ARC-9: Phase 1b/2 Study to Evaluate Etrumadenant (AB928)-Based Treatment Combinations in Patients with Metastatic Colorectal Cancer

Abstract TPS150

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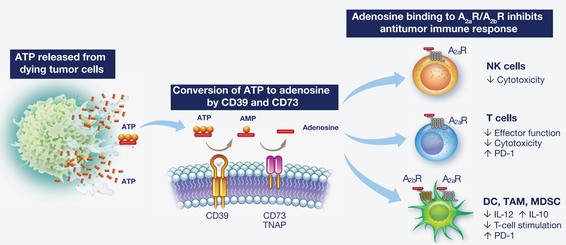
THE ADENOSINE AXIS IN CANCER

- Standard chemotherapy regimens may contribute to immunosuppression by elevating intratumoral levels of adenosine triphosphate (ATP) in the tumor microenvironment (TME) where the enzymes CD39 and CD73 successively convert ATP to 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, ultimately enabling tumors to evade destruction[2]
- Additionally, $A_{2b}R$ 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 through MAP kinase pathway activation mediates unique functions, such as cancer cell intrinsic survival and dendritic cell activation and function[4]
- Thus, adenosine receptor blockade may be necessary to overcome adenosine-dependent immunosuppression and lead to enhanced therapeutic efficacy of some chemotherapeutic agents[2]

Figure 1. Critical Role of Adenosine Pathway in the Immunosuppressive TME



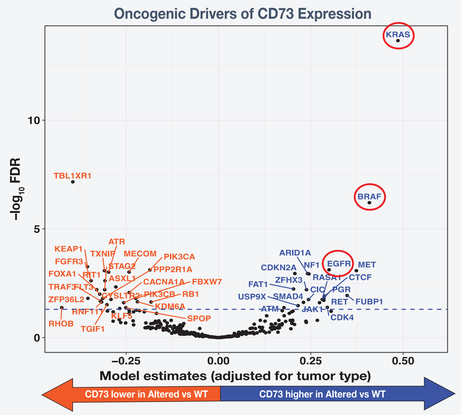
AMP, adenosine monophosphate; ATP, adenosine triphosphate; $A_{2a}R/A_{2b}R$, adenosine receptors 2a/2b; DC, dendritic cell; IL, interleukin; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed cell death protein-1; TAM, tumor-associated macrophage; TME, tumor microenvironment; 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 $A_{2b}R$ in addition to $A_{2a}R$
- Currently, there are 4 ongoing global phase 1/1b disease-specific platform studies to assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of etrumadenant in combination with chemotherapy and/or anti-programmed cell death protein 1 (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/PD correlation, and a well-tolerated safety profile of etrumadenant + chemo/immunotherapy

ADENOSINE BIOLOGY IN CRC

- In multiple analyses of human tumors, colorectal cancer (CRC) has been shown to have some of the highest expression levels of CD73 and $A_{2b}R$ compared with other tumor types[6,7]
- Additionally, *KRAS, BRAF,* and *EGFR* mutations found in metastatic CRC (mCRC) are associated with CD73 overexpression[8,9] (**Figure 2**)
- *KRAS* and *BRAF* mutant tumors not only produce higher levels of adenosine but may also respond, in an autocrine $A_{2b}R$-mediated fashion, to those increased adenosine levels by activating growth pathways synergistic with the oncogenic mutation
- In preclinical studies, etrumadenant + oxaliplatin synergistically inhibited murine tumor growth and increased the number of intratumoral CD8+ T cells[10]
- For these reasons, patients with mCRC may be particularly sensitive to etrumadenant in combination with platinum-based standard-of-care (SOC) chemotherapy and further evaluation of etrumadenant-based combination therapy for mCRC is warranted

Figure 2. Correlation of *KRAS, BRAF*, and *EGFR* Mutations with Elevated CD73 Expression



FDR, false discovery rate; WT, wild type.

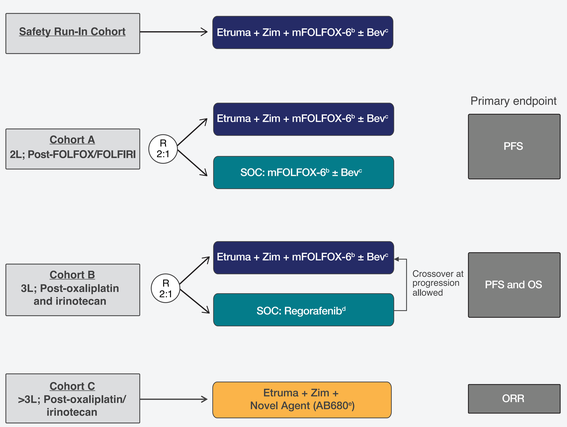
RATIONALE FOR ETRUMADENANT COMBINATIONS IN CRC

- Platinum-based chemotherapy, specifically leucovorin and 5-fluorouracil (5-FU) plus oxaliplatin (FOLFOX), is a SOC treatment for patients with mCRC[5]
  - Bevacizumab, a recombinant humanized monoclonal antibody (mAb) targeting vascular endothelial growth factor (VEGF), is commonly combined with fluorouracil-based chemotherapy in first-line (1L) and second-line (2L) treatment and improves overall survival compared with chemotherapy alone for patients with mCRC[11,12]
  - In patients with mCRC who have progressed on chemotherapy, the multi-kinase inhibitor regorafenib is considered a SOC as third-line (3L) treatment[13]
- Despite these existing approved combination therapies, patients with mCRC have a 5-year survival rate of 15%[14]
  - A high unmet need exists for novel mCRC treatments with improved safety and enhanced efficacy, which can induce durable clinical benefits
- In a phase 1/1b study (ARC-3; NCT03720678), etrumadenant + mFOLFOX-6 was well-tolerated without significant evidence of additive toxicity in patients with mCRC[15]
  - Combination treatment was associated with disease control in patients with *RAS/BRAF*-mutated mCRC and in patients with 3L+ disease previously treated with FOLFOX and/or FOLFIRI (partial response and/or stable disease >4 months)
  - Encouraging deep responses were observed across 1L to 3L+ patients, and 6 patients were able to pursue alternative therapy with curative intent
- In a phase 1 dose escalation (NCT03677973), AB680, the first clinical-stage small-molecule inhibitor of CD73, was well-tolerated in healthy volunteers and found to be dose-proportional at higher doses[16]
- In early clinical trials, the combination of adenosine receptor and programmed death-ligand 1 (PD-L1) inhibition demonstrated antitumor activity in patients with advanced solid tumors[17]
  - Zimberelimab, a human mAb targeting PD-1 with an anticipated safety profile similar to that of other approved anti–PD-1 mAbs, has been evaluated in combination with etrumadenant
  - A phase 1 study (NCT03629756) of etrumadenant + zimberelimab treatment demonstrated a favorable safety profile and evidence of clinical activity in patients with advanced solid tumors[18]
- Thus, combination therapy that includes SOC regimens with inhibitors of the adenosine and PD-1 pathways may hold promise for increasing efficacy without introducing significant new toxicity

ARC-9 STUDY OVERVIEW

- ARC-9 is a phase 1b/2, randomized, open-label, multi-cohort study designed to evaluate safety and clinical activity of etrumadenant (150 mg orally [PO] QD) in combination with SOC regimens or novel therapeutics in patients with mCRC (**Figure 3**)
- Upon demonstration of an acceptable safety profile in the initial safety run-in cohort, patients will be enrolled in Cohorts A, B, or C
- Cohort eligibility is based on prior anticancer treatment history; study treatment will be administered as follows:
  - **Safety run-in cohort:** Etrumadenant + standard doses of zimberelimab (240 mg intravenous [IV] once every 2 weeks [Q2W]) and mFOLFOX-6 ± bevacizumab (5 mg/kg IV Q2W)
  - **Cohort A:** Etrumadenant + zimberelimab + mFOLFOX-6 ± bevacizumab **or** mFOLFOX-6 ± bevacizumab
  - **Cohort B:** Etrumadenant + zimberelimab + mFOLFOX-6 ± bevacizumab **or** regorafenib (final dose after ramp up: 160 mg PO QD)
  - **Cohort C:** Etrumadenant + zimberelimab + novel agent (AB680: RP2D IV Q2W)
- Patients randomized to Cohort A (2L) will be stratified by *KRAS* mutation status and those randomized to Cohort B (3L) will be stratified by region (United States vs the rest of the world)
- Patients with disease progression in the SOC arm of Cohort A (2L) will have the option to enroll in Cohort B (3L), and those with disease progression in the SOC arm of Cohort B (3L) may crossover to the etrumadenant + zimberelimab + mFOLFOX-6 ± bevacizumab arm
- Cohort C consists of a single arm to allow inclusion of novel agents as they become available with built-in early stopping rules for futility

Figure 3. ARC-9 Study Design[a]



[a] Radiographic disease evaluation will be performed at screening and every 8 weeks thereafter. [b] mFOLFOX-6 dosage and administration: oxaliplatin 85 mg/m^2 IV Q2W; leucovorin 400 mg/m^2 IV Q2W; 5-FU 400 mg/m^2 IV bolus and 2,400 mg/m^2 IV infusion on Days 1 and 2. [c] Bevacizumab will be administered to all patients for whom it is not contraindicated. [d] Regorafenib dosage and administration: 160 mg PO QD with dose ramp up starting at 80 mg on Week 1, to 120 mg on Week 2, to 160 mg PO on Week 3 for the first cycle, followed by 160 mg for 21 days out of the 28-day cycle thereafter. [e] AB680 has been chosen as the first novel combination agent. 5-FU, 5-fluorouracil; Bev, bevacizumab; Etruma, etrumadenant; FOLFIRI, leucovorin, 5-FU, irinotecan; IV, intravenous; L, line; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q2W, once every 2 weeks; R, randomize; SOC, standard-of-care; Zim, zimberelimab.

- This study will be conducted at sites in the United States, France, Germany, Italy, Spain, and South Korea
- Selected inclusion and exclusion criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria for ARC-9

Key inclusion criteria	• Adults with pathologically confirmed metastatic colorectal adenocarcinoma • ≥1 measurable lesion per RECIST v1.1 • ECOG PS of 0 or 1 • Life expectancy ≥3 months • Cohort A (2L): disease progression following 1 line of treatment • Cohort B (3L): disease progression following 2 lines of treatment • For patients in Cohorts A and B who received an oxaliplatin-containing chemotherapy, disease progression must not occur within 2 months of the last dose of oxaliplatin
Key exclusion criteria (Cohorts A and B)	• Prior treatment with immune checkpoint blockade therapies including anti-cytotoxic T-lymphocyte-associated protein-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies • Mutation in the *BRAF* oncogene; patients with unknown *BRAF* status will be required to undergo testing at a local laboratory and provide results at screening

ECOG PS, Eastern Cooperative Oncology Group performance status; L, line; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

- Primary efficacy endpoints include progression-free survival (PFS; Cohorts A and B), overall survival (OS; Cohort B), and objective response rate (ORR; Cohort C) according to RECIST v1.1
- Secondary endpoints include ORR (Cohorts A and B), duration of response (DoR; Cohorts A, B, and C), and disease control rate (DCR; Cohorts A, B, and C) according to RECIST v1.1, OS (Cohort A), PK (all cohorts), and immunogenicity (all cohorts)
- Incidence and severity of adverse events and serious adverse events will be monitored and recorded for all cohorts
- Patients will be evaluated for response every 8 weeks until disease progression, the start of a new anticancer therapy, withdrawal, death, or the end of the study

CONCLUSIONS

- Etrumadenant with mFOLFOX-6 has been well-tolerated without significant evidence of additive toxicity in patients with mCRC
  - Combination treatment was associated with substantial disease control rate across all lines of therapy, including those with microsatellite stable and *RAS/BRAF*-mutated mCRC[15]
  - Encouraging deep responses were observed across 1L-3L+ patients, with several patients being taken to definitive cure with surgical resection/radiotherapy of remnant lesions[15]
  - Patients with 3L+ disease previously treated with FOLFOX and/or FOLFIRI have shown encouraging clinical benefit (partial response and/or stable disease >4 mo) with etrumadenant in combination, warranting further exploration[15]
- ARC-9 is a phase 1b/2 clinical trial for patients with mCRC aimed at investigating the efficacy and safety of etrumadenant in combination with SOC regimens or novel therapeutics
- This study further investigates etrumadenant-based therapies based on prior treatment history in patients with mCRC for whom there is a high unmet need

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