SITC Annual Meeting

7-9 November 2025

National Harbor, Maryland

Abstract #170

Peripheral Pharmacodynamic Analysis of Anti-CD39 Monoclonal Antibody AB598 in a First-In-Human Phase I Trial in Patients with Advanced Solid Tumors

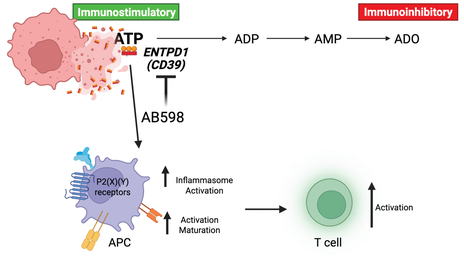
Jacob A. Van Winkle[1], Urvi Vani[1], Omar Kabbarah[1], Haiying Zhou[1], Lisa Seitz[1], Amy E. Anderson[1]

Institutions: [1]Arcus Biosciences, Inc., Hayward CA, USA

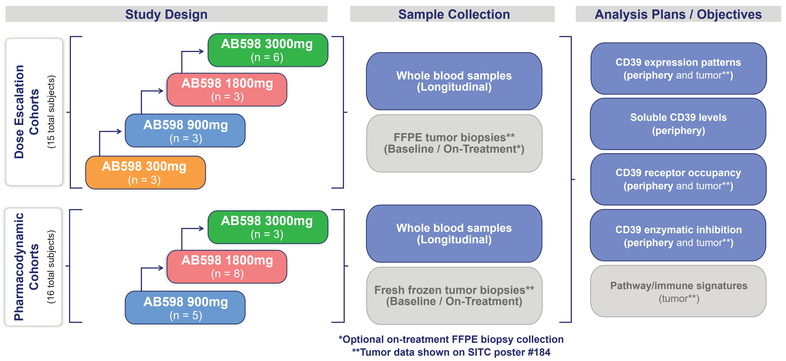
Background

CD39 is a cell surface enzyme that degrades extracellular ATP which can function as a potent immunostimulatory signal in the tumor microenvironment. AB598 is a novel, humanized, Fc-silent anti-CD39 antibody that binds to CD39 and inhibits its enzymatic activity, which may subsequently potentiate enhanced antitumor immunity.

ARC-25 (NCT05891171) is an ongoing phase 1/1b first-in-human trial to evaluate the safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of both AB598 monotherapy and AB598 in combination with zimberelimab (anti-PD-1) and FOLFOX chemotherapy in patients with advanced solid tumors.



Study Design



*Optional on-treatment FFPE biopsy collection
**Tumor data shown on SITC poster #184

Methods

Study Design
The phase 1 stage of ARC-25 evaluated AB598 monotherapy in patients with advanced or metastatic solid tumors for whom standard therapies were unavailable or ineffective. Patients (n = 31) enrolled across four dose levels of AB598 given intravenously (IV) every 3 weeks (Q3W) in dose escalation and PD cohorts.

CD39 Expression and Receptor Occupancy (RO) on Peripheral Immune Cells
Longitudinal whole blood (WB) samples were collected in sodium heparin blood collection tubes (BCT) and stained for flow cytometry analysis. Surface staining was performed using antibodies against HLA-DR, CD11c, CD86, CD3, CD14, CD16, CD19, and CD39 (non-competitive and competitive) followed by intracellular staining using FOXP3 and CD39 (non-competitive) antibodies. CD39 expression and RO were quantified using CD39 non-competitive and competitive antibodies, respectively, on immune cell types including B cells, regulatory T cells (Treg), non-regulatory T cells (Non-Treg T), classical monocytes (Cl mono), intermediate monocytes (Int mono), non-classical monocytes (NC mono), dendritic cells (DCs), and neutrophils (Neutrpl).

Total soluble CD39 (sCD39) and AB598-bound sCD39 in Plasma
Total sCD39 and AB598-bound sCD39 were analyzed in sodium heparin plasma samples using custom sandwich ELISAs. Total sCD39 was assessed in all patient samples. AB598-bound sCD39 was assessed in a subset of patients from dose escalation cohorts at cycle 1 and at trough timepoints (C1D1 Pre, C2D1, C3D1, C4D1, and end of treatment (EOT)).

ENTPD1 (CD39) Gene Expression in Peripheral Immune Cells
RNA was isolated from whole blood collected into PAXgene RNA tubes. cDNA was amplified with TaqMan Fast Advanced Master Mix using IDT PrimeTime primer/probe sets. *ENTPD1* (CD39) and housekeeping gene expression was quantified using custom-designed gene blocks as standard curves and by normalizing to input template abundances.

CD39 Enzymatic Inhibition on Total Leukocytes
Cellular CD39 enzymatic inhibition was assessed in total leukocytes isolated from sodium heparin BCTs using an AMPGlo assay after blocking non-CD39 ATPase activity with TNAP and CD73 inhibitors. CD39 enzymatic activity was quantified as the change in relative light units (RLU) between conditions treated *ex vivo* with excess AB598 versus isotype.

Data Analysis
Unless otherwise indicated, all available patient blood samples were analyzed. Flow cytometry analyses were performed using FlowJo. ELISA data interpolation was performed in GraphPad Prism using non-linear regression methods. Plotted data are individual patient or group mean responses; where plotted, error bars indicate ±1 standard deviation (SD).

Results

CD39 is Abundantly Expressed by Peripheral Immune Cells in Cancer Patients

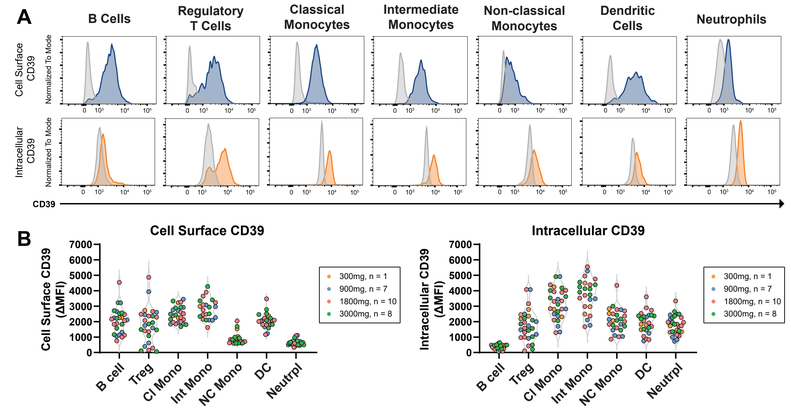


Figure 1. Cell surface CD39 and intracellular CD39 protein levels were measured in WB samples from ARC-25 patients (n=26). **A)** Representative histograms of CD39 expression at baseline (prior to AB598 treatment) are shown by immune cell type. Colored histograms indicate CD39-stained populations; grey histograms indicate negative staining controls. **B)** Quantification of baseline cell surface and intracellular CD39 for individual patients shows broad expression of CD39 protein across multiple immune cell populations where ΔMFI is the difference between the CD39-stained population and negative staining control.

AB598 Maintains Complete Target Engagement of CD39 on Peripheral Immune Cells and Inhibits Peripheral CD39 Enzymatic Activity

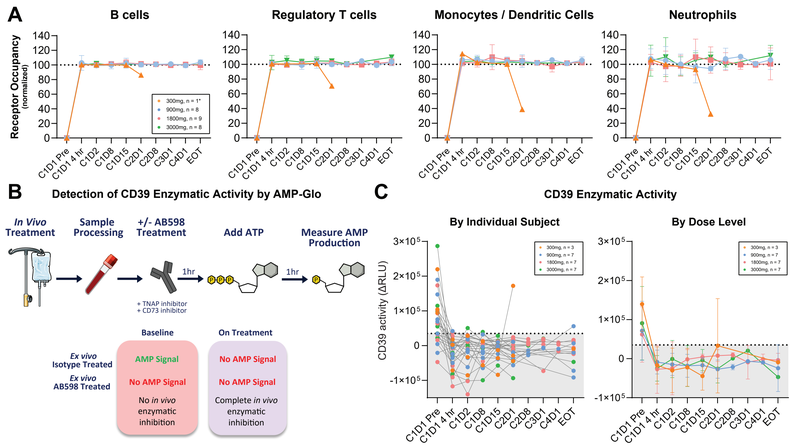


Figure 2. A) CD39 cell surface RO was assessed in WB samples from ARC-25 patients (n=26). **B)** CD39 enzymatic inhibition on total leukocytes was confirmed in a subset of patients (n=24). **C)** The change in AMP production (indicative of CD39 enzymatic activity) is shown for individual patients and by dose level. The dashed line and shaded area indicate the lower limit of quantification. Complete, sustained RO and CD39 enzymatic inhibition were achieved in all patients at AB598 doses of 900 mg or higher.

Results

AB598 Decreases Peripheral Immune Cell Surface CD39 and Intracellular CD39 without Altering *ENTPD1* Transcription

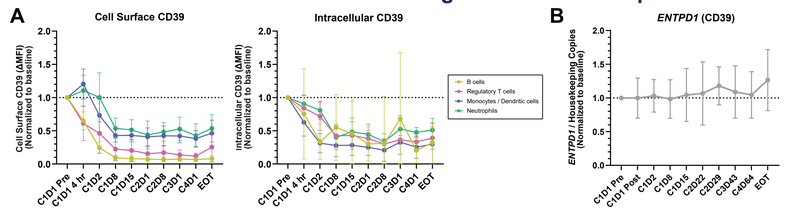


Figure 3. A) Changes in cell surface and intracellular CD39 expression were assessed in longitudinal WB samples from ARC-25 patients (n=26), revealing sustained loss of total cellular CD39 on peripheral immune cells following AB598 treatment. **B)** No significant changes were observed in *ENTPD1* (CD39) gene expression of total leukocytes in WB (n=30) at the assessed timepoints. Data shown are mean expression changes in blood samples where complete target engagement on peripheral immune cells was confirmed (no dose-dependent trends observed, not shown).

AB598 Maintains High Coverage of Soluble CD39 in Patient Plasma

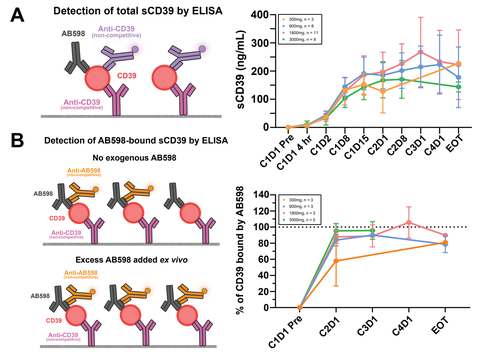


Figure 4. A) Total soluble CD39 (sCD39) in patient plasma was assessed using an AB598-non-competitive sandwich ELISA (n=31). Increases in sCD39 correspond with loss of membrane-associated CD39 protein from peripheral immune cells. **B)** AB598 binding to sCD39 was confirmed in a subset of patients (n=14) by a second sandwich ELISA which captures total sCD39 (non-competitively with AB598), then detects any AB598 bound to captured sCD39 (non-competitively with CD39). Detection of AB598 is dependent on CD39 binding by AB598. *Ex vivo* AB598 spike-in conditions were used to create complete binding controls with full saturation of sCD39. Endogenous AB598-bound sCD39 was normalized to the complete binding control for each individual sample. High levels of sCD39 binding by AB598 were observed across dose levels.

Conclusions

- **CD39 is abundantly expressed by peripheral immune cells, including B cells, regulatory T cells, monocytes, dendritic cells, and neutrophils**
- **AB598 achieves and maintains complete binding and inhibition of CD39 activity on peripheral immune cells at 900mg or higher doses**
- **Dosing with AB598 leads to a rapid and sustained decreases in peripheral immune cell-associated CD39 with corresponding increases in circulating sCD39**
- **Peripheral immune cell transcription of *ENTPD1* (CD39) remains stable after AB598 dosing**
- **AB598 maintains high coverage of sCD39 in plasma**

Accompanying tumor PD data is presented at poster #184

Acknowledgements: We thank the patients who provided clinical samples for ARC-25. We also thank all participating investigators, clinical staff, and the study team involved in ARC-25.