inhibition of adenosine signaling with AB928 and/or AB680 in combination with anti-PD-1 therapy is hypothesized to:

- Enhance the efficacy of hormone therapy (Enzalutamide)
- Enhance the efficacy of chemotherapy (Docetaxel)
- Enhance the efficacy of an anti-PD-1 antibody

ARC-6 STUDY OVERVIEW

ARC-6 IS A PHASE 1B/2 MULTI-COHORT PLATFORM STUDY EVALUATING COMBINATIONS OF AB928 IN mCRPC

- ARC-6 is a planned Phase 1b/2, open-label, multi-cohort platform study to evaluate the efficacy and safety of AB928 combination therapy in participants with mCRPC. Each cohort will independently assess AB928 plus zimberelimab in combination with standard of care (SOC; enzalutamide, docetaxel) or AB928 plus AB680 with or without zimberelimab.
- In Phase 1b, up to 15 participants will receive investigational products at the single-agent recommended dose with SOC per label guidance.
- Provided safety and activity stopping criteria are not met, further accrual will proceed in Ph2 and, depending on treatment cohort, may involve randomization to enzalutamide or docetaxel.
- Cohort eligibility is informed by prior treatment history.

Indication	Patient Population	Combination
mCRPC	ASI and taxane exp.	AB928 + Zimberelimab
	ASI and taxane exp.	AB928 + Zimberelimab + AB680
	ASI exp.; taxane naive	AB928 + Zimberelimab + Docetaxel
	Abi exp.	AB928 + Zimberelimab + Enzalutamide

ARC-5 Cohort (Open to enrollment)

Planned ARC-6 Combination Cohorts

Abiraterone=Abi; Experienced=exp.; ASI=androgen synthesis inhibitor

- Safety assessments will include the incidence of adverse events (AEs) and dose-limiting toxicities (DLTs) graded according to NCI CTCAE 5.0.
- Investigator-assessed antitumor response (radiologic, prostate specific antigen) will follow PCWG3 criteria.
- Tumor and peripheral blood samples will be collected to describe the PK profile, PD effects, and characterize the biomarker status of AB928 in combination.

CONCLUSIONS

- This planned Ph1b/2 study is the first to target the adenosine axis using a dual $A_{2a}R/A_{2b}R$ antagonist (AB928) together with a small molecule CD73 inhibitor (AB680), anti-PD-1 antibody (zimberelimab), and SOC for mCRPC.
- Study initiation is ongoing in the United States; results will be shared in upcoming scientific conferences.

ACKNOWLEDGEMENTS

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REFERENCES

1. Bendell et al., AACR 2019 Abstract CT026; 2. Ardiani et al., Oncotarget (2014) 5(19): 9335; 3. Hodge et al., Intl. J. Cancer (2013) 133: 624.