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


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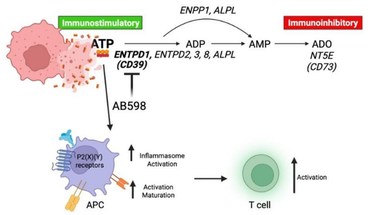
ARCUS BIOSCIENCES
Immunological Modulation Following AB598 Treatment

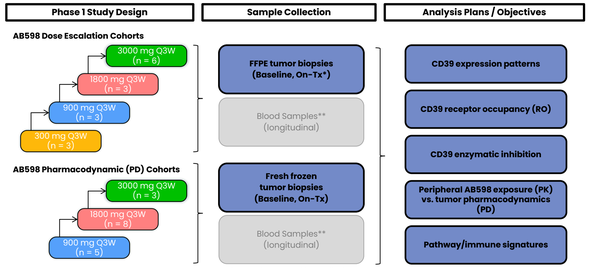
## Background




AB598 is a novel, humanized, Fc-silent anti-CD39 antibody that potently binds to CD39 and inhibits its enzymatic activity. The inhibition of CD39 contributes to the stabilization of extracellular ATP levels, providing a potent immunostimulatory signal in the tumor microenvironment (TME) and potentially leading to enhanced antitumor immunity. ARC-25 (NCT05891171) is a phase 1/1b trial to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AB598 monotherapy and combination therapy with zimberelimab (anti-PD-1) and standard-of-care chemotherapy (FOLFOX).

## Methods

### ARC-25 Dose Escalation Study Design, Sample Collection, and Analysis Plans




**Study Design:** The phase 1 portion 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 cohorts; PD cohorts enrolled at three dose levels after each dose was evaluated by a dose escalation committee (DEC).

**Tumor Biopsy Collections:** Formalin-fixed paraffin-embedded (FFPE) biopsies were requested at screening for patients in dose escalation cohorts; an optional on-treatment (On-Tx, collected at C2D8) biopsy was collected where medically feasible. Collection of fresh frozen biopsies at baseline and on-treatment were mandatory in PD cohorts.

**CD39 Expression in Solid Tumors:** CD39 protein expression was evaluated by immunohistochemistry (IHC) in biopsies of multiple solid tumor types from patients enrolled in ARC-25. CD39 transcript levels were measured in non-small cell lung cancer (NSCLC, Kim et al, GSE131907), colorectal cancer (CRC, Khaliq et al, GSE2009997), and pancreatic ductal adenocarcinoma (PDAC, Lin et al, GSE154778) by single cell RNA sequencing (scRNA-seq).

**Tumor Receptor Occupancy (RO):** Fresh frozen tumor biopsies were used to quantify total CD39 versus unbound CD39 by IHC using AB598- non-competitive and competitive anti-CD39 antibodies (Abcam EPR20461 and AB598.mIgG2A, respectively). Exogenous controls for complete receptor occupancy (~100% RO) were created by pre-incubating tissue sections with excess AB598 (100 nM) prior to IHC.

**Tumor Enzymatic Inhibition:** Fresh frozen tumor biopsies were used to quantify changes in CD39 enzymatic activity by enzyme histochemistry (EHC). Exogenous controls for complete CD39 inhibition (~0% CD39$^+$ EHC area of positivity) were created by pre-incubating tissue sections with excess AB598 (100 nM) prior to EHC.

**PK/PD Correlation:** AB598 serum concentration was measured by a validated PK ELISA and correlated to tumor PD readouts (CD39 RO and enzymatic inhibition). Models were developed to describe the PK/PD relationship.

**Gene Expression in Tumors:** RNA sequencing was performed on paired frozen and FFPE tumor biopsies. Samples were separated into Low Exposure (n=3) and High Exposure (n=10) groups and were hierarchically clustered within each group based on changes in individual gene expression, cell enrichment (xCell), and Single Sample Gene Set Enrichment Analysis (ssGSEA) scores.

## Results

### CD39 (*ENTPD1*) is Abundantly Expressed in Solid Tumors

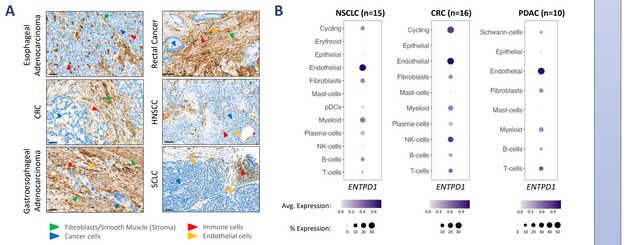



**Figure 1.** (A) Immunohistochemistry (IHC) shows expression of CD39 in a variety of cells within the tumor microenvironment, including stromal fibroblasts, smooth muscle, endothelia, and infiltrating immune cells in ARC-25 baseline tumor biopsies. Scale bars represent 50 µm unless otherwise indicated. (B) Tumor *ENTPD1* transcript levels in NSCLC, CRC, and PDAC tumors by scRNA-seq similarly reveal high expression by endothelial cells, fibroblasts, myeloid cells, and other immune cell lineages.

### AB598 Binds to Intratumoral CD39 and Achieves Complete Receptor Occupancy

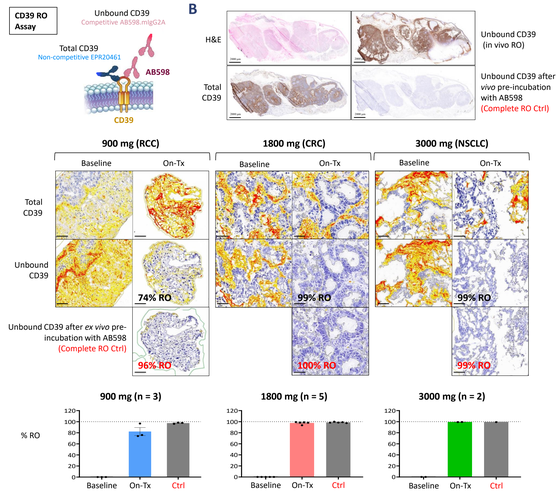



**Figure 2.** (A) CD39 Receptor Occupancy (RO) assay schema and (B) proof-of-concept IHC conditions in human tonsil. (C) Representative IHC images from a patient at each dose level show tumoral CD39 protein remaining stable in biopsies taken before and on-tx with AB598. Low levels of unbound CD39 were detected on-tx at 900 mg, with full target engagement at doses of 1800 mg and 3000 mg. (D) Percentage of CD39 RO in tumor tissue by HALO digital quantification as measured by IHC for each patient in the cohort. "Ctrl" refers to Complete RO controls produced by pre-incubating on-tx sections with excess AB598 *ex vivo*. Scale bars represent 50 µm unless otherwise indicated.

## Results

### AB598 Fully Inhibits CD39 Enzymatic Activity in Tumors

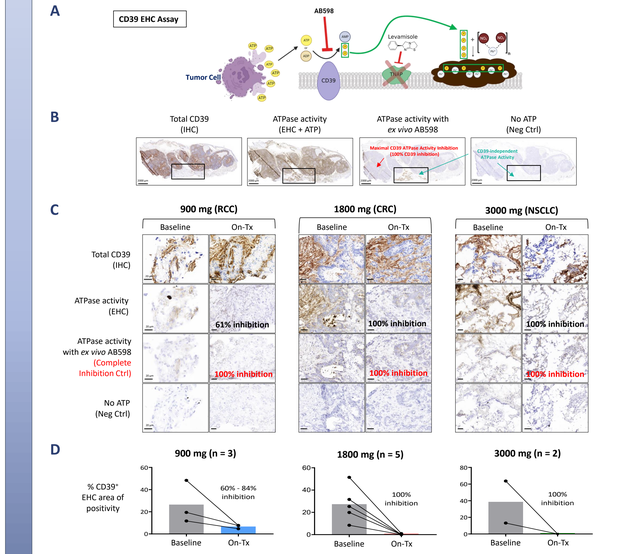



**Figure 3.** (A) CD39 enzyme histochemistry (EHC) assay schema and (B) proof-of-concept EHC conditions in human tonsil. (C) Representative EHC images from a patient at each dose level show CD39 protein localizing within areas of CD39 EHC positivity. CD39 enzyme activity shows a marked reduction on treatment in areas of CD39 expression at 900 mg, and full CD39 enzyme inhibition at the 1800 and 3000 mg doses. (D) Percentage of tissue area with CD39-specific enzymatic activity and range of CD39-specific inhibition achieved in individual patients for each dose level are shown. Scale bars represent 50 µm unless otherwise indicated.

### AB598 Serum Concentration Correlates with Tumor Target Engagement

| PK / PD Assay | 900 mg (n = 3) | | | 1800 mg (n = 5) | | | | | 3000 mg (n = 2) | |
|---|---|---|---|---|---|---|---|---|---|---|
| % RO | 74.0% | 76.0% | 97.0% | 99.3% | 98.1% | 98.8% | 93.4% | 98.3% | 100% | 98.8% |
| % Inhibition | 60.0% | 61.0% | 84.0% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| AB598 (µg/mL) | 50.9 | 53.2 | 151 | 231 | 254 | 364 | 241 | 84.7 | 294 | 396 |

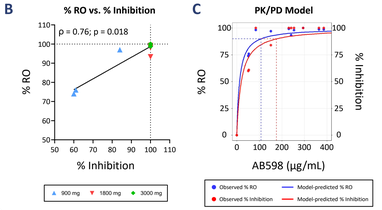



**Figure 4.** (A) Summary of PK/PD data in PD cohort patients (n is evaluable pairs of tumor biopsies). (B) Tumor CD39 RO and enzyme inhibition have high positive correlation. Plot shows linear regression, Spearman coefficient (ρ) and significance (p, two-tailed, 10 XY pairs). (C) CD39 RO (blue dashed line) and CD39 enzymatic inhibition (red dashed line) of 90% were achieved at AB598 concentrations of 107 ug/mL and 176 ug/mL, respectively, based on PK/PD modeling.

## Results

### Tumor Gene Expression and Pathway Analysis Reveals Immune Modulation in Antigen-Presenting Cells and T cells Following AB598 Treatment

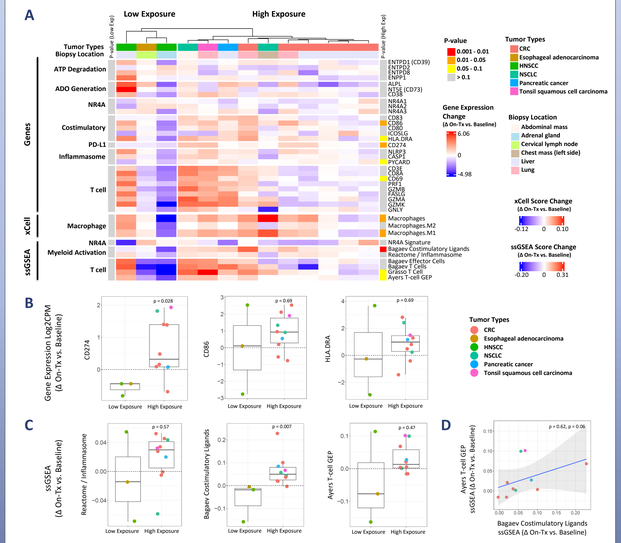



**Figure 5.** (A) Heatmap showing change (on-tx vs. baseline) in genes (log2CPM), cell enrichment (xCell), and gene pathways (ssGSEA) following AB598 treatment. P values were calculated using paired Wilcoxon test for Low and High Exposure groups separately. (B) Delta plots of genes and (C) gene pathways in AB598 low- and high-exposure groups (on-tx versus baseline). P values comparing low and high exposure groups were calculated using unpaired Wilcoxon test; costimulatory and Ayers T-cell GEP signatures are positively correlated. (D) Scatter plot of the change in the Bagaev co-stimulatory ligand pathway versus Ayers T-cell GEP in High Exposure patients (n=10) are shown, along with Spearman coefficient (ρ) and significance (p). Grey area denotes 95% confidence interval.

## Conclusions

- CD39 is abundantly expressed by various cell types in the tumor microenvironment - primarily by endothelial, fibroblasts, and immune cells.
- Total tumoral CD39 protein remained stable following AB598 treatment.
- Complete intratumoral CD39 target engagement, measured by receptor occupancy (RO) and the inhibition of enzymatic activity, is achieved at ≥ 1800 mg Q3W of AB598.
- AB598 monotherapy leads to increased myeloid activation, including enhanced costimulatory ligand, antigen presentation, and inflammasome signatures which may potentiate T cell activation in a subset of advanced solid tumors.
- *Peripheral blood biomarker analysis is presented on SITC Poster #170.*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