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TAC-003, A TLR9 AGONIST ANTIBODY CONJUGATE FOR TARGETED IMMUNOTHERAPY OF NECTIN-4 EXPRESSING TUMORS

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Background Activation of Toll-Like Receptor 9 (TLR9) by unmethylated CpG oligodeoxynucleotides (CpG ODNs) promotes innate and adaptive immune responses. Tumor microenvironment (TME) modulation using TLR9 agonists has emerged as a promising strategy in cancer immunotherapy with evidence of clinical activity in melanoma when CpG ODNs are injected intratumorally.¹ However, most solid tumors are not amenable to intratumoral therapeutic intervention. A systemically delivered, tumor targeted, TLR9 agonist has potential to ignite anti-tumor immunity in multiple cancer types. Nectin-4 is a cell adhesion molecule with limited expression in normal tissues but over-expressed in many solid tumor types and is a clinically validated cancer-associated antigen.² We developed a Toll-like Receptor Agonist Antibody Conjugate (TRAAC) comprised of a novel Nectin-4 antibody conjugated to a potent CpG ODN, for systemic administration and activation of TLR9 in the immune microenvironment of Nectin-4 expressing cancers. Previously, we showed that Nectin-4 TRAAC induces immune activation leading to durable anti-tumor efficacy, including in checkpoint inhibitor refractory tumors.³ Here, we expand on the mode of action of the Nectin-4 TRAAC clinical candidate, TAC-003, and show that systemic administration of a TAC-003 murine surrogate results in tumor honing, pro-inflammatory responses within the TME and superior efficacy, as compared to a Nectin-4 antibody drug conjugate (ADC). Importantly, TAC-003 showed a favorable safety profile.

Methods TAC-003 in vitro activity was evaluated by flow cytometry using human peripheral blood-derived immune cells co-cultured with cancer cells bearing various levels of Nectin-4 expression. Biodistribution and efficacy studies were performed in mouse syngeneic tumor models using a TAC-003 murine surrogate. The safety profile of TAC-003 was assessed in cynomolgus monkeys.

Results In vitro, TAC-003 induces activation of innate and adaptive immune cells, resulting in increased cytokine levels and up-regulation of co-stimulatory molecules. TAC-003 enhances cancer cell phagocytosis, in a manner that correlates with Nectin-4 expression levels. In vivo, the TAC-003 murine surrogate binds to Nectin-4 expressing cancer cells, leading to its preferential accumulation in tumor as compared to normal tissues with low/no Nectin-4 expression. Accordingly, mice treated with TAC-003 murine surrogate show increased levels of pro-inflammatory cytokines in tumor as compared to spleen. This differentiated mechanism of action results in superior anti-tumor efficacy when compared to a Nectin-4 ADC. TAC-003 shows a favorable safety profile in toxicity studies performed in cynomolgus monkeys.

Conclusions The preclinical data presented here provides compelling rationale for further development of TAC-003 as an immunotherapy for Nectin-4-expressing solid tumors.

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