ARC-4: Efficacy and Safety of Etrumadenant (AB928) plus Carboplatin, Pemetrexed and a PD-1 Antibody in Participants with Metastatic Non-Small Cell Lung Cancer

Poster # 1309P

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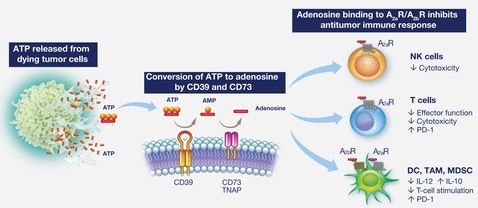
INTRODUCTION

The Adenosine Axis in Cancer

- Dying tumor cells release high levels of ATP into the tumor microenvironment (TME) where CD39 and CD73 convert it 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, $A_{2A}R$ 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, 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 Immunosuppressive Tumor Microenvironment



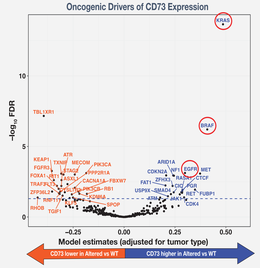
AMP, adenosine monophosphate; ATP, adenosine triphosphate; $A_{2A}R/A_{2B}R$, adenosine receptors 2a/2b; DC, dendritic cell; IL, interleukin; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-1, programmed cell death protein-1; TAM, tumor-associated macrophage; TNAP, tissue nonspecific alkaline 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 $A_{2B}R$
- Currently, there are 4 ongoing global phase 1/1b disease-specific platform 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

ARC-4 Study Rationale

- For locally advanced or metastatic non-small cell lung cancer (NSCLC), first-line treatment can include platinum-containing chemotherapy. Median overall survival and 5-year survival rates associated with these regimens are low[6]
- For non-squamous NSCLC with sensitizing mutations in epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) are commonly used as first-line therapy[7]; however, only a subset of tumors have these mutations and development of TKI-resistance is common[8]
- Addition of PD-1/PD-L1-targeted immunotherapy to platinum chemotherapy has improved outcomes for some patients with NSCLC[9,10]; however, many either do not initially respond or responses are short-lived, so an urgent unmet need remains for these patients
- Combination therapy that includes antagonism of the adenosine and PD-1/PD-L1 pathways with platinum chemotherapy may hold promise for enhancing treatment efficacy without additional toxicity
  - Lung adenocarcinomas have high expression of $A_{2B}R$, CD73, and PD-1, suggesting that the adenosine and PD-1 pathways may be particularly important for tumor growth and persistence[11,12]
  - Additionally, tumors with mutations in *EGFR*, *KRAS*, and *BRAF* have higher CD73 expression compared with tumors without those mutations (**Figure 2**)
  - In patients with NSCLC, the adenosine pathway is a potential mechanism of resistance to anti–PD-1 therapy[13,14] and high tumor expression of CD73 is associated with poor prognosis[15], which may indicate a therapeutic advantage to combination $A_{2B}R/A_{2B}R$ and PD-1 blockade
  - In mice, etrumadenant monotherapy had minimal effects on tumor growth, but enhanced the antitumor efficacy of an anti–PD-L1 antibody or chemotherapy without additive toxicity (data not shown)

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



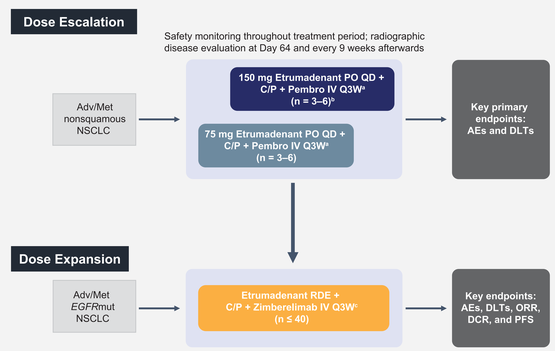
FDR, false discovery rate; WT, wild type.

METHODS

Study Design

- ARC-4 is an ongoing phase 1/1b, multicenter, open-label, dose escalation and dose expansion study to evaluate safety, tolerability, PK, pharmacodynamics, and clinical activity of etrumadenant + carboplatin/pemetrexed + pembrolizumab or zimberelimab (anti–PD-1 antibody) in patients with locally advanced, metastatic, or recurrent NSCLC (**Figure 3**)
  - **Dose escalation:** Etrumadenant (75 or 150 mg) orally (PO) once daily (QD) was administered with standard intravenous (IV) doses of carboplatin (AUC 5 mg/mL/min), pemetrexed (500 mg/m^2), and pembrolizumab (200 mg) once every 3 weeks (Q3W) based on a 3+3 design
  - **Dose expansion:** Patients with sensitizing *EGFR* mutations were enrolled and received etrumadenant (150 mg PO QD) with standard IV doses of carboplatin, pemetrexed, and zimberelimab (360 mg Q3W)

Figure 3. ARC-4 Study Design



[a] Carboplatin AUC 5 mg/mL/min, pemetrexed 500 mg/m^2, pembrolizumab 200 mg IV Q3W; [b] When a minimum of 3 patients available for toxicity completed the DLT evaluation period (1 chemotherapy cycle) for a given etrumadenant dose, subsequent patients were enrolled at the higher etrumadenant dose; [c] Zimberelimab 360 mg. Adv, advanced; AE, adverse event; AUC, area under the curve; C, carboplatin; DLT, dose-limiting toxicity; *EGFR*, epidermal growth factor receptor; EOT, end of treatment; IV, intravenously; Met, metastatic; mut, mutated; NSCLC, non-small cell lung cancer; P, pemetrexed; Pembro, pembrolizumab; PO, orally; Q3W, every 3 weeks; QD, once daily.

ARC-4 (NCT03846310) Design Features

- The primary objective is to evaluate the safety and tolerability of etrumadenant combination therapy in patients with NSCLC; secondary objectives include determination of clinical activity and PK
- Eligible patients are adults with pathologically-confirmed non-squamous NSCLC that is locally advanced, metastatic, or recurrent with progression, at least 1 measurable lesion per RECIST v1.1, and ECOG performance status of 0 or 1
- For the dose escalation, one of the following criteria must have also be met: 1) no alternative or curative therapy exists; 2) tumor had a genetic mutation/rearrangement for which targeted therapy exists but has no available standard TKI **and** patient has not had prior chemotherapy or anti–PD-1/PD-L1-based therapy; 3) patients were treatment-naive or were considered appropriate study candidates by the principal investigator
- For the dose expansion, patients must have had a sensitizing *EGFR* mutation and have had disease progression or been intolerant to ≥ 1 approved TKI; they must also have had no prior chemotherapy or anti–PD-1/PD-L1-based therapy for locally advanced or metastatic disease
- Study treatment may continue until disease progression, unacceptable toxicity, consent withdrawal, or by the investigator's decision

Statistical Analysis

- Safety analyses included all patients who received ≥ 1 etrumadenant dose; summary statistics are shown for treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs), TEAE severity and relationship to study drugs
- The efficacy-evaluable population included all patients who received ≥ 1 dose of etrumadenant and had ≥ 1 post-baseline disease assessment; clinical activity was assessed according to RECIST v1.1 criteria

RESULTS

Patient Baseline Characteristics

- As of August 5, 2020, 14 patients have received etrumadenant + chemo/immunotherapy; all but 3 received 150 mg etrumadenant (**Table 1**)
- Four patients in the dose escalation were previously treated with a checkpoint inhibitor (CPI)
- Within study patient medical records, the following genetic data were available:
  - Among the tumors of the 7 patients treated in the dose escalation, 1 had an *EGFR* mutation, 1 had a *BRAF* mutation, and 1 had a *KRAS* mutation
  - All 7 patients treated in the dose expansion had tumors with *EGFR* mutations

RESULTS

Table 1. Baseline Patient Demographics and Characteristics

Parameter	Dose Escalation: 75 mg Etrumadenant QD + C/P + Pembro Q3W n = 3	Dose Escalation: 150 mg Etrumadenant QD + C/P + Pembro Q3W n = 4	Dose Expansion: 150 mg Etrumadenant QD + C/P + Zim Q3W n = 7	Total N = 14
Median age (range), years	62 (50-80)	65.5 (48-74)	68 (54-77)	66 (48-80)
Male, n (%)	2 (67)	1 (25)	3 (43)	6 (43)
Race, n (%)				
White	3 (100)	4 (100)	2 (29)	9 (64)
Asian	0	0	4 (57)	4 (29)
Not reported	0	0	1 (14)	1 (7)
Prior therapies for metastatic disease, n (%)				
0	1 (33)	1 (25)	0	2 (14)
1	1 (33)	0	5 (71)	6 (43)
2	0	1 (25)	2 (29)	3 (21)
3	1 (33)	1 (25)	0	2 (14)
4	0	1 (25)	0	1 (7)
CPI-experienced patients, n (%)	1 (33)	3 (75)	0	4 (29)
EGFR mutation, n (%)	1 (33)	0	7 (100)	8 (57)
BRAF mutation[a], n (%)	0	1 (25)	0	1 (7)
RAS mutations (*KRAS* and *NRAS*)[b], n (%)	0	1 (25)	0	1 (7)

[a] 7 patients did not have available data; [b] 10 patients did not have available data. C, carboplatin; CPI, checkpoint inhibitor; *EGFR*, epidermal growth factor receptor; P, pemetrexed; Pembro, pembrolizumab; Q3W, once every three weeks; QD, once daily; Zim, zimerelimab.

Safety Analyses

- As of August 5, 2020, no dose-limiting toxicities had been reported in any dose cohort
- All patients reported ≥ 1 TEAE and 14 TEAEs were reported by ≥ 4 patients in any arm; the most common TEAEs were anemia (50%), neutrophil count decreased (43%), nausea (43%), and pyrexia (43%; **Table 2**)
- Etrumadenant-related TEAEs were reported by 8/14 (57%) patients and most were Grade 1 or 2
  - Two patients (150 mg etrumadenant; 1 each in dose escalation and expansion) experienced Grade 3 events (platelet count decreased, white blood cell decreased, thrombocytopenia) or Grade 4 events (thrombocytopenia) that were also considered related to carboplatin/pemetrexed
- Of all patients, 3/14 (21%) experienced etrumadenant-related TESAEs; all were Grade 1 or 2 events, except for 1 event of Grade 4 thrombocytopenia that was also considered related to carboplatin/pemetrexed
- In total, 5/14 (36%) patients discontinued any study treatment due to TEAEs
- One patient in the 75 mg etrumadent dose escalation group died from respiratory failure 36 weeks after the start of study treatment; the death was attributed to disease progression and was not considered related to any study drug

Table 2. Treatment-Emergent Adverse Events

Patients, n (%)	Dose Escalation: 75 mg Etrumadenant QD + C/P + Pembro Q3W n = 3	Dose Escalation: 150 mg Etrumadenant QD + C/P + Pembro Q3W n = 4	Dose Expansion: 150 mg Etrumadenant QD + C/P + Zim Q3W n = 7	Total N = 14
Any TEAE	3 (100)	4 (100)	7 (100)	14 (100)
Grade ≥ 3	3 (100)	3 (75)	3 (43)	9 (64)
Any TESAE	1 (33)	2 (50)	3 (43)	6 (43)
Grade ≥ 3	1 (33)	2 (50)	1 (14)	4 (29)
Etrumadenant-related TEAEs	2 (67)	1 (25)	5 (71)	8 (57)
Etrumadenant-related TESAEs	0	1 (25)	2 (29)	3 (21)
Any study treatment d/c due to TEAEs	1 (33)	3 (75)	1 (14)	5 (36)
Deaths due to TEAEs	1 (33)	0	0	1 (7)
TEAEs in ≥ 4 patients, n (%)				
Anemia	3 (100)	4 (100)	0	7 (50)
Neutrophil count decreased	3 (100)	1 (25)	2 (29)	6 (43)
Nausea	2 (67)	2 (50)	2 (29)	6 (43)
Pyrexia	1 (33)	2 (50)	3 (43)	6 (43)
Rash maculopapular	2 (67)	1 (25)	2 (29)	5 (36)
Fatigue	1 (33)	2 (50)	2 (29)	5 (36)
Hypokalemia	0	2 (50)	2 (29)	4 (29)
Blood creatinine increased	1 (33)	1 (25)	2 (29)	4 (29)
ALT increased	2 (67)	1 (25)	1 (14)	4 (29)
AST increased	3 (100)	1 (25)	0	4 (29)
Dehydration	1 (33)	2 (50)	1 (14)	4 (29)
Dyspnea	3 (100)	0	1 (14)	4 (29)
Constipation	3 (100)	0	1 (14)	4 (29)
Dizziness	1 (33)	1 (25)	2 (29)	4 (29)

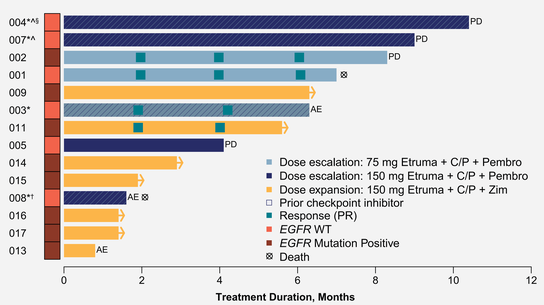
ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, carboplatin; d/c, discontinuation; P, pemetrexed; Pembro, pembrolizumab; Q3W, once every 3 weeks; QD, once daily; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; Zim, zimberelimab.

Clinical Activity

- As of August 5, 2020, there were 6/14 (43%) patients who remained on active treatment; the best overall responses for 13 evaluable patients are shown in **Figures 3 and 4**
- In the dose escalation:
  - Etrumadenant 75 mg – 3 partial responses (PRs)
  - Etrumadenant 150 mg – 2 stable disease (SD), 1 disease progression (PD; mixed response), 1 clinical progression
  - Notable responders included a TKI-experienced patient with an *EGFR*-mutated tumor that failed 3 prior lines of therapy and a CPI-experienced patient who had PD while on ipilimumab/nivolumab
- In the dose expansion:
  - Etrumadenant 150 mg – 1 PR (ongoing), 4 SD (all ongoing), 1 PD

RESULTS

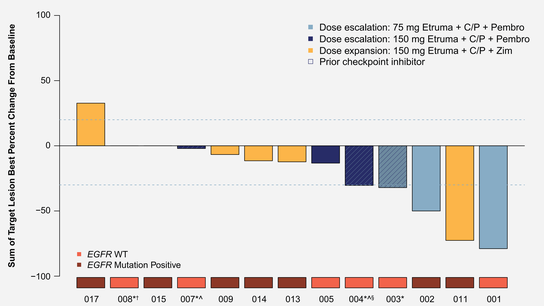
Figure 3. Time on Treatment and RECIST v1.1 Response



* Patients who were CPI-experienced; ^ Patient 004 had a *KRAS*-mutated tumor; patient 007 had a *BRAF*-mutated tumor; § Patient had a new non-target lesion at the first disease assessment; † Patient discontinued the study prior to the first disease assessment and was considered non-evaluable. AE, discontinuation due to adverse event; C, carboplatin; CPI, checkpoint inhibitor; EGFR, epidermal growth factor receptor; Etruma, etrumadenant; P, pemetrexed; PD, progressive disease; Pembro, pembrolizumab; PR, partial response; WT, wild type; Zim, zimberelimab.

Best Overall Response

Figure 4. Waterfall Plot of Best Percent Change from Baseline in Sum of Target Lesions



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CONCLUSIONS

- The combination of etrumadenant + chemotherapy + anti–PD-1 antibody had a manageable safety profile in patients with locally advanced, metastatic, or recurrent NSCLC; etrumadenant 150 mg PO QD was identified as the recommended dose for expansion
- Clinical activity with combination treatment was seen across multiple treatment cohorts, including responses in patients with *EGFR*-mutated tumors with recurrent disease after prior TKI or immunotherapy
- Dose expansion is ongoing in patients with *EGFR*-mutated NSCLC who have progressed after one or more TKIs with randomization triggered to begin post-futility assessment

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