Mechanisms of resistance to immunotherapy include low tumor mutational burden, loss of HLA, evasion of CD8+ T-cell recognition, induction of TME suppressor cells, and regulatory T cells. Thus, an ideal next-generation immunotherapy would be effective as a single-agent in both T-cell proficient and deficient tumor environments (TMEs).

SBT6050, a HER2-directed TLR8 agonist antibody conjugate, is designed to overcome primary resistance to and synergize with checkpoint inhibitors (CPIs) in CPI refractory models. SBT6050 is being advanced in solid tumors, and recently, the SBT6050 surrogate has been advanced in a xenograft model. The data presented here demonstrate the following:

- SBT6050 potently activates human myeloid cells only in the presence of HER2-expressing tumor cells.
- SBT6050 elicits a broad spectrum of anti-tumor mechanisms, encompassing T cell dependent and independent mechanisms.
- SBT6050 surrogate in mice is efficacious as a single agent in a HER2 expressing tumor model deficient in T, B, and NK cells.
- SBT6050 surrogate in mice is efficacious as a single agent in a checkpoint inhibitor (CPI) refractory, HER2 expressing syngeneic model.

The single agent efficacy of the SBT6050 surrogate in CPI refractory models can be further enhanced in combination with anti-PD1.

SBT6050 is on ImmunoTAC™ Conjugate Designed for Systemic Administration with TME-Localized Activity

**Introduction**

**SBT6050**, a HER2-Directed TLR8 Agonist Antibody Conjugate, Designed to Overcome Primary Resistance to and Synergize with Checkpoint Inhibition in HER2-Expressing Tumors

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**Figure 1:** SBT6050 Drives a Broad Spectrum of T Cell Dependent and Independent Anti-Tumor Immune Mechanisms

**Figure 2:** SBT6050 Mouse Surrogate Matches the Profile of SBT6050

**Figure 3:** SBT6050 Surrogate Induces Robust Single Agent Tumor Clearance in T, B, and NK Cell Deficient Mice

**Figure 4:** SBT6050 Surrogate Induces Durable Single Agent Efficacy in a CPI Refractory Syngeneic Model

**Figure 5:** SBT6050 Surrogate is Efficacious as a Single Agent and in Combination with Anti-PD1 in a CPI Refractory Model

**Figure 6:** SBT6050 Surrogate Alone and in Combination with CPI Upregulates Intratumoral Chemokines and Cytokines

**Conclusions**

- SBT6050 potently activates multiple anti-tumor immune mechanisms in a HER2-dependent manner, enabling tumor localized activity via systemic delivery.
- SBT6050 mouse surrogate is curative as a single agent in a syngeneic model lacking T, B, and NK cells, demonstrating the potential of myeloid cells to mediate robust efficacy.
- SBT6050 surrogate demonstrates potent single agent activity and durable anti-tumor responses upon re-challenge in tumor models with low tumor infiltrating lymphocytes, highlighting the potential for clinical activity in tumors displaying immune evasive characteristics.
- The combination of SBT6050 surrogate with anti-PD1 further enhanced the significant single agent activity observed with the SBT6050 surrogate alone in a CPI refractory mouse tumor model. These data show the potential for SBT6050 to reprogram a TAM rich TME and provide benefit as a single agent in HER2 expressing tumors.

**SBT6050**, an ImmunoTAC™ antibody conjugate, is currently in preclinical development for patients with moderate or high HER2-expressing tumors and is projected to enter the clinic in 2020.

**Expression levels were determined using publicly available RNA Seq datasets.**