A Phase 1/1b Study of SBT6050, a HER2-directed Monoclonal Antibody Conjugated to a Toll-like Receptor 8 Agonist, in Subjects With Advanced HER2-expressing Solid Tumors

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SILVERBACK™ THERAPEUTICS

Introduction

- New strategies are needed to improve treatment outcomes for patients with human epidermal growth factor receptor 2 (HER2)-expressing cancers. One strategy is to activate or reprogram myeloid cells found in the tumor microenvironment (TME) to increase tumor cell killing.
- Toll-like receptor 8 (TLR8) is highly expressed in myeloid cells that are prevalent in the TME, including dendritic cells (DCs) and macrophages, and modulates their pro-inflammatory activity.
- SBT6050 is a product candidate comprising a selective small molecule TLR8 agonist conjugated to a HER2-directed monoclonal antibody.
- 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 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.
- Using an SBT6050 mouse surrogate in vivo, curative single-agent activity was observed in multiple murine tumor models, including a model deficient in T, B, and NK cells.
- SBT6050 was well tolerated in preclinical toxicology studies in nonhuman primates, supporting a first-in-human starting dose that has the potential to be pharmacologically active, with a short escalation to potentially clinically active doses.
- Preclinical studies also support combinations with checkpoint inhibitors and with trastuzumab to potentially further enhance antitumor activity.

Figure 1: SBT6050 is an ImmunoTAC™ Therapeutic Designed for Systemic Administration with TME-Localized Activity

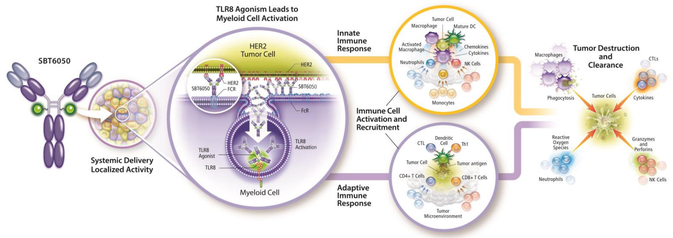


Table 1: Human Myeloid-Restricted Expression Profile Supports Development of a TLR8-Selective Payload

	Cell Type	TLR4	TLR7	TLR8	TLR9	STING	RIG-I
Myeloid Cells	Dendritic Cells	+++	+/-	++++	-	++	++
	Macrophages	++++	+	+++	-	++	++
Non-Myeloid	Fibroblasts	++	++	-	-	+++	+++
	Endothelial Cells	+++	++	-	-	+	++
Tumor	HER2+ Tumor Cell	-	-	-	-	++	++

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

Table 2: HER2 Expression is Common in Many Solid Tumors

Solid Tumor	Frequency of HER2 expression (IHC 2+/3+) rate and/or amplification
Breast cancer	30%[a, b]
Gastric cancer	23%[c]
Esophageal cancer	3-39%[d]
Non-small cell lung cancer (NSCLC)	16-32%[e, f]
Head and neck squamous cell carcinoma (HNSCC)	3-50%[g, h]
Colorectal cancer	6-13%[i, j]
Biliary tract cancer, including gallbladder cancer	26%[k]
Bladder cancer	9%[l]
Uterine (endometrial) cancer	17-33%[m]
Ovarian cancer	5-19%[d]

Table 2: a. Wolf et al. J Clin Oncol 31(31): 3997-4013; b. Rossi et al. Oncologist 17(11):1418-1425; c. VanCutsem et al. Gastric Cancer 18(3):475-484; d. Omar et al. Pathogenesis 2(3):1-9; e. Hirsch et al. Semin Oncol (1 Suppl 1): 75-82; f. Langer et al. Int J Radiat Oncol Biol Phys 58(3):991-1002; g. Birkeland et al. JAMA Otolaryngol Head Neck Surg 142(6): 599-567; h. Fong et al AJPCP 13(6) 2891-6; i. Seo et al PLoS One 9(5) e98528; j. Valtorta et al. Mod Pathol 28(11); k. Galdy et al. Cancer Met Rev 36:141-157; l. Lae et al Ann Oncol. 21(4):815-819; m. Diver et al. Oncologist 20(9): 1058-1068

Figure 2: SBT6050 Kills Tumors by Activating both Innate and Adaptive Immunity when HER2 is Expressed

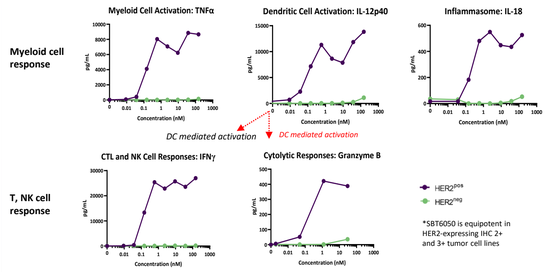
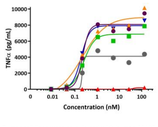


Figure 2: PBMCs were co-cultured with HER2^{pos} (BT-474) or HER2^{neg} (MDA-MB-468) tumor cell lines in the presence of SBT6050 as indicated. Supernatants were evaluated 24 hours later by MSD assay or ELISA. No activation of PBMCs was observed when co-cultured with tumor cell lines and unconjugated HER2 mAb (data not shown).

Figure 3: SBT6050 Activates Myeloid Cells Only in the Presence of 2+ and 3+ Levels of HER2 Expression



Tumor Cell Line	HER2 #/Cell ($x10^6$)	IHC Score
SKBR3	1.10	3+
NCI-N87	0.65	3+
BT-474	0.47	3+
MDA-453	0.08	2+
ZR-75-1	0.04	1+/2+
MDA-468	<0.02	0

Figure 3: Tumor cell lines were co-cultured with human PBMC and the indicated concentrations of SBT6050. Activation was determined by TNFα production.

Figure 4: SBT6050-S Induces Robust Single Agent Activity in T, B, and NK Cell Deficient Mice

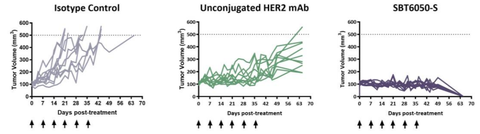


Figure 4: SCID-Beige mice (n=10) bearing NCI-N87 gastric tumors were treated with 10 mg/kg unconjugated HER2 mAb, 10 mg/kg isotype control, or 10 mg/kg SBT6050 mouse surrogate (SBT6050-S). Arrows indicate timing of doses administered. SBT6050-S = SBT6050 mouse surrogate (HER2-TLR7); mice do not express a functional homolog of human TLR8, but mouse TLR7 phenotypically matches the myeloid expression of human TLR8. Unconjugated HER2 mAb denotes SBT6050-S without an agonist payload. Isotype control matched to unconjugated HER2 mAb.

Figure 5: In the EMT6 Model, Refractory to anti-PD-1 Treatment, the Combination of SBT6050-S and Anti-PD-1 Drives Robust Anti-Tumor Activity

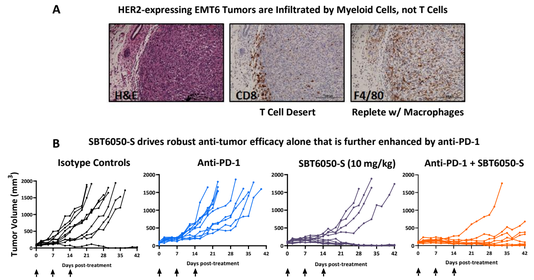


Figure 5: **(A)** IHC of untreated EMT6 tumors. **(B)** Tumor growth curves for mice bearing HER2-expressing EMT6 tumors, treated once per week for 3 weeks with SBT6050-S at 10 mg/kg, anti-HER2 antibody (SBT6050-S without payload) at 10 mg/kg alone or in combination with anti-PD-1.

SBT6050-101 Study Schema

Single Agent

- SBT6050 dosed SC Q2 weeks
- Treatment continues until progression, unacceptable toxicity, or maximum 2 years

Part 1: single agent dose escalation

HER2-expressing (IHC 2+ or 3+) or HER2-amplified advanced cancers

Dose level 1 (0.3 mg/kg) n = 3
Dose level 2 n = 3
Dose level 3 n = 3
Dose level 4 n = 3
Dose expansion #1 n = 9
Dose expansion #2 n = 9

Part 2: tumor specific expansion[a] cohorts

- Cohort A: HER2-positive breast cancer n=40
- Cohort B: HER2-low breast cancer n=30
- Cohort C: HER2-positive gastric /GEJ cancer n=40
- Cohort D: HER2-expressing NSCLC n=40
- Cohort E: HER2-expressing solid tumors n=30

Pembrolizumab combination

- SBT6050 dosed SC Q2 weeks
- Pembrolizumab IV, 400 mg Q6 weeks
- Treatment continues until progression, unacceptable toxicity, or maximum 2 years

Part 3: combination dose escalation

HER2-positive breast and gastric cancer, HER2-expressing or amplified biliary tract, colorectal, endometrial, HNSCC, NSCLC, and urothelial cancer

Dose level 1 n = 3
Dose level 2 n = 3
Dose level 3 n = 3
Dose level 4 n = 3

Part 4: combination expansion cohort

HER2$^{2/3+}$amplified solid tumors n=30

PD threshold to open pembrolizumab combination was met in patients dosed in the first cohort in Part 1:

- CRP elevation to ≥ 150 mg/L, and
- IP-10 and/or MCP-1 levels increase 3- to 5-fold from baseline, and
- Induction of additional PD markers indicative of on-target mechanism of action such as IFNγ

Definitions:

- HER2-positive: HER2 IHC 3+ or HER2 IHC 2+/HER2 amplified
- HER2-expressing: HER2 IHC 2-3+, or HER2 amplified
- HER2 low: HER2 IHC 2+/HER2 not amplified

Abbreviations:

CRP = C-reactive protein
GEJ = gastric/gastroesophageal junction
HER2 = human epidermal growth factor receptor 2
HNSCC = head and neck squamous cell carcinoma
IFNγ = interferon gamma
IHC = immunohistochemistry
IP-10 = interferon-inducible protein 10
mBC = metastatic breast cancer
MCP-1 = monocyte chemoattractant protein-1
MoA = mechanism of action
NSCLC = non-small-cell lung carcinoma
PD = pharmacodynamic
Q = every
SC = subcutaneous

Figure shows *estimated* number of cohorts in Part 1 and Part 3, planned number of cohorts for Part 2

[a] Expansion cohorts A, B, C, and D will enroll subjects in 2 stages using a Simon 2-stage design, while Cohort E will be a single-stage enrollment.

Study Overview

- SBT6050-101 is an ongoing, first-in-human, open-label, multicenter study enrolling subjects from the US, Australia and (planned) South Korea.
- The study has 4 parts: a single-agent dose-escalation followed by tumor-specific expansion cohorts (Parts 1 and 2, respectively), and a pembrolizumab combination dose escalation and subsequent expansion cohort (Parts 3 and 4, respectively).
- The Part 3 dose-escalation may enroll in parallel with Part 1, and the expansion cohorts in Parts 2 and 4 may enroll in parallel with each other.

Study Objectives

Primary
- To estimate the MTD (maximum tolerated dose) and determine the RP2D (recommended phase 2 dose) of SBT6050 as monotherapy (Part 1) and in combination with pembrolizumab (Part 3)
- To evaluate the safety and tolerability of SBT6050 alone (Parts 1 and 2) or in combination with pembrolizumab (Parts 3 and 4)
- To assess the antitumor activity of SBT6050 alone (Part 2) or in combination with pembrolizumab (Part 4)

Secondary
- To assess preliminary antitumor activity (Parts 1 and 3)
- To assess pharmacokinetics (PK)
- To assess the immunogenicity of SBT6050

Exploratory
- To assess potential biomarkers of activity and safety
- To assess the immunogenicity of SBT6050 in combination with pembrolizumab (Parts 3 and 4)

Study Population

Key Inclusion Criteria

- Advanced or metastatic HER2-expressing (IHC2+ or 3+) or HER2-amplified solid tumors (see figure for cohort-specific requirements)
- Subjects must have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and have previously received all therapies known to confer clinical benefit
- Tumor lesion amenable for biopsy (except first 3 subjects in monotherapy dose level 1)
- Age > 18 years of age
- ECOG Performance Status of 0 or 1
- Adequate hematologic, hepatic, renal and cardiac function

Key Exclusion Criteria

- History of allergic reactions to certain components of SBT6050 or similar drugs
- Untreated brain metastases (brain MRI is required for subjects with breast cancer, NSCLC, or signs/symptoms suggestive of central nervous system disease)
- Active autoimmune disease or a documented history of autoimmune disease or syndrome
- HIV infection, active hepatitis B or hepatitis C infection

Study Status

SBT6050-101 is actively enrolling in the US and Australia, and in start-up in South Korea

The pharmacodynamic threshold to initiate the Part 3 pembrolizumab combination dose escalation has been reached, based on data from subjects in monotherapy cohort 1

www.clinicaltrials.gov identifier: NCT04460456

Global Recruitment Planned

Current Active Sites:
San Antonio, TX
Houston, TX
Nashville, TN
Pittsburgh, PA
Boston, MA
Sydney, AU

In Start Up:
Perth, AU
Melbourne, AU
Seoul, SK