A Systematically Administered, Conditionally Active TLR8 Agonist for the Treatment of HER2-Expressing Tumors

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**Introduction**

Clinical development of systemically administered innate immune cell agonists has been hindered by acute toxicity due to peripheral activation of the targeted cell types. Intratumoral administration, the route of delivery typically used for innate immune cell agonists, is limited by tumor accessibility and is dependent on absorptive responses.

Agomir of TLR8 (roll-like receptor B) has been shown to drive anti-tumor immune responses. Here, we describe a TLR8 agonist conjugate. SBT6050 is designed for systemic administration, that utilizes cell surface expression of HER2 to localize activation of TLR8 for the treatment of HER2-expressing tumors.

- SBT6050 activates human monocytes and macrophages only in the presence of HER2-expressing tumor cells with moderate or high expression levels.
- Systemic delivery of a SBT6050 surrogate in mice shows durable, single agent efficacy in a checkpoint refractory tumor model without the induction of peripheral cytokine production or associated CRS-like toxicity.
- SBT6050 is currently in preclinical development for patients with moderate or high HER2-expressing tumors and is projected to enter the clinic in 2020.

**SBT6050 is Designed for Systemic Administration with TME-Localized Activity**

**Human TLR8 Expression Profile Supports Development of a TLR8-Selective Payload**

**Figure 1: SBT6050 Induces a HER2-Dependent Pro-Inflammatory, Th1-Polarizing Myeloid Cell Response**

**Figure 2: Delivery of TLR8 Agonist to Myeloid Cells Requires Moderate to High HER2 Expression and FcγR Interactions**

**Figure 3: HER2-TLR7 is a Mouse Surrogate for SBT6050**

**Figure 4: HER2-TLR7 Monotherapy Results in Tumor Clearance Without Significant Systemic Cytokine Release**

**Figure 5: HER2-TLR7 Induces Durable Anti-Tumor Immunity That Protects Against Tumor Re-challenge**

**Figure 6: HER2-TLR7 Treatment Activates Intratumoral Infiltrating and Adaptive Immune Responses**

**Conclusions**

- SBT6050 activates human myeloid cells only in the presence of HER2-expressing cells, enabling systemic administration with tumor-localized activity.
- Systemic administration of a SBT6050 mouse surrogate results in durable anti-tumor efficacy in the absence of peripheral cytokine production, consistent with tumor-specific activity.
- In mice HER2-expressing tumors, a surrogate molecule of SBT6050 drives activation of both innate and adaptive immune responses characterized by activation of tumor-associated myeloid cells, infiltration of neutrophils, persistent increases in local cytokine and chemokine production, and the generation of a robust, neo-Ag-specific anti-tumor CT1 response.
- SBT6050 is currently in preclinical development for patients with moderate or high HER2-expressing tumors and is projected to enter the clinic in 2020.