SBT6050, a HER2-Directed TLR8 Therapeutic, is a Systemically Administered, Tumor-Targeted Human Myeloid Cell Agonist

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Despite advances in treatment options for patients with HER2-expressing tumors, significant unmet medical need remains. Checkpoint inhibition (CPI) therapy has been largely ineffective in HER2-expressing tumors (1+ and 2+ by IHC), likely due to the absence of T cell infiltrates. In contrast, it is well established that HER2-expressing tumors are replete with myeloid cells offering the opportunity for instrumental immune activation. Local administration, the typical delivery route used for immune therapeutics/myeloid cell agonists, is limited by tumor accessibility and a need to co-administer an adjuvant that can elicit a robust and monovalent antibody conjugated to a patient and highly specific TLR agonist, allowing for systemic delivery of a myeloid cell agonist with activity localized to HER2-expressing tumor sites.

The data presented here demonstrates the following:

- SBT6050 potently activates human myeloid cells in the presence of HER2-expressing tumor cells with 2+ and 3+ levels of expression.
- Activation of myeloid cells by SBT6050 drives an innate immune response for direct tumor killing and also nucleates a T cell response.
- SBT6050 mouse surrogate (SBT6050-S) efficacies as a single agent in HER2-expressing tumor-infiltrating lymphocyte (TIL) deficient tumor models.
- SBT6050 and trastuzumab recapitulate distinct profiles on H2R.
- Combination of SBT6050 and trastuzumab in a mouse tumor model leads to enhanced efficacy compared to either agent alone.

Collectively, these data support clinical evaluation of SBT6050 as a single agent and in combination with trastuzumab in relevant HER2-expressing tumor types.

**Introduction**

**Table 1. Expression levels were determined using publicly available RNA-Seq datasets.**

**Table 2.**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Type</th>
<th>Expression Level</th>
<th>Expression Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+ Tumor Cells</td>
<td>+++++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Myeloid Cells</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Monocytes</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Endothelial Cells</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

**Table 2:** Human TLR8 Myeloid-Restricted Expression Profile Supports Development of a TLR8-Selective Payload

**Figure 2:** HER2 And TLR8 Are Adjacent In Human Tumor

**Figure 3:** SBT6050 Designed to Activate Myeloid Cells in the Presence of 2+ and 3+ Levels of HER2 Expression

**Figure 4:** SBT6050 Drives a Broad Spectrum of T Cell Dependent and Independent Anti-Tumor Immune Mechanisms

**Figure 5:** SBT6050 Mouse Surrogate (SBT6050-S) Matches the Functional Profile of SBT6050 on Human Myeloid Cells

**Figure 6:** SBT6050-S Induces Durable Single-Agent Efficacy in a T Cell Excluded Synergistic Model

**Figure 7:** SBT6050-S Induces Robust Single Agent Tumor Clearance in T, B, and NK Cell Deficient Mice

**Figure 8:** Combination of SBT6050-S and Trastuzumab Enhances In Vivo Efficacy

**Figure 9:** Tumor cell lines were co-cultured with human PBMC and the indicated concentrations of SBT6050. Activation was determined by TNFα production.

**Figure 10:** Tumor cell lines were co-cultured with human PBMC and the indicated concentrations of SBT6050. Protection From Tumor Re-challenge is HER2 Independent

**Table 3:**

<table>
<thead>
<tr>
<th>Tumor Cell</th>
<th>HER2 #/Cell</th>
<th>TLR8</th>
<th>Macrophages</th>
<th>Tumor (H&amp;E)</th>
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<tbody>
<tr>
<td>SK-BR-3</td>
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<td>~0.21</td>
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<td>BT-474</td>
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<td>NCI-N87</td>
<td>~0.22</td>
<td>~0.22</td>
<td>~0.22</td>
<td>~0.22</td>
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</tbody>
</table>

**Conclusions**

- SBT6050, a HER2-directed monoclonal antibody conjugated to a potent and highly specific TLR agonist, activates multiple and tumor-immune mechanisms in a HER2-dependent manner, allowing for systemic delivery and tumor-localized activity.
- SBT6050-S demonstrates robust, durable single agent efficacy in tumor models with low tumor infiltrating lymphocytes, highlighting the potential for clinical activity with SBT6050 in HER2-expressing malignancies.
- SBT6050-S is curative in a single agent in a HER2-expressing mouse model lacking T, B, and NK cells, demonstrating the potential of myeloid cells to mediate robust efficacy.
- The combination of a low dose of SBT6050-S together with trastuzumab is a HER2-positive mouse tumor model enhanced the single agent activity observed with either agent alone.
- Collectively, these data support clinical evaluation of SBT6050 as a single agent and in combination with trastuzumab in relevant HER2-expressing tumor types.

SBT6050 is currently in late preclinical development for patients with moderate or high HER2-expressing tumors and is projected to enter the clinic later this year.