787 AB598, A CD39 INHIBITORY ANTIBODY, PROMOTES IMMUNE-MEDIATED TUMOR CONTROL

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Background AB598 inhibits the enzymatic activity of CD39, the dominant ATPase in the tumor microenvironment (TME). CD39 inhibition allows ATP levels to rise locally, leading to the activation of myeloid cells, increased tumor-specific activated T cells, and enhanced control of tumor growth. AB598 is potent and specific, inhibiting human CD39 with sub-nanomolar potency. It effectively inhibits human CD39, but it does not inhibit murine CD39 posing a challenge for studying CD39 inhibition in immune-competent syngeneic tumor models.

Methods The effectiveness of AB598 in combating tumors with an intact immune system was assessed utilizing a human CD39 knock-in (hCD39KI) mouse model in which the human CD39 extracellular domain is inserted into the mouse CD39 locus mimicking the natural distribution and expression pattern of CD39 in mice. This model allows the evaluation of CD39 inhibition in a relevant immune context in solid tumors in combination with chemotherapy and/or immunotherapy. In vivo studies utilized a modified version of AB598 known as AB598.mIgG2a, which contains a murine Fc-silent domain. Complementing the syngeneic studies are human xenograft studies and a co-culture system allowing further mechanistic inquiry.

Results Using an in vitro co-culture system, we demonstrate that chemotherapy can cause ATP release from tumor cells, resulting in myeloid cell activation in the presence of AB598. Using a MOLP8 xenograft model we present a coordinated data set where AB598.mIgG2a administration results in decreased intratumoral enzymatic inhibition and increased intratumoral ATP with full peripheral target occupancy, inhibition of peripheral enzymatic activity, and decreased cell surface CD39 on peripheral immune cells. Taking advantage of the mismatched species in the xenograft system (human tumor and mouse immune cells) and the specificity of AB598 for human CD39, we show that the decrease in cell surface CD39 is AB598-dependent. In the hCD39KI mouse MC38 tumor model, we demonstrate that treatment with AB598.mIgG2a results in increased myeloid cell activation, consistent with the findings from the in vitro co-culture system. Immune subpopulations of hCD39KI mice treated with AB598.mIgG2a exhibited a reduction in cell surface CD39.

Conclusions Our findings highlight the ability of AB598 to inhibit enzymatic activity in vitro and in vivo resulting in increased ATP levels that activate immune subpopulations and ultimately the adaptive immune system. This study provides a rationale for combining CD39 inhibition with chemotherapy that induces ATP release and checkpoint inhibition in clinical settings. AB598 is currently in a Phase 1 trial in advanced cancer patients.

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