SBT6290, A SYSTEMICALLY ADMINISTERED NECTIN-4-DIRECTED TLR8 IMMUNOTAC (TM) THERAPEUTIC, IS A POTENT HUMAN MYELOID CELL AGONIST FOR THE TREATMENT OF NECTIN-4-EXPRESSING TUMORS

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Background SBT6290 is a novel therapeutic comprised of a selective TLR8 agonist conjugated to a Nectin-4-specific monoclonal antibody, designed for systemic delivery and tumor-localized activation of human myeloid cells. Nectin-4 is a cell surface adhesion molecule that is overexpressed in a wide variety of solid tumors including triple negative breast, head and neck, lung, and urothelial cancers, with limited expression in normal tissues. Many solid tumors, including those expressing Nectin-4, are resistant to immunotherapy due to immune-suppressive mechanisms, loss of HLA, low neoantigen availability, and or minimal T cell infiltrates. These tumors, however, are often replete with myeloid cells. Activation of these cells has emerged as a promising approach in overcoming resistance mechanisms to current cancer immunotherapies. TLR8 is highly expressed in myeloid cell types prevalent in human tumors, including conventional DCs and macrophages. Agonism of TLR8 in human myeloid cells activates a broad spectrum of anti-tumor immune mechanisms, including proinflammatory cytokine production, repolarization of suppressive myeloid cells, and the priming of CTL responses. Here, we show that SBT6290 potently activates human myeloid cells in a Nectin-4-dependent manner and that a mouse surrogate conveys single agent anti-tumor activity in preclinical studies. These data support the development of SBT6290 for the treatment of patients with Nectin-4-expressing tumors.

Methods SBT6290 activity was characterized in vitro using coculture systems consisting of human immune cells and Nectin-4-expressing tumor cells. The in vivo efficacy of the SBT6290 surrogate was evaluated as a single agent in mouse tumor models expressing Nectin-4.

Results Studies with human immune cells show that SBT6290 potently induces multiple anti-tumor immune activities including proinflammatory cytokine and chemokine production, repolarization of suppressive myeloid cells, and the priming of T and NK cell cytolytic activity. This activity requires the presence of Nectin-4 expressing tumor cells and the engagement of Fc gamma receptors on the surface of the myeloid cells by the conjugate to facilitate delivery of SBT6290 into myeloid cells. Notably, SBT6290 is >100 fold more potent than the free, unconjugated TLR8 agonist. Systemic administration of a SBT6290 surrogate in mice results in robust single agent efficacy in tumor models intrinsically resistant to checkpoint blockade, including the EMT6 model engineered to express human Nectin-4.

Conclusions The preclinical data described here show the potential for SBT6290 to drive robust, single agent anti-tumor responses and support the clinical development of SBT6290 for patients with Nectin-4 expressing tumors.
Background TGFβ production by solid tumors and their microenvironment is a major mechanism used by tumors to avoid immunosurveillance. Blockade of TGFβ has been shown to promote an anti-tumor response; however, systemic blockade of TGFβ has also been associated with toxicity. We hypothesized that a PD1 x TGFβR2 bispecific antibody could selectively block the suppressive activity of TGFβ on tumor T cells and enhance their anti-tumor activity while avoiding the toxicity associated with systemic blockade.

Methods We engineered bispecific antibodies that simultaneously engage PD1 and TGFβR2 using Xencor’s XmAb platform. The anti-TGFβR2 arm was tuned for optimal activity by introducing affinity-modulating amino acid substitutions. The activity of PD1 x TGFβR2 bispecifics was evaluated in vitro using a signaling assay to measure phosphorylated SMAD (pSMAD) by flow cytometry with exogenous TGFβ in unactivated and activated PBMC. In vivo activity was evaluated by monitoring the engraftment of human PBMC in NSG mice (huPBMC-NSG). Anti-tumor activity was assessed in huPBMC-NSG mice engrafted with established human cancer cell lines. Antibodies against other T cell targets were also incorporated into TGFβR2 bispecifics, and similarly evaluated in vitro and in vivo.

Results PD1 x TGFβR2 bispecifics were confirmed to bind PD1 and block binding of TGFβ to TGFβR2. In vitro, we found that T cells from activated, serum-deprived PBMC exhibited robust induction of pSMAD in response to TGFβ and PD1 x TGFβR2 bispecifics selectively inhibited pSMAD induction in PD1-positive T cells as demonstrated by over a 100-fold potency increase compared to an untargeted anti-TGFβR2 control. Additionally, we saw an enhancement of potency when evaluating blocking activity in activated (PD1-high) vs. unactivated (PD1-low) T cells. Similar selectivity was measured when comparing inhibition of pSMAD induction for activated T cells versus other PD1-negative, TGFβ-responsive immune cells. Intriguingly, TGFβR2 bispecifics incorporating antibodies against other T cell targets allowed for the targeting of a broader population of T cells while still conferring potent selectivity against target-negative cells. In vivo, treatment of huPBMC-NSG mice with TGFβR2 bispecifics promoted superior T cell engraftment and combined additively with PD1 blockade. Furthermore, TGFβR2 bispecific treatment of huPBMC-NSG mice containing established MDA-MB-231 triple-negative breast cancer tumors promoted an anti-tumor response that was also augmented with PD1 blockade.

Conclusions Multiple PD1 x TGFβR2 bispecifics were engineered to selectively block TGFβR2 on PD1-positive T cells and evaluated in vitro and in vivo. Compelling activity, including additivity with PD1 blockade, suggests that clinical development is warranted for the treatment of human malignancies.