

991

AB598, A THERAPEUTIC ANTI-HUMAN CD39 ANTIBODY, BINDS AND INHIBITS CD39 ENZYMATIC ACTIVITY *IN VIVO* TO PROMOTE ANTI-TUMOR IMMUNITY

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Background AB598 is being developed as a novel cancer immunotherapy which potently binds and inhibits CD39 enzymatic activity. CD39 catalyzes the conversion of extracellular adenosine triphosphate (ATP) into adenosine monophosphate (AMP), resulting in decreased amounts of immunostimulatory ATP and increased levels of immunosuppressive adenosine in the tumor microenvironment (TME). By blocking CD39 in the TME, local levels of ATP increase, leading to myeloid cell activation and improved tumor control. AB598 is highly potent and specific, binding and inhibiting human CD39 with sub-nanomolar potency. AB598 binds and inhibits both human and cynomolgus monkey CD39 but not murine CD39, presenting a challenge for studying CD39 inhibition in an immune-competent syngeneic tumor model.

Methods Human CD39 knock-in (hCD39KI) mice were employed to examine the preclinical anti-tumor efficacy of AB598 in animals with a fully competent immune system. The use of a murine model with natural expression and distribution of human CD39, targetable by AB598, allowed for a more physiological assessment of CD39 inhibition in solid tumors compared to the alternative use of human cancer cells growing in immuno-deficient mice. Combination of CD39 inhibition with chemotherapy was explored. A murinized version of AB598, ch39_mIgG2a, which contains a murine Fc silent domain was used for *in vivo* studies.

Results Real-time measurement of ATP showed the ability of oxaliplatin to induce ATP release in MC38 tumor cells *in vitro*. In a hCD39KI mouse MC38 tumor model, ch39_mIgG2a in combination with oxaliplatin significantly inhibited tumor growth compared to treatment with either single agent. The combination was well tolerated and no decreases in body weight were observed. Analysis of cytokines in the periphery resulted in no significant increases after ch39_mIgG2a administration. Analysis of tumors from both MC38 and 4T1 models revealed substantial inhibition of intratumoral CD39 enzymatic activity in ch39_mIgG2a-treated mice. Tumor draining lymph nodes in the MC38 model showed a decrease in cell surface CD39 in ch39_mIgG2a mice, a finding supported by peripheral receptor occupancy studies. Relative percentages of the immune cells in the lymph nodes were unaffected, suggesting internalization or downregulation, not cellular depletion, as the mechanism for the decrease in cell-surface CD39.

Conclusions Our results indicate the superb ability of AB598 to inhibit enzymatic activity and tumor growth *in vivo* and provide a rationale for the combination of CD39 inhibition with ICD-inducing chemotherapy in the clinic.

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