CD47 ANTIBODY, AO-176 DEMONSTRATES POTENT ANTI-TUMOR ACTIVITY IN PRE-CLINICAL SOLID TUMOR XENOGRAFTS AS A SINGLE AGENT AND IN COMBINATION WITH MULTIPLE CLASSES OF THERAPEUTICS

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Background CD47 is a cell surface protein expressed on tumors that binds SIRPα on macrophages and dendritic cells resulting in a "don’t eat me" signal that allows tumors to evade phagocytosis. The highly differentiated monoclonal antibody, AO-176 directly targets CD47 and blocks this signal. AO-176 is currently being tested in phase 1 clinical trials in solid tumors and multiple myeloma. The purpose of this study was to assess in vivo efficacy of AO-176 in solid tumor models as a single agent and in combination with multiple classes of therapeutics including chemotherapeutics, monoclonal antibodies and T-cell checkpoint inhibitors.

Methods CD47 expression levels on solid tumor types were assessed by immunohistochemistry using a tumor tissue microarray. Cell-based binding was performed using flow cytometry under acidic and physiologic pH conditions to characterize the functional activity of AO-176 in the two pH environments representing tumor and normal physiologic environments. In vivo studies were performed using models of solid cancers.

Results All 12 solid tumor indications assessed were positive for cell membrane localized CD47 (3.3–98.6 H-scores). Cell-based binding of AO-176 to solid cancer cell lines was significantly greater (1.6–25-fold decrease in EC50, 11–39% increase in Bmax) in acidic conditions as compared to a neutral pH environment, demonstrating improved binding in the lower pH environments associated with solid tumors. AO-176 treatment in solid tumor xenograft models resulted in potent anti-tumor activity as a monotherapy (40–58% TGI) and in combination with paclitaxel in an ovarian model (99% TGI), cisplatin in an ovarian model (84% TGI), cisplatin in a gastric model (76% TGI), and an anti-VEGFR-2 in a gastric model (86% TGI). In vivo efficacy of CD47 blockade alone (~33% TGI) and in combination with anti-PD-1 (74% TGI) and anti-PD-L1 (80% TGI) T-cell checkpoint inhibitors was observed in a syngeneic model of colon cancer using a surrogate anti-CD47 blocking antibody.

Conclusions AO-176 is a differentiated anti-CD47 agent that in addition to blocking the don’t eat me signal, directly kills cancer cells, shows lower binding to normal cells such as RBCs and demonstrates increased binding activity in acidic conditions as found in the microenvironment of solid tumors. AO-176 also elicits potent anti-tumor activity in xenograft and syngeneic models as a single agent and in combination with chemotherapeutics, monoclonal antibodies and T-cell checkpoint inhibitors. AO-176 is currently in clinical trials as a single agent and in combination in patients with select solid cancers (NCT03834948) and in multiple myeloma (NCT04445701).