

A PHASE 1/2 STUDY OF SBT6050 COMBINED WITH TRASTUZUMAB DERUXTECAN (T-DXD) OR TRASTUZUMAB AND TUCATINIB WITH OR WITHOUT CAPECITABINE IN PATIENTS WITH HER2-EXPRESSING OR HER2-AMPLIFIED CANCERS

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.393>

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Background SBT6050 is a novel therapeutic comprising a selective small molecule toll-like receptor 8 (TLR8) agonist linked to the HER2-directed monoclonal antibody pertuzumab, allowing for combination with trastuzumab-based agents and regimens. SBT6050 is designed to activate myeloid cells in tumors expressing moderate to high levels of HER2. TLR8 agonism directly activates myeloid cells, including macrophages and dendritic cells (DCs), and secondarily activates NK and T cells, inducing a broad spectrum of anti-tumor immune mechanisms. SBT6050 is currently being tested as a single agent and in combination with checkpoint inhibitors (NCT04460456). Initial results show early evidence of anti-tumor effects, activation of myeloid and NK/T cells, and a safety profile consistent with an immune activator that is generally non-overlapping with that of T-DXd or tucatinib-based regimens. A strong scientific rationale supports the combination of SBT6050 with T-DXd and SBT6050 with trastuzumab and tucatinib ± capecitabine. Both treatment regimens drive tumor cell death and release of tumor neoantigens. SBT6050 can enhance tumor neoantigen presentation and subsequent activation of T cell responses through its direct activation of DCs. SBT6050 combined with T-DXd or trastuzumab and tucatinib ± capecitabine is postulated to drive increased anti-tumor T cell responses. In addition, T-DXd and trastuzumab support antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) and SBT6050 can enhance both functions. SBT6050 activates myeloid cells to secrete cytokines that amplify ADCC by NK cells. Additionally, SBT6050 activation downmodulates SIRPα on the surface of myeloid cells which can increase ADCP through attenuation of the CD47-SIRPα interaction. Consistent with this mechanism of action, in preclinical studies in mice, the combination of trastuzumab and a mouse surrogate of SBT6050 led to enhanced activity in the HER2-positive NCI-N87 human tumor xenograft model compared to either agent alone.

Methods Protocol SBT6050-201 is a phase 1/2, open-label, dose-escalation and expansion study evaluating SBT6050 in combination with either T-DXd (Part 1) or tucatinib and trastuzumab +/- capecitabine (Part 2). Eligible patients are at least 18 years old, have HER2-positive metastatic breast cancer, gastric/GEJ cancer, colorectal cancer, or HER2-expressing or amplified NSCLC, and have received at least one prior therapy for metastatic disease. Patients will receive SBT6050 subcutaneously q3wk starting at a dose with demonstrated pharmacodynamic activity in phase 1. Pharmacodynamic markers of myeloid and NK/T cell activation will be assessed in peripheral blood and on-treatment tumor biopsies. Circulating tumor DNA will be evaluated as an exploratory assessment.

Ethics Approval This clinical study has not yet obtained ethics approval or started enrollment. All participants will be required to give informed consent before taking part.