**The ADENOSINE AXIS IN CANCER**

- Standard chemotherapy regimens may contribute to immunosuppression by elevating immune cell levels of adenosine-triphosphate (ATP) and adenosine-monophosphate (AMP), which deplete both ATP and AMP through the action of the adenosine systemic pathway.

- By binding adenosine receptors (A2aR and A2bR) expressed on immune cells, adenosine promotes immunosuppression by inhibiting critical components of the adaptive immune response, ultimately enabling tumors to evade destruction.

- Adenosine A2aR signaling impairs the activation, proliferation, and cytotoxic activity of effector T cells.

- Initial research focused on A2aR as the most relevant adenosine receptor in cancer (Figure 1). However, A2aR and A2bR can act synergistically in specific immune cell populations by activating unique functions, such as cancer cell intrinsic survival and dendritic cell activation and function.

- Thus, adenosine receptor blockade may be necessary to overcome adenosine-dependent immunosuppression and lead to enhanced therapeutic efficacy of some chemotherapeutic agents.

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

**RATIONAL FOR ETRUMADENANT COMBINATIONS IN CRC**

- Platinum-based chemotherapy, specifically leucovorin and 5-fluorouracil (F-U) plus infusional FOLFOX, is a SOC regimen for CRC.

- Bivalirudin, a recombinant humanized monoclonal antibody (mAb) targeting vascular endothelial growth factor (VEGF), is commonly combined with fluoropyrimidines plus platinum-based chemotherapy in first-line (1L) and second-line (2L) treatment and improves overall survival compared with chemotherapy alone for patients with CRC.

- In patients with CRC who have progressed on chemotherapy, the multi-kinase inhibitor regorafenib is considered a SOC in all and 3L treatment (3L) regimens.

- Despite these existing options, patients with CRC have a 5-year survival rate of 15%.

- A high proportion exist for novel mAb-combination treatments with improved safety and enhanced efficacy, which can induce durable clinical benefit.

- In a phase 1/2b study (ARC-2; NCT03793154, etrumadenant + FOLFOX-6), etrumadenant + FOLFOX-6 was well tolerated without significant evidence of additive toxicity in patients with CRC.

- Combination treatment was associated with disease control in patients with CRC/RAS-mutated CRC and in patients with CRC previously treated with FOLFOX-4 and/or FOLFIri (partial response and/or stable disease >4 months).

- Encouraging deep responses were observed in 1L, 2L, and 3L patients, and 6 patients (3%) achieved a durable antitumor response with coadministration of etrumadenant.

- In a phase 1 dose escalation (NCT02797703; ABC), the final stage I/II small molecule inhibitor of CD73 was well tolerated in healthy volunteers and found to be dose-proportional at higher doses.

- In a phase I/II clinical trial, combination of adenosine receptor and programmed death ligand-1 (PD-L1) inhibitors demonstrated antitumor activity in patients with advanced solid tumors.

- Zimberelimab, a human mAb targeting PD-1 with an anticipated safety profile similar to that of pembrolizumab, has been evaluated in combination with etrumadenant.

- A phase I/II study (NCT03219295) of etrumadenant + zimberelimab treatment demonstrated objective responses and evidence of clinical activity in patients with advanced solid tumors.

- Thus, combination therapy that includes CRC regimens with inhibitors of the adenosine axis and combination with platinum-based standard-of-care (SOC) chemotherapy and further evaluation of etrumadenant-based combination therapy for mCRC is warranted.

**ARC-9 STUDY OVERVIEW**

- ARC-9 is a phase 1/2a, randomized, open-label, multi-cohort study designed to evaluate the activity of etrumadenant (150 mg study [PO] QD) in combination with SOC regimens or novel therapeutics in patients with mCRC (Figure 2).

- Upon demonstration of an acceptable safety profile in the initial safety-in-cohort, patients will be enrolled in Cohort A, B, or C.

- Patients randomized to Cohort A (2L) will be stratiﬁed by adenomatous polyposis or those randomized to Cohort B (3L) will be stratiﬁed by United States and/or the rest of the world.

- Patients with disease progression in the SOC of Cohort A (2L) will have the option to enroll in Cohort B (3L), and those with disease progression in the SOC of Cohort B (3L) may enroll in Cohort C (3L).

- Cohort D: Combination of erlotinib with zimberelimab (novel agent; ABZ) in patients previously treated with FOLFOX-4 (invasive CRC).

- The primary endpoint is progression-free survival (PFS) in patients previously treated with FOLFOX-4 in the 3L setting or who are refractory to anti-VEGF treatment.

- Key exclusion criteria: Patients with brain metastases, vaccination (vaccines with adenosine-driven platform), or patients enrolled in active clinical trials that potently block A2bR in function.

- **Key inclusion criteria:** Patients with measurable unresectable CRC who have progressed on standard of care (SOC) regimens.

- **Key endpoints:** Progression-free survival (PFS), overall survival (OS), and safety and tolerability.

- **Key safety endpoints:** SAEs, DLTs, discontinuations, treatment-emergent AEs, and drug-related AEs.

- **Key primary efficacy endpoints:** duration of response (DoR), time to disease progression (TTP), and overall survival (OS).

- **Key regulatory approvals:** This study is part of an ongoing and active clinical trial sponsored by Arcus Biosciences, Inc.

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**CONCLUSIONS**

- etrumadenant with mFOLFOX-6 has well-tolerated safety and significant activity in patients with mCRC.

- Combination treatment was associated with substantial disease control rate across all lines of therapy, including those with measurable CRC and mCRC/mCRC-mutated CRC.

- Many patients who experienced stable disease or partial response to treatment were able to continue treatment and achieve improved safety compared with other treatments.

**ACKNOWLEDGMENTS AND DISCLOSURES**

- All authors contributed to this study and have reviewed and approved the final manuscript.

- No authors have conflicts of interest to disclose.

- **References**

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