A NECTIN-4 TARGETED TLR9 AGONIST ANTIBODY CONJUGATE INDUCES ROBUST IMMUNE CELL ACTIVATION AND ANTI-TUMOR RESPONSES

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Background Novel therapies that engage 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 the induction of adaptive immunity. Several CpG-based TLR9 agonists have demonstrated clinical activity in melanoma by inducing a pro-inflammatory tumor microenvironment (TME), when administered intratumorally. However, intratumoral delivery has various development challenges that need to be addressed, including limited tumor indications, injection site variability and poor pharmacokinetics. A systemically delivered TLR9 agonist with favorable safety profile has potential to provide innate and adaptive anti-tumor immunity across multiple tumor types. We developed a Toll-like Receptor Agonist Antibody Conjugate (TRAAC) comprised of a CpG oligodeoxynucleotide conjugated to a novel Nectin-4-targeting antibody for systemic administration and TME delivery of a potent TLR9 agonist. Nectin-4 is a cancer associated antigen over-expressed in many solid tumor types with limited expression in normal tissues. Additionally, Nectin-4 over-expression correlates with poor prognosis. Activation of myeloid cells via TLR9 signaling within the TME may promote pro-inflammatory signals countering immunosuppressive pathways, thereby resulting in initiation and enhancement of anti-tumor responses. Here we present preclinical data demonstrating that Nectin-4 TRAAC triggers TLR9 signaling, induces myeloid and dendritic cell activation, phagocytosis, cytokine production and lymphocyte activation, resulting in potent anti-tumor efficacy.

Methods In vitro activity of Nectin-4 TRAAC was evaluated using human peripheral blood mononuclear cells (PBMCs) co-cultured in presence of Nectin-4 expressing cancer cells. The anti-tumor efficacy of Nectin-4 TRAAC as a monotherapy was evaluated using syngeneic models.

Results Nectin-4 TRAAC induced both innate and adaptive anti-tumor immune mechanisms in human PBMC co-cultured with Nectin-4-expressing cancer cell lines. Nectin-4 TRAAC potently activated myeloid cells, leading to enhanced phagocytosis, increased expression of co-stimulatory molecules, secretion of pro-inflammatory cytokines and B, T and NK cell activation. In both immunogenic and checkpoint inhibitor (CPI) refractory syngeneic tumor models, single agent Nectin-4 TRAAC treatment led to durable tumor regression and eradication across a range of Nectin-4 expression levels. Animals in which Nectin-4 TRAAC treatment led to tumor clearance were protected from tumor growth upon rechallenge, demonstrating that Nectin-4 TRAAC induces potent anti-tumor immunological memory.

Conclusions The preclinical data shown here provide a strong rationale for pursuing Nectin-4 TRAAC for the treatment of Nectin-4-expressing solid tumors, including those that are refractory to CPI therapy.

REFERENCES