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

Poster # 687TiP

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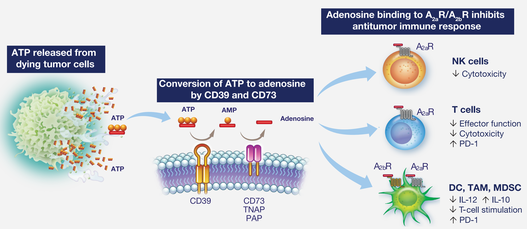
THE ADENOSINE AXIS IN PROSTATE CANCER

- Standard of care (SOC) regimens may contribute to immunosuppression by elevating intratumoral levels of adenosine triphosphate (ATP) in the tumor microenvironment (TME) where the enzymes CD39 and CD73 convert ATP to adenosine; in prostate cancer, the highly expressed protein, prostatic acid phosphatase (PAP), produces additional adenosine[1,2] (**Figure 1**)
- By binding adenosine receptors 2a and 2b ($A_{2a}R$ and $A_{2b}R$) expressed on immune cells, adenosine promotes immunosuppression by inhibiting critical components of the antitumor immune response and ultimately enables tumor cells to evade destruction[2]
- Additionally, $A_{2a}R$ signaling impairs the activation, proliferation, and cytotoxic activity of effector T cells[3]
- Initial research focused on $A_{2a}R$ as the most relevant adenosine receptor in cancer physiology; however, $A_{2b}R$ signaling mediates unique functions, such as dendritic cell activation and function[4]
- Thus, targeting the adenosine axis in combination with standard chemotherapy regimens or immunotherapy may have a more profound effect on activating and inducing sustained antitumor immunity in prostate cancer

Figure 1. Critical Role of Adenosine Pathway in Immunosuppressive Tumor Microenvironment



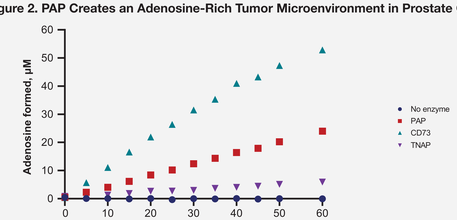
AMP, adenosine monophosphate; ATP, adenosine triphosphate; $A_{2a}R/A_{2b}R$, adenosine receptors 2a/2b; DC, dendritic cell; IL, interleukin; MDSC, myeloid-derived suppressor cell; NK, natural killer; PAP, prostatic acid phosphatase; PD-1, programmed cell death protein-1; TAM, tumor-associated macrophage; TNAP, tissue nonspecific alkaline phosphatase.

- Etrumadenant (AB928) is an orally bioavailable, small-molecule, selective dual antagonist of $A_{2a}R$ and $A_{2b}R$ that was specifically designed to block the immunosuppressive effects associated with high adenosine concentration within the TME; it is the only adenosine receptor antagonist in active clinical trials that potently blocks $A_{2a}R$ and $A_{2b}R$
- AB680 is a potent and selective small-molecule inhibitor of CD73 designed to eliminate a major pathway of extracellular adenosine production, offering the potential to reverse adenosine-mediated immune suppression within the TME; it is the first small-molecule CD73 antagonist to enter clinical development and uniquely inhibits both soluble and membrane-bound CD73
- Currently, there are 4 ongoing global phase 1/1b disease-specific studies to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary clinical activity of etrumadenant in combination with chemotherapy and/or anti–PD-1 antibody[5]
  - Based on dose escalation data from these studies, etrumadenant 150 mg once daily (QD) was selected as the recommended dose for expansion (RDE) based on PK, PK/pharmacodynamics correlation, and a well-tolerated safety profile of etrumadenant + chemo/immunotherapy

ADENOSINE BIOLOGY IN PROSTATE CANCER

- In prostate tumors, PAP plays a similar role to CD73 in converting adenosine monophosphate (AMP) to adenosine[2] (**Figure 2**)
- Serum PAP levels are increased in patients with prostate cancer, particularly in those with metastatic disease, compared with healthy adults[6]

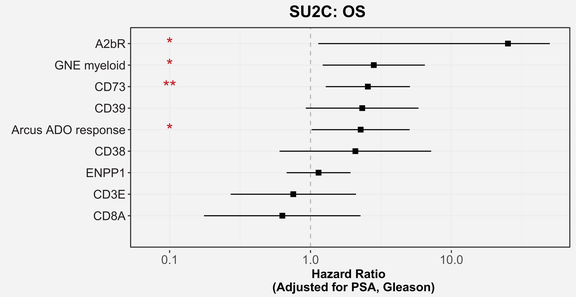
Figure 2. PAP Creates an Adenosine-Rich Tumor Microenvironment in Prostate Cancer[a]



[a] Assays were conducted with 1 mM AMP and 1 nM enzyme concentration at pH 7.4. AMP, adenosine monophosphate; PAP, prostatic acid phosphatase; TNAP, tissue nonspecific alkaline phosphatase.

- The biology of $A_{2b}R$ continues to be elucidated; however, its importance in myeloid-rich or unique tumor types is becoming increasingly evident[8]
- In metastatic castrate-resistant prostate cancer (mCRPC), adenosine axis expression and myeloid signatures were negatively correlated with overall survival (OS), with $A_{2b}R$ being one of the most prognostic genes evaluated (**Figure 3**)
- As the only dual adenosine receptor antagonist, etrumadenant may have distinctive potential to co-opt the adenosine-rich and $A_{2b}R$-driven biology in mCRPC

Figure 3. $A_{2b}R$ Expression Correlates with Unfavorable Survival in Metastatic Prostate Cancer[a]



[a] Published SU2C gene expression dataset[9] was internally analyzed to assess the prognosis of gene sets via hazard ratio; * $P < .1$; ** $P < .01$.
$A_{2b}R$, adenosine 2b receptor; ADO, adenosine; ENPP1, ectonucleotide pyrophosphate/phosphodiesterase 1; OS, overall survival; PSA, prostate-specific antigen; SU2C, Stand-Up-2-Cancer.

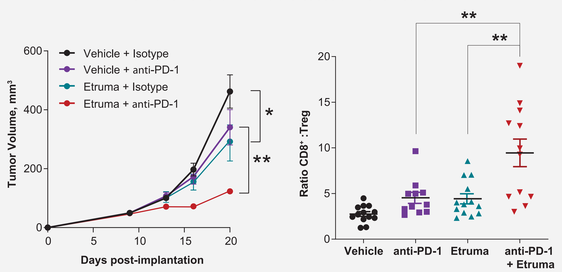
RATIONALE FOR ETRUMADENANT COMBINATIONS

- Because adenosine is highly immunosuppressive, available standard therapies may be less effective in adenosine-rich tumors such as mCRPC
- Despite approval of multiple new agents over the last decade that significantly improve OS, clinical benefit is rarely durable with a median OS of 2–3 years[10]; novel therapies are greatly needed
- Although single-agent PD-1 pathway inhibition has not substantially improved clinical outcomes, using checkpoint inhibition to reinvigorate potential pre-existing immunity supports its potential as a backbone for combination therapy approaches

Adenosine Inhibition Enhances PD-1 Activity in Tumor Models

- Treatment with etrumadenant or AB680 in combination with anti–PD-1 has displayed inhibition of tumor growth in multiple murine tumor models (**Figure 4** and data not shown)
- In preclinical models, etrumadenant or AB680 + anti–PD-1 leads to an increase in intratumoral $CD8^+$ T cells and a decrease in Tregs

Figure 4. Combination of Etrumadenant with anti–PD-1 Results in Significant Reduction in B16F10 Tumor Growth and Increased Immune Activation



* $P < .05$; ** $P < .01$; Etruma, etrumadenant; PD-1, programmed cell death protein-1; Treg, regulatory T cell.

- In early clinical trials, the combination of $A_{2a}R$ and programmed death-ligand 1 (PD-L1) inhibition has antitumor activity in some patients with late-line mCRPC[7]
- Etrumadenant in combination with zimberelimab (AB122), a human monoclonal antibody (mAb) targeting PD-1, is currently being evaluated in an ongoing phase 1 study in patients with advanced solid tumors (NCT03846310); early data suggest that etrumadenant + zimberelimab is well-tolerated and has clinical benefit in heavily pretreated patients across tumor types[5]

Inhibition of the Adenosine and PD-1 Pathways in Combination with Androgen Deprivation Therapy May Have a Synergistic Antitumor Effect

- Anti–PD-1 monotherapy in androgen synthesis inhibitor- and taxane-experienced patients with mCRPC has recently demonstrated minimal clinical activity but potential survival benefit[11]; these data and observed clinical activity of $A_{2a}R$ antagonism + anti–PD-L1 therapy in patients with late-line mCRPC supports further evaluation of this combination approach
- Androgen receptor (AR) overexpression is a major mechanism by which prostate tumors develop resistance to androgen deprivation therapy and thus evolve from a hormone-sensitive to a castrate-resistant disease state[12]
- Enzalutamide, an AR antagonist, has been shown to increase the sensitivity of prostate tumor cells to T cell-mediated killing[12]
- Early clinical data suggest that enzalutamide plus anti–PD-1 treatment can result in sustained clinical activity in some patients with mCRPC who are abiraterone-experienced or -intolerant[13]; however, additional therapeutic approaches are needed to improve the efficacy of this approach

Immune Modulation Induced by Certain Chemotherapy Regimens is an Important Component of Antitumor Activity

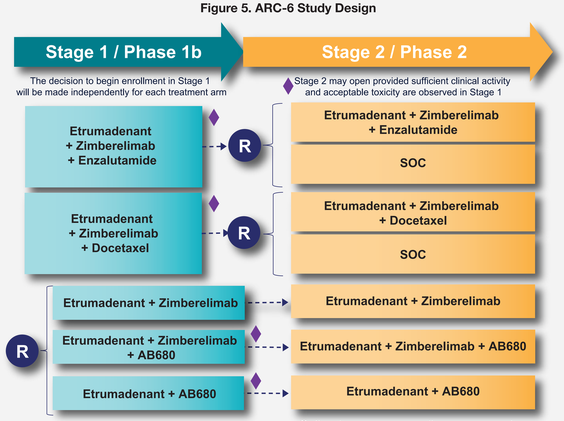
- Historically, the antitumor effect of cytotoxic chemotherapies such as docetaxel has been largely attributed to direct tumor cell killing; however, more recent data suggest that docetaxel, in combination with immunotherapy, can exert an immunomodulatory effect on immune cells that enhances their ability to mount a robust antitumor response[14]
- These distinct and complementary mechanisms by which docetaxel may contribute to antitumor immunity lend support to the inclusion of chemo/immunotherapy approaches in clinical trials
- In patients with mCRPC, docetaxel plus anti–PD-1 therapy has clinical activity in some patients[15], but there remains an unmet need for efficacy in a greater proportion of patients, especially in those that are late-line
- One mechanism that may limit the efficacy of docetaxel plus immunotherapy may be the immunosuppression caused by high levels of adenosine in prostate tumors; thus, adding an adenosine receptor antagonist to chemo/immunotherapy may enhance antitumor activity

ARC-6 STUDY OVERVIEW

ARC-6 is a Phase 1b/2 Multi-Cohort Randomized Study Evaluating Combinations of Etrumadenant in mCRPC

- ARC-6 (NCT04381832) is a phase 1b/2, randomized, open-label, multi-cohort study evaluating the efficacy and safety of etrumadenant combination therapy in patients with mCRPC (**Figure 5**)
  - Phase 1b (≤ 15 patients) will independently assess etrumadenant + zimberelimab alone, in combination with an SOC backbone (enzalutamide or docetaxel), or etrumadenant + AB680 ± zimberelimab
  - Phase 2 (≤ 25 patients) will further assess an etrumadenant-based combination explored in phase 1 versus an appropriate SOC control

Figure 5. ARC-6 Study Design



R, randomization; SOC, standard of care.

- Patient eligibility will be based on prior anticancer therapy history (**Figure 6**)

Figure 6. Key Eligibility Criteria for ARC-6

	Etrumadenant + Zimberelimab + Enzalutamide	Etrumadenant + Zimberelimab + Docetaxel	Etrumadenant + AB680 ± Zimberelimab	Etrumadenant + Zimberelimab
Measurable disease **OR** non-measurable disease	✓	✓	✓	✓
Prior 2nd generation ASI	Abiraterone[a] ✓ Enza/others ✗	✓	✓	✓
Prior taxane chemotherapy	✗[b]	✗	✓[c]	✓[c]
Prior checkpoint inhibitor	✗	✗	✗	✗

[a] Prior abiraterone is required; [b] Limited taxane regimens are allowed in the hormone-sensitive setting; [c] Up to 2 prior taxanes are allowed.
ASI, androgen synthesis inhibitor; Enza, enzalutamide.

- Study objectives and endpoints are listed in **Table 1**

Table 1. ARC-6 Objectives and Endpoints

Primary Objectives	Corresponding Endpoints
• To evaluate the antitumor activity of etrumadenant-based treatment combinations • To evaluate the safety of etrumadenant-based treatment combinations	• ORR: composite proportion of patients with a PSA and/or radiographic CR and PR as determined by the investigator according to the PCWG3 criteria • Incidence and severity of AEs and SAEs
Secondary Objectives	**Corresponding Endpoints**
• To evaluate PSA response rate, radiographic response rate, and clinical efficacy • To determine the PK profile for components of etrumadenant-based treatment combinations • To assess immunogenicity of the biologic component(s) of combination therapy where appropriate	• Proportion of patients with a PSA CR and PR as defined by PCWG3 • Proportion of patients with radiographic CR and PR as defined by PCWG3 • DCR • Serum/plasma concentration and PK parameters for components of etrumadenant-based combination therapy • Number and percentage of participants who develop ADAs to the biologic component(s) of combination therapy

ADA, anti-drug antibody; AE, adverse event; CR, complete response; DCR, disease control rate; ORR, objective response rate; PCWG3, Prostate Cancer Working Group 3; PK, pharmacokinetics; PR, partial response; PSA, prostate-specific antigen; SAE, serious adverse event.

- Exploratory endpoints include characterizing the relationship between tissue and blood-based biomarkers and clinical response or resistance to etrumadenant-based combination therapy and using tumor tissue/blood-based biomarkers in the development of diagnostic tests related to etrumadenant-based combination therapy
- Data permitting, analyses of overall survival and progression-free survival may be performed

CONCLUSIONS

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

ACKNOWLEDGMENTS AND DISCLOSURES

The authors gratefully acknowledge the patients, their families, and their caregivers for their participation in this clinical trial. In addition, they would like to thank the ARC-6 Principal Investigators and study staff for their efforts in carrying out the study. SK Subudhi has been a consultant for Amgen, Apricity Health, AstraZeneca, Bayer, Bristol Myers Squibb, Cancer Now, DAVA Oncology, Dendreon, Exelixis, Janssen Oncology, MEDACorp, and Polaris Pharma; has received honoraria from the Parker Institute of Cancer Immunotherapy and the Society for Immunotherapy of Cancer; has ownership interest in Apricity Health; and has received research funding from AstraZeneca, Bristol Myers Squibb, and Janssen. Medical writing support was provided by Amanda Martin, PhD, and Kendall Foote, PhD, of Medical Expressions (Chicago, IL) and was funded by Arcus Biosciences, Inc. This study is sponsored by Arcus Biosciences, Inc.

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