ARC-3: Updated Results of Etrumadenant (AB928) + mFOLFOX-6 in Patients with Metastatic Colorectal Cancer

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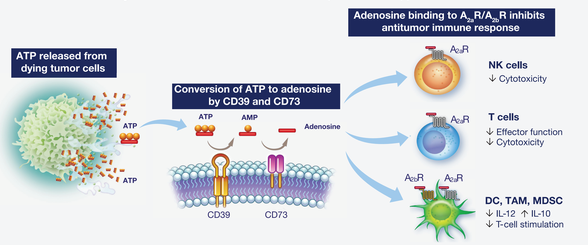
INTRODUCTION

The Adenosine Axis in Cancer

- Standard-of-care (SOC) 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 (particularly activation, proliferation, and cytotoxic activity of effector T cells[3]), ultimately enabling tumors to evade destruction[2]
- 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 pathway blockade may be necessary to overcome adenosine-dependent immunosuppression leading to enhanced therapeutic efficacy of some chemotherapeutic agents[5]

Figure 1. Critical Role of Adenosine Pathway in 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 cells; NK, natural killer; TAM, tumor-associated macrophage; TME, tumor microenvironment.

- Etrumadenant 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 and selectively blocks $A_{2a}R$ and $A_{2b}R$
- There are several ongoing randomized Phase 1b/2 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[6,8]
  - Based on dose-escalation data, 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

ARC-3 Study Rationale

- Platinum-based chemotherapy, specifically 5-fluorouracil plus oxaliplatin (FOLFOX), is a SOC treatment for patients with metastatic colorectal cancer (mCRC)[7]
- Despite recent therapeutic advances, patients with mCRC have a 5-year survival rate of 15%, which leaves a great unmet need for novel mCRC treatments with improved safety, enhanced efficacy, and that can induce durable clinical benefits[9]
- In multiple analyses of human tumors, CRC has been shown to have some of the highest expression levels of CD73 and $A_{2b}R$ compared with other tumor types[9,10]
- Additionally, *KRAS* and *BRAF* mutations are found at frequencies of 47% and 13%, respectively,[11] in mCRC and are associated with CD73 overexpression[12,13]
- *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[14]
- Initial results from the ARC-3 study showed that etrumadenant + modified FOLFOX-6 (mFOLFOX-6) in patients with mCRC was well tolerated and associated with disease control, including in patients with microsatellite stable disease and *RAS*/*BRAF*-mutated mCRC[15,16]
  - In patients receiving ≥third-line treatment (3L+), tumor mutational burden (TMB) and CD73 expression levels were associated with improved clinical outcomes[15]
- Herein we present final ARC-3 results from the 3L+ cohort of patients with mCRC, with a focus on long-term outcomes including progression-free survival (PFS) and overall survival (OS)

METHODS

ARC-3 Study Design

- ARC-3 (NCT03720678) was a Phase 1/1b, multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, PK, and clinical activity of etrumadenant + mFOLFOX-6 in patients with advanced mCRC
  - **Dose-escalation:** Etrumadenant (75 or 150 mg QD) + standard mFOLFOX-6 was evaluated in a 3+3 design; patients were monitored for dose-limiting toxicities for 28 days
  - **Dose-expansion:** Etrumadenant at the RDE in combination with standard mFOLFOX-6
- The primary objective was to assess safety and tolerability of etrumadenant + mFOLFOX-6; secondary objectives included evaluation of clinical activity
- Eligible patients had histologically confirmed CRC that was metastatic or locally advanced and unresectable, ≥1 measurable lesion per RECIST v1.1, and an ECOG performance status 0-1
- Baseline screening or archival tumor tissue and on-treatment biopsies (if medically feasible) were collected from all patients to evaluate *KRAS* and *BRAF* mutation status, microsatellite instability, TMB, immune composition, and disease characteristics before and after treatment
- Patients were allowed to receive study treatment until disease progression, unacceptable toxicity, or investigator decision
  - If needed, patients could discontinue 5-fluorouracil and oxaliplatin according to SOC guidelines and continue etrumadenant and/or other study treatments until the aforementioned criteria were met

Statistical Analysis

- Safety analyses included all 3L+ patients who received ≥1 dose of any study drug
  - Summary statistics were provided for treatment-emergent adverse events (TEAEs) and serious TEAEs (TESAEs), TEAE severity, and TEAE relationship to study drugs
- Efficacy analyses included all 3L+ patients who had a baseline and ≥1 post-baseline assessment or discontinued study treatment due to progressive disease or death
  - Clinical activity was assessed according to RECIST v1.1 criteria
  - Disease control rate (DCR) was defined as the percentage of patients with a best overall response of complete response (CR), partial response (PR), or stable disease (SD)

RESULTS

Patient Baseline Characteristics

- As of February 26, 2021, 23 patients received etrumadenant (75 mg: n=2; 150 mg: n=21) + mFOLFOX-6 as a 3L+ treatment (ie, patients had previously received ≥2 treatment lines for metastatic disease)
  - 150 mg etrumadenant QD was selected as the RDE based on PK, PK/PD correlation, and a well tolerated safety profile in the dose-escalation portion of the study
- For all patients, the mean age was 52 years; most patients were white (83%) and not Hispanic (87%; **Table 1**)
- The majority of patients had received prior FOLFOX (20/23; 87%) and/or FOLFIRI (21/23; 91%) for metastatic disease
- Of 3L+ patients with available genetic sequencing data (15/23):
  - All 15 patients had tumors that were microsatellite stable via exome sequencing
  - 7/15 (47%) had *KRAS* G12/13X mutations
  - 1/15 (7%) had a non-V600X *BRAF* mutations
  - None had *NRAS* mutations

Table 1. Patient Demographics and Characteristics

Parameter	Dose-Escalation		Dose-Expansion	All Patients (N=23)
	75 mg etruma QD + mFOLFOX-6 Q2W[a] (n=2)	150 mg etruma QD + mFOLFOX-6 Q2W[a] (n=7)	150 mg etruma QD + mFOLFOX-6 Q2W[a] (n=14)	
Mean age (SD), years	44 (9)	53 (10)	53 (7)	52 (8)
Sex, male, n (%)	1 (50)	5 (71)	8 (57)	14 (61)
Race, n (%)				
White	2 (100)	5 (71)	12 (86)	19 (83)
Black	0	2 (29)	1 (7)	3 (13)
Asian	0	0	1 (7)	1 (4)
Ethnicity, not Hispanic, n (%)	2 (100)	6 (86)	12 (86)	20 (87)
Prior therapies for metastatic disease, n (%)				
2	0	1 (14)	6 (43)	7 (30)
3+	2 (100)	6 (86)	8 (57)	16 (70)
Median prior treatments for metastatic disease, (range)	3 (3–3)	4 (2–7)	3 (2–6)	3 (2–7)

[a] mFOLFOX-6 regimen: oxaliplatin: 85 mg/m² IV Q2W; leucovorin 400 mg/m² IV Q2W; and 5-FU 400 mg/m² IV bolus + 2,400 mg/m² (continuous 46-hour infusions on Days 1–2).[17,18] 5-FU, 5-fluorouracil; etruma, etrumadenant; IV, intravenously; Q2W, once every 2 weeks; QD, once daily; SD, standard deviation.

Safety Analyses

- As shown in **Table 2**, 22 patients (96%) reported ≥1 TEAE and 16 TEAEs were reported by >30% of patients; the most common TEAEs were fatigue (70%), thrombocytopenia (57%), diarrhea (52%), and nausea (52%)
- Etrumadenant-related TEAEs occurred in 16/23 (70%) of patients; of those patients, 11/16 (69%) had Grade 1 or 2 TEAEs which accounted for 109/117 (93%) of all reported etrumadenant-related TEAEs
- Five patients reported ≥Grade 3 etrumadenant-related TEAEs that were also possibly related to mFOLFOX-6: diarrhea (n=1), neutropenia (n=2), hyperglycemia (n=1), aspartate aminotransferase increased (n=1)
- ≥Grade 3 TESAEs were reported by 9/23 (39%) of patients; of these events, those that occurred in more than 1 patient were small intestinal obstruction (n=2) and sepsis (n=2)
- There were no deaths that occurred due to etrumadenant-related TEAEs
- Five patients (22%) had TEAEs that resulted in etrumadenant discontinuation; of those patients, 2 had TEAEs that were deemed related to etrumadenant (blood creatinine increased [Grade 1] and thrombocytopenia [Grade 1])
- Fourteen 3L+ patients (61%) reported ≥1 TEAE of peripheral neuropathy; of those patients, 12 had Grade 1 events and 6 had Grade 2 events
  - Notably, no Grade 3 neuropathy was observed in this heavily pretreated patient population

Table 2: Treatment-Emergent Adverse Events

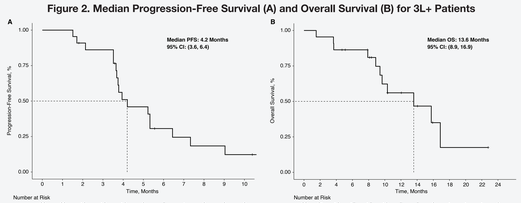
Parameter, n (%)	Dose-Escalation		Dose-Expansion	All Patients (N=23)
	75 mg etruma QD + mFOLFOX-6 Q2W (n=2)	150 mg etruma QD + mFOLFOX-6 Q2W (n=7)	150 mg etruma QD + mFOLFOX-6 Q2W (n=14)	
Any TEAE	2 (100)	7 (100)	13 (93)	22 (96)
Grade ≥ 3	1 (50)	7 (100)	10 (71)	18 (78)
Any TESAE	1 (50)	5 (71)	3 (21)	9 (39)
Grade ≥ 3	1 (50)	5 (71)	3 (21)	9 (39)
Etruma-related TEAEs[a]	1 (50)	6 (86)	9 (64)	16 (70)
Etruma-related TESAEs[a]	0	0	0	0
Study treatment d/c due to TEAEs	0	2 (29)	8 (57)	10 (44)
Etruma d/c due to TEAEs	0	1 (14)	4 (29)	5 (22)
Deaths due to TEAEs	0	1 (14)	0	1 (4)
TEAEs in >30% of all patients				
Fatigue	1 (50)	6 (86)	9 (64)	16 (70)
Thrombocytopenia	0	4 (57)	9 (64)	13 (57)
Diarrhea	1 (50)	6 (86)	5 (36)	12 (52)
Nausea	1 (50)	5 (71)	6 (43)	12 (52)
Neutropenia	1 (50)	3 (43)	7 (50)	11 (48)
Anemia	1 (50)	4 (57)	6 (43)	11 (48)
AST increased	0	4 (57)	6 (43)	10 (44)
ALT increased	0	3 (43)	6 (43)	9 (39)
Hyperbilirubinemia	0	1 (14)	7 (50)	8 (35)
Abdominal pain	2 (100)	2 (29)	4 (29)	8 (35)
Blood alkaline phosphatase increased	0	3 (43)	5 (36)	8 (35)
Neuropathy peripheral	1 (50)	1 (14)	6 (43)	8 (35)
Decreased appetite	0	4 (57)	4 (29)	8 (35)
Hyponatremia	0	2 (29)	5 (36)	7 (30)
Cough	1 (50)	3 (43)	3 (21)	7 (30)
Chills	0	2 (29)	5 (36)	7 (30)

[a] Events may also be considered related to some components of the mFOLFOX-6 treatment regimen. ALT, alanine aminotransferase; AST, aspartate aminotransferase; d/c, discontinuation; etruma, etrumadenant; Q2W, once every 2 weeks; QD, once daily; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Clinical Activity

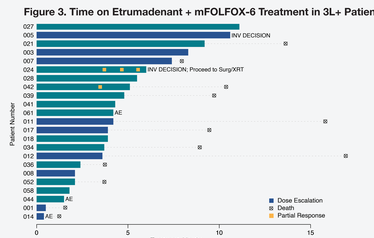
- Of 22 efficacy evaluable 3L+ patients, median PFS was 4.2 months with a median OS of 13.6 months (**Figure 2**), which compares favorably with current SOC in late-line patients with mCRC (median PFS: 2.0 and 1.9 months; median OS: 7.1 and 6.4 months, for trifluridine and tipiracil vs regorafenib, respectively[19,20])
- Late-line patients with higher TMB and tumor expression of CD73 had better outcomes (PFS and OS), consistent with our previous findings[15]
  - This is notable because, in other studies of late-line patients with CRC, high TMB was associated with lower OS[21] and high CD73 expression is a negative prognostic factor[22] associated with diminished response to FOLFOX in mCRC[23]
  - The improved outcomes observed in ARC-3, compared with the expected clinical trends, may be reflective of an etrumadenant-mediated effect

Figure 2. Median Progression-Free Survival (A) and Overall Survival (B) for 3L+ Patients



- Median time on treatment for 3L+ patients was 4.2 months (range: 0.4-11.1 months; **Figure 3**)

Figure 3. Time on Etrumadenant + mFOLFOX-6 Treatment in 3L+ Patients

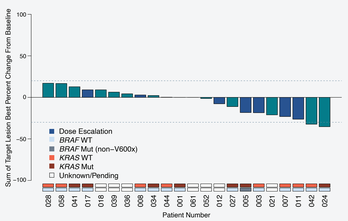


AE, adverse event; INV DECISION, investigator decision for discontinuation; L, line; Mut, mutation; Surg/XRT, surgery/radiotherapy; WT, wild type.

Best Overall Response

- In the 3L+ setting, PRs were observed in 2/22 patients (Objective Response Rate, ORR: 9.1%) and 17 patients had SD as best overall response (**Figure 4**)
  - Both PRs and 11/17 SDs were achieved in patients with microsatellite stable disease; samples were not available for the 6 remaining patients with SD
- For all 3L+ patients, the investigator-assessed 8-week and 16-week DCRs were 86% and 46%, respectively

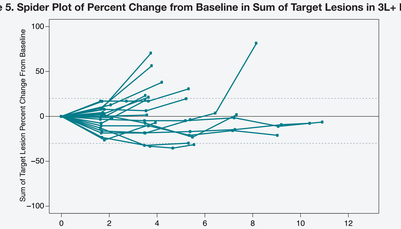
Figure 4. Waterfall Plot of Best Percentage Change from Baseline in Sum of Target Lesions in 3L+ Patients[a]



[a] 1 patient who discontinued the study prior to the first disease assessment is not included in this analysis. L, line; Mut, mutation; WT, wild type.

- Percentage change in the sum of target lesions over time for each 3L+ patient is shown in **Figure 5**

Figure 5. Spider Plot of Percent Change from Baseline in Sum of Target Lesions in 3L+ Patients



CONCLUSIONS

- Final results of etrumadenant + mFOLFOX-6 in 3L+ patients with mCRC demonstrate that this combination regimen was well tolerated with a safety profile lacking additive toxicity and consistent with previous findings[15,16]
- In 3L+ patients, a median PFS of 4.2 months and median OS of 13.6 months was achieved, which compares favorably with current SOC in late-line patients with mCRC (median PFS: 2.0 and 1.9 months; median OS: 7.1 and 6.4 months, for trifluridine and tipiracil vs regorafenib, respectively[19,20])
- Etrumadenant combination treatment was associated with an 8-week DCR of 86% (2 PR and 17 SD) and an ORR of 9.1% (2 PR) in 3L+ patients, which compares favorably with the ORR for current SOC therapies (trifluridine and tipiracil: 1.6%;[19] regorafenib: 1%[20])
- Based on the encouraging data observed, a Phase 1/2 randomized, multicohort study (ARC-9; NCT04660812) evaluating etrumadenant + zimberelimab (PD-1 monoclonal antibody)-based combinations has been initiated in previously-treated patients with mCRC (**Table 3**)

Table 3. ARC-9 Study Design

Cohort	Therapy Line	Arms
A	2L, post-FOLFOX/FOLFIRI	**Exp:** etruma + mFOLFOX-6 + zim ± bev[a] **SOC:** mFOLFOX-6 ± bev[a]
B	3L, post-oxaliplatin and irinotecan	**Exp:** etruma + mFOLFOX-6 + zim ± bev[a] **SOC:** regorafenib
C	>3L, post-oxaliplatin/irinotecan	**Exp:** etruma + zim + novel agent

[a] Administered if bev is not contraindicated. bev, bevacizumab; Exp, experimental; etruma, etrumadenant; L, line; SOC, standard-of-care; zim, zimberelimab.

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