Background New strategies are needed to improve outcomes in human epidermal growth factor receptor 2 (HER2)-expressing cancers. SBT6050 is a novel therapeutic comprising a specific small molecule toll-like receptor (TLR) 8 agonist conjugated to a HER2-directed monoclonal antibody. TLR8 is highly expressed in myeloid cells that are prevalent in human tumors, including dendritic cells (DCs) and macrophages, and modulates their pro-inflammatory activity. SBT6050 is designed to activate human myeloid cells only in the presence of moderate-to-high HER2 expression (immunohistochemistry [IHC] 2+ or 3+) and binds to the same epitope as pertuzumab. In preclinical studies, SBT6050 potently induces a broad spectrum of antitumor immune mechanisms, including proinflammatory cytokine and chemokine production, inflammasome activation, and indirect activation of T and natural killer (NK) cells. TLR8 agonism has emerged as a promising approach to overcome resistance to immune checkpoint inhibitors in tumors lacking T-cell infiltrates, as these cancers are often replete with myeloid cells. Using an SBT6050 mouse surrogate in vivo, curative single-agent efficacy was observed in multiple murine tumor models, including a model deficient in T, B, and NK cells. In preclinical toxicology studies in nonhuman primates, SBT6050 was well tolerated, supporting a first-in-human starting dose that is predicted to be pharmacologically active, with a short escalation to projected clinically active doses. Preclinical studies also support combinations with checkpoint inhibitors and with trastuzumab to further enhance antitumor activity.

Methods SBT6050-101 is an ongoing phase 1/1b, first-in-human, open-label, multicenter study. Eligible subjects are adults with histologically confirmed, HER2-expressing (IHC 2+ or 3+), locally advanced (unresectable) and/or metastatic cancer. Subjects must have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and have previously received all therapies known to confer clinical benefit. SBT6050 is given subcutaneously every 2 weeks and treatment may continue for up to 2 years or until disease progression, unacceptable toxicity, or other reason for discontinuation. The trial objectives are to evaluate the safety and tolerability of SBT6050 and to identify the maximum tolerated dose and recommended phase 2 dose (RP2D). The study has 2 parts: Part 1, consisting of a dose escalation using a standard 3+3 design, and Part 2, consisting of 5 parallel expansion cohorts based on tumor type and HER2 expression level and treated with SBT6050 at the RP2D. Pharmacokinetics, immunogenicity, and antitumor activity will be evaluated and pharmacodynamic markers of myeloid cell activation will be assessed in peripheral blood and on-treatment tumor biopsies.

Results N/A

Conclusions N/A