# Clinical Pharmacokinetic/Pharmacodynamic Relationship for AB598, an anti-CD39 Monoclonal Antibody in Patients with Advanced Cancer

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## BACKGROUND

- AB598 is a novel, humanized, Fc-silent anti-CD39 monoclonal antibody that potently binds to CD39 and inhibits its enzymatic activity with sub nanomolar potency. AB598 is under investigation in a first-in-human, multicenter, non-randomized, open-label phase 1 study in patients with advanced solid tumors (NCT05891171).

## OBJECTIVE

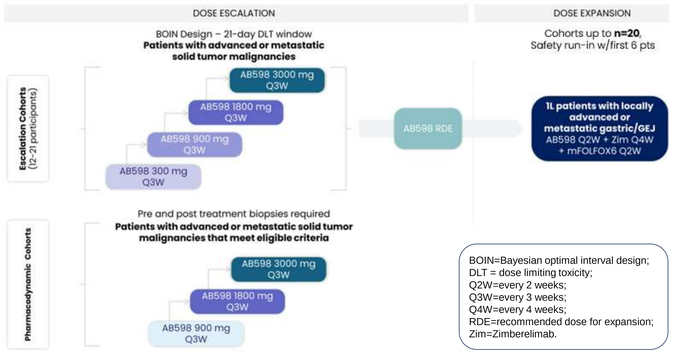
- To characterize the pharmacokinetics (PK) of AB598 in cancer patients
- To describe the relationship between AB598 PK and tumor pharmacodynamic (PD) markers (CD39 receptor occupancy [RO] and CD39 enzymatic inhibition [EHC]) to inform the selection of an appropriate dose for future clinical trials.

## STUDY DESIGN & METHODS

**Study Design**

- Patients with advanced malignancies were enrolled in the two-phase study – monotherapy (AB598) and combination therapy (AB598+Zimberelimab+mFOLFOX) phases (Figure 1).
- Serial PK samples were collected to characterize AB598 PK profile in cycle 1; thereafter, sparse samples were collected. Paired PK and tumor PD samples were collected at baseline and at cycle 2 day 8 from select patients enrolled in the dose escalation phase at 900 mg, 1800 mg and 3000 mg IV Q3W.

**Figure 1: ARC-25 Study Design**




**Methods**

- Tumor Receptor Occupancy: Fresh frozen tumor biopsies were used to quantify total CD39 versus unbound CD39 by immunohistochemistry (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.
- AB598 serum concentration was measured using a validated ELISA method.
- PK parameters were estimated using Phoenix WinNonlin (v8.4) software.
- PK and PK/PD models were developed to describe AB598 PK and the relationship between tumor PD markers and AB598 concentrations, respectively (R software, v4.5.1).

## RESULTS: PK & PK/PD Relationship

**Figure 2: Mean (SD) AB598 Plasma Concentration vs. Time Profile of AB598 Following Multiple Doses**

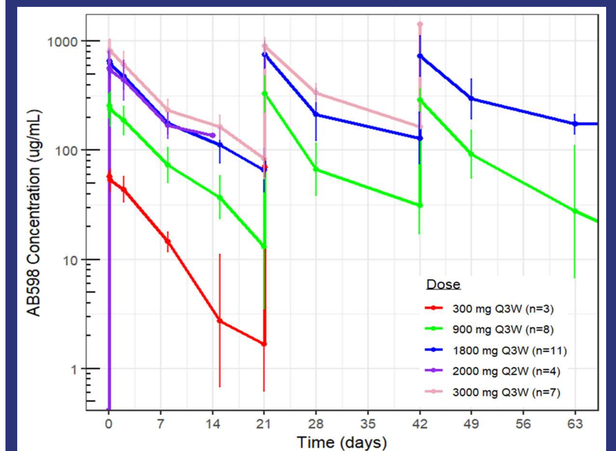



**Figure 3: Dose Normalized AUC Exposure vs. Dose Following Single Doses of AB598 300 – 3000 mg**

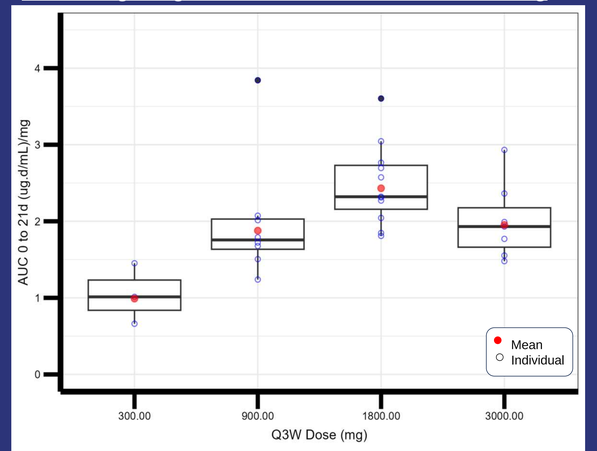
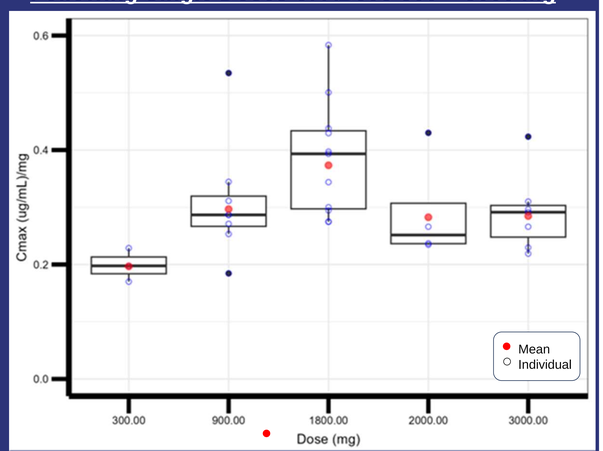



**Figure 4: Dose Normalized $C_{max}$ Exposure vs. Dose Following Single Doses of AB598 300 – 3000 mg**




- A total of 33 patients were included in the PK analysis set.
- AB598 was well tolerated; no dose limiting toxicities were observed, and the maximum tolerated dose was not reached.
- AB598 exposure was approximately dose proportional over 900 – 3000 mg Q3W, with limited drug accumulation after multiple doses (Figure 2, 3, 4) .
- Half-life ranged 6 – 8 days in the linear dose range of 900 mg – 3000 mg Q3W.
- 90% CD39 receptor occupancy and CD39 enzymatic inhibition were achieved at AB598 concentrations of 107 ug/mL and 176 ug/mL, respectively, based on PK/PD model (Figure 5).
- Based on modeling and simulation, 3000 mg Q3W and 2000 mg Q2W yield similar steady state exposure, therefore 2000 mg Q2W was selected as the expansion dose.
- Expansion dose of 2000 mg Q2W achieves both 90% receptor occupancy and 90% enzymatic inhibition (Figure 6).

**Figure 5: Model Predicted and Observed Individual AB598 Tumor PD markers vs. Concentration Profiles**

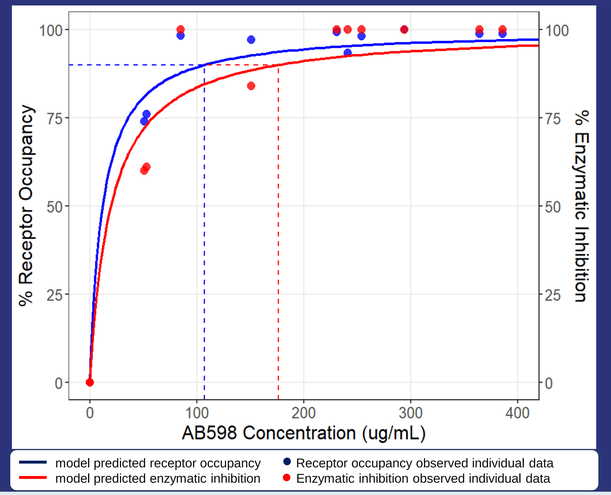
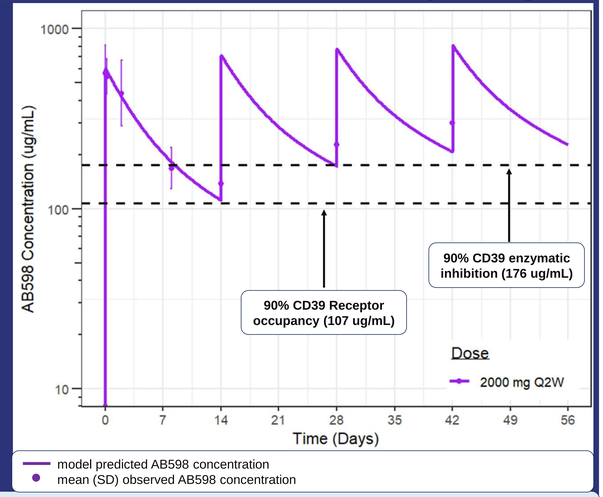



**Figure 6: Model Predicted and Observed Mean AB598 Concentration vs Time Profile Following 2000 mg Q2W**




## CONCLUSION

- **AB598 exhibited linear, time-invariant PK across 900 mg – 3000 mg dose range.**
- **AB598 half-life is consistent with other anti-CD39 monoclonal antibodies[1,2].**
- **Doses ≥ 1800 mg Q3W may be optimally efficacious.**
- **2000 mg IV Q2W is an appropriate expansion dose to achieve effective concentrations.**

**References:** 1. Powderly J, et al. IPH5201, an Anti-CD39 mAb, as Monotherapy or in Combination with Durvalumab in Advanced Solid Tumors. Cancer Res Commun. 2025 Sep 1;5(9):1690-1700. doi: 10.1158/2767-9764.CRC-25-0361. PMID: 40899626; PMCID: PMC12451260.
2.. Patnail A et al. 135P First-in-human phase I trial of SRF617, a potent inhibitor of CD39 activity, as monotherapy or in combination, in patients (pts) with advanced solid tumors. Annals of Oncology. 2021 Dec. 32:S1435-S1436. 2021. DOI:10.1016/j.annonc.2021.10.154