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ALTA-002, A SIRP α -DIRECTED TLR9 AGONIST ANTIBODY CONJUGATE ACTIVATES MYELOID CELLS AND PROMOTES ANTI-TUMOR IMMUNITY

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Background Novel therapies engaging both innate and adaptive immune responses may engender durable anti-tumor immunity. Activation of toll-like receptor 9 (TLR9) by unmethylated CpG oligonucleotides promotes innate inflammatory responses and induces adaptive immunity. Immune cells expressing TLR9 encompass B cells and myeloid cells (including dendritic cells and plasmacytoid dendritic cells). Recently, several TLR9 agonists have demonstrated clinical benefit in patients with melanoma when administered intra-tumorally.¹ Specifically designed for systemic administration, we developed a novel Toll-like Receptor Agonist Antibody Conjugate (TRAAC) molecule comprised of a differentiated TLR-9 agonist (T-CpG) conjugated to an antibody against SIRP α (ALTA-002). Signal regulatory protein α (SIRP α) is a myeloid inhibitory receptor that suppresses immune activation following binding of its ligand CD47. Blockade of CD47-SIRP α myeloid checkpoint pathway has been shown to promote myeloid-mediated anti-tumor functions leading to the induction of adaptive immunity.² Additionally, SIRP α is highly expressed in various tumor types including renal cell carcinoma and melanoma.³ Here we present preclinical data demonstrating that ALTA-002 delivers T-CpG to SIRP α expressing myeloid cells, triggering TLR9 signaling, cell activation and immune modulation resulting in robust anti-tumor efficacy.

Methods In vitro activity of ALTA-002 was evaluated using human PBMCs co-cultured in the presence of SIRP α positive and negative tumor cells. Anti-tumor efficacy of mouse ALTA-002 surrogate was evaluated in multiple syngeneic tumor models with varying immunogenicity profiles.

Results In vitro co-culture of human PBMC and SIRP α positive or negative tumor cells with ALTA-002 stimulates myeloid cells, leading to increased IRF7 induction, expression of co-stimulatory molecules, and cytokine secretion. In vitro treatment with ALTA-002 led to enhanced phagocytic engulfment by human monocyte-derived macrophages across multiple SIRP α positive and negative tumor cell lines. Following systemic delivery of a mouse ALTA-002 surrogate, durable anti-tumor activity was observed in both SIRP α positive and negative expressing tumors. ALTA-002 treated mice with eradicated tumors suppressed tumor growth upon tumor re-challenge, indicating tumor-specific immune memory.

Conclusions These results demonstrate the unique properties of systemically administered ALTA-002, which integrates TLR9 activation and blockade of CD47-SIRP α interaction on myeloid cells to engender both innate and adaptive anti-tumor immune responses. These data support the development of ALTA-002 as an anti-cancer therapeutic for a variety of tumor malignancies.

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Ethics Approval In vivo studies were approved by the Institutional Animal Care and Use Committee of Tallac Therapeutics.

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