SBT6290, a Systemically Administered Nectin4-Directed TLR8 ImmunoTAC® Product Candidate, is Designed for Tumor-localized Activation of Myeloid Cells

Abstract

SBT6290 is a novel product candidate comprised of a selective TLR8 agonist conjugated to a Nectin4-specific monoclonal antibody, designed for systemic delivery and tumor-localized activation of myeloid cells. Nectin4 is a cell surface molecule implicated in various processes associated with oncogenesis and in frequently overexpressed in multiple solid tumor types including bladder, triple negative breast, head and neck, and non-small cell lung cancer, among others, with limited expression in normal tissues. Nectin4-expressing solid tumor cells display substantial myeloid cell infiltration. Activation of myeloid cells in the tumor microenvironment has emerged as a promising approach for achieving anti-tumor immunity and in overcoming resistance mechanisms to current cancer immunotherapies. TLR8 agonists in human myeloid cells activate a broad spectrum of anti-tumor immune mechanisms, including proinflammatory cytokine production, upregulation of expression myeloid cells, and the printing of CTL. Here, we show that SBT6290 activates human myeloid cells in a Nectin4-dependent manner and that a SBT6290 mouse surrogate confers single agent anti-tumor activity in preclinical studies.

SBT6290 induces multiple anti-tumor immune mechanisms.

- SBT6290 activity in Nectin4-specific and requires SBT6290 engagement by its receptor on the surface of material cells to facilitate uptake of the conjugate into myeloid cells and subsequent reprogramming to a more pro-inflammatory state.

SBT6290 is >100-fold more active than free, unconjugated TLR8 agonist and is active on tumor cells with Nectin4 overexpression corresponding to levels found in primary tumor samples.

SBT6290 is a monoclonal antibody, designed for systemic delivery and tumor

Introduction

Non-Medullary Cells

Myeloid Cells

Dendritic Cells

Macrophages

Filaggrins

Endothelial Cells

Nectin4® Tumor Cells

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

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Figure 2: Solid Tumors from Multiple Tissues Often Overexpress Nectin4 and Display Substantial Myeloid Infiltrate

Figure 3: SBT6290 Displays Selective Binding to Nectin4 and Blocking of the TIGIT/Nectin4 Interaction

Figure 4: SBT6290 is >100 Fold More Active Than Free, Unconjugated TLR8 Agonist and Activates Human Myeloid Cells in a Nectin4- and Fc-Dependent Manner

Figure 5: Nectin4 Expression Levels Observed in Tumors Support SBT6290 Activity

Figure 6: SBT6290 Induces a Broad Spectrum of Anti-Tumor Immune Mechanisms in a Nectin4-Dependent Manner

Figure 7: SBT6290 Mice Surrogate (SBT6290-S) Matches the Functional Profile of SBT6290 on Myeloid Cells

Conclusions

- SBT6290, a selective TLR8 agonist conjugated to a Nectin4-specific monoclonal antibody, activates human myeloid cells in a Nectin4-dependent manner.
- SBT6290 mouse surrogate confers single agent anti-tumor activity in preclinical studies.
- SBT6290 induces multiple anti-tumor immune mechanisms including proinflammatory cytokine and chemokine production, inflammasome activation, direct activation of dendritic cells and indirect activation of T and NK cell cytolytic activity.
- Treatment with SBT6290 surrogate in mice results in intra-tumoral myeloid and T cell activation, frequent tumor clearance, and increased overall survival.
- These data support the continued preclinical development of SBT6290 for Nectin4-expressing tumors.
- An IND is planned in the 4th quarter of 2021.