SBT6290, a Systematically Administered Nectin4-Directed TLR8 ImmunoTAC Therapeutic, is a Potent Human Myeloid Cell Agonist For the Treatment of Nectin4-Expressing Tumors

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SBT6290 is a prodrug candidate comprised of selective TLR8 agonist conjugated to a nectin-specific monoclonal antibody, designed for systemic delivery and tumor-localized activity of myeloid cells. Nectin4 is a surface adhesion molecule that is upregulated in multiple solid tumor types including bladder, triple-negative breast, head and neck, and non-small cell lung cancers, with limited expression in normal tissues. Many solid tumors, including those expressing Nectin4, are resistant to immunotherapy due to immune-suppressive mechanisms, loss of HLA, low frequencies of T cells, and/or low T cell infiltration. 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, upregulation of suppressive myeloid markers, and the printing of CTLA-4.

Here we present preclinical data supporting the continued development of SBT6290 for Nectin4-expressing tumor treatment:

• SBT6290 activates multiple tumor immune mechanisms in in vitro studies.
• SBT6290 activity is dependent upon Nectin4 expression on tumors and the engagement of its receptor on the surface of myeloid cells.
• A mouse surrogate of SBT6290 (SBT290-5) carries a single agent anti-tumor activity in a Nectin4-expressing mouse tumor model.

Figure 1: SBT6290 is Comprised of a TLR8 Agonist Conjugated to a Nectin4-Specific Monoclonal Antibody Designed for Tumor-Localized Activity

Table 1: Human Myeloid Cell-Restricted Expression Profile Supports Development of a TLR8-Selective Payload

Conclusions

• SBT6290, a Nectin4-directed monoclonal antibody conjugated to a TLR8-specific agonist, activates myeloid cells in a Nectin4-dependent manner, enabling tumor-localized activity via systemic delivery.
• SBT6290 induces multiple anti-tumor immune mechanisms including proinflammatory cytokine production, inflammasome activation, and T and NK cell cytolytic activity.
• Treatment with SBT6290 surrogates in mice results in increased overall survival in a tumor model known to be intrinsically resistant to checkpoint blockade.

We believe these data support the continued development of SBT6290 for Nectin4-expressing tumors.