Interim results of a Phase 1/1b study of SBT6050 monotherapy and pembrolizumab combination in patients with advanced HER2-expressing or amplified solid tumors

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Introduction

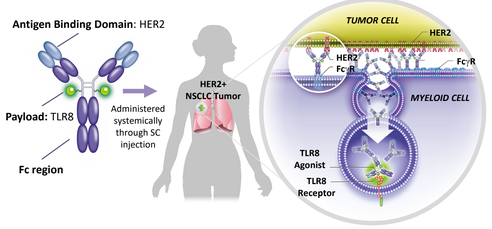
SBT6050 comprises a TLR8 agonist linker-payload conjugated to the HER2-directed antibody pertuzumab. SBT6050 is designed to directly activate and reprogram myeloid cells (e.g., macrophages, dendritic cells, myeloid-derived suppressor cells [MDSCs] and monocytes) and secondarily activate natural killer (NK) and T cells in HER2-expressing tumors (IHC 2+ and 3+).

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 NK cells as evidenced by the production of IFNγ.

There is strong scientific rationale, supported by preclinical data, to combine SBT6050 with SOC therapies, including checkpoint inhibitors and trastuzumab-based agents and regimens.

A phase 1 dose escalation and expansion study with SBT6050 alone and in combination with PD-1 inhibitors was initiated in patients with advanced HER2-expressing solid tumors (NCT04460456). Interim results of the dose escalation parts are presented here.

SBT6050 is designed to localize TLR8 activation of myeloid cells in tumors via a HER2 antibody



SBT6050-101 study schema and patient characteristics

Part 1: monotherapy dose escalation

SBT6050 SC injection Q2W
HER2-expressing (IHC 2+ or 3+) or HER2-amplified advanced cancers

0.3 mg/kg | 0.6 mg/kg | 0.9 mg/kg | 1.2 mg/kg

Part 3: pembrolizumab combination dose escalation

SBT6050 SC injection Q2W; pembrolizumab 400 mg IV Q6W
HER2-expressing (IHC 2+ or 3+) or HER2-amplified advanced cancers

0.15 mg/kg | 0.3 mg/kg | 0.6 mg/kg

Part 2: monotherapy tumor specific cohorts

SBT6050 SC injection Q2W

HER2^{expressing} breast, gastric/GEJ, NSCLC, and other solid tumors

Part 4: pembrolizumab combination expansion cohort

SBT6050 SC injection Q2W; pembrolizumab 400 mg IV Q6W

HER2^{expressing} solid tumors

Part 5: cemiplimab combination expansion cohort

SBT6050 SC injection Q3W; cemiplimab 350 mg IV Q3W

HER2^{positive} gastric/GEJ cancer, HER2^{expressing} NSCLC

HER2 status:
HER2^{positive} = HER2 IHC 3+ or IHC 2+/amplified
HER2^{expressing} = HER2 IHC 2+, or IHC 3+, or amplified
HER2^{low} = HER2 IHC 2+/ not amplified

Key eligibility criteria
- Received prior therapies known to confer clinical benefit
- Measurable disease per RECIST 1.1
- Exclusion: Patients with untreated brain metastases, active autoimmune disease or a documented history of autoimmune disease or syndrome

Assessments
- CT scans every 8 weeks until week 24, then every 16 weeks
- Baseline and on-treatment tumor biopsies were mandatory starting at 0.6 mg/kg
- Peripheral blood: pharmacokinetic and pharmacodynamic markers

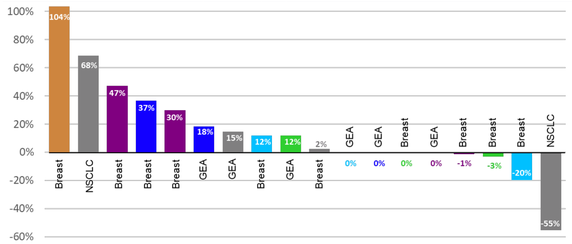
	Enrolled (n)	Remaining on treatment (n)	Median # Doses SBT6050 (Min, Max)
Part 1: SBT6050 monotherapy			
0.3 mg/kg	6	0	3.5 (1, 17)
0.6 mg/kg	15	3	2 (1,6)
0.9 mg/kg	7	4	2 (1,4)
1.2 mg/kg	4	2	4.5 (2,11)
Part 3: SBT6050 plus pembrolizumab			
0.15 mg/kg + pembro	4	1	4 (1, 11)
0.3 mg/kg + pembro	4	3	5 (2, 6)
All dose levels	40	13	3 (1, 17)

- Interim data as of August 1, 2021
- Patients discontinued study treatment due to progression of disease (n=17), withdrawal of consent (n=7), adverse event not related to treatment (n=1), or investigator decision (n=2)
- A total of 10 patients in the 0.6 (n=6) and 0.9 (n=4) mg/kg monotherapy cohorts received corticosteroid premedication (single dose of methylprednisolone) with each dose
- Patients experiencing DLTs received a reduced dose after the first or second injection

Baseline Characteristics and Demographics	Total, n=40
Median Age (min, max)	61.0 (21.0, 81.0)
Gender	
Male, n (%)	16 (40.0%)
Female, n (%)	24 (60.0%)
Median Number Prior Anti-Cancer Therapies (min, max)	4.5 (1.0, 12.0)
ECOG Performance Status	
0, n (%)	11 (27.5%)
1, n (%)	29 (72.5%)
Primary Tumor Type	
Breast, n (%)	17 (42.5%)
Gastroesophageal[1], n (%)	9 (22.5%)
NSCLC, n (%)	2 (5%)
Other[2], n (%)	12 (30%)
HER2 expression (local assessment)	
HER2 positive (IHC 3+ or IHC 2+/amplified), n (%)	24 (60%)
HER2 IHC 2+, not amplified or unknown, n (%)	10 (25%)
HER2 amplified/IHC unknown, n (%)	3 (7.5%)
HER2 missing, n (%)	3 (7.5%)

[1] Includes esophageal, gastric, gastroesophageal junction cancers. [2] "Other" tumor types enrolled were appendiceal, fallopian tube, ovarian, thymic, metastasis of unknown origin, gallbladder, ampullary, colorectal, urothelial cancers

Best % change in target lesion* for patients with tumor types prioritized for expansion cohorts (breast cancer, gastroesophageal adenocarcinoma [GEA], and NSCLC)



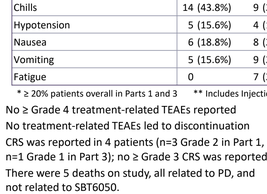
Part 1: SBT6050 monotherapy
0.3 mg/kg | 0.9 mg/kg | 0.6 mg/kg | 1.2 mg/kg

Part 3: SBT6050 + pembrolizumab
0.15 mg/kg + 400 mg pembrolizumab | 0.3 mg/kg + 400 mg pembrolizumab

Overall response in patients with RECIST-evaluable CT scans (n=24) was PR: n=1, SD: n=8, PD: n=15. Figure includes patients with tumor types prioritized for expansion cohorts (breast, gastroesophageal, NSCLC), who have restaging CT scans evaluable per RECIST. Excludes patients receiving corticosteroid pre-medication.
* As determined by sum of diameters

SBT6050 exposures reflect saturation of HER2-mediated clearance at doses ≥ 0.6 mg/kg

(A) Serum PK profiles



(B) Dose-proportional increases in AUC at doses ≥ 0.6 mg/kg

SBT6050 dose (mg/kg)	AUC (µg*d/mL)
0.15 + pembro	0.10 ± 0.17
0.3 + pembro	1.57 ± 1.19
0.3	1.16 ± 0.76
0.6	5.84 ± 2.57
0.9	8.14 ± 3.55
1.2	12.6 ± 2.6

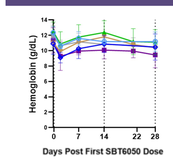
(A) Mean (± SD) profiles shown **(B)** Mean (± SD) AUC values shown. Mean values increased greater than dose proportionally up to 0.6 mg/kg (~5-fold from 0.3 to 0.6 mg/kg), but proportionally at dose levels ≥0.6 mg/kg

Free payload is rarely detected in circulation

Dose Range (mg/kg)	Frequency of Free Payload Detection (n=136 blood samples)		Free Payload Concentrations (nM)	Reference Payload Potency (nM)
0.15 to 1.2	Not quantifiable	133	Below LLOQ	EC_{50} ~100 LAC ~50
	Quantifiable	3	0.05-0.09	

Payload levels were determined with a validated LCMS-based assay with a lower limit of quantitation (LLOQ) of 0.02 ng/mL (~0.04 nM). The 50% effective and lowest active concentrations (EC_{50} and LAC, respectively) were determined by in vitro studies with human peripheral blood mononuclear cells.

Transient decreases in hemoglobin are considered on-target and are similar across dose levels



TLR8 activation can lead to downregulation of SIRPα expression on myeloid cells, which likely results in phagocytosis of aging circulating RBCs.

n=number of patients (only patients with data available up to day 28 are shown), mean (± SD) shown.

Hashed vertical lines indicate SBT6050 dosing.

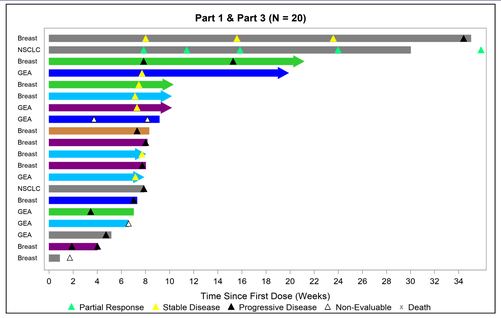
Most frequent* treatment-related treatment emergent adverse events (TEAEs), by maximum severity

	SBT6050 Monotherapy (n=32)			SBT6050 + Pembrolizumab (n=8)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Injection site reaction**	15 (46.9%)	11 (34.4%)	1 (3.1%)	5 (62.5%)	2 (25%)	0
Pyrexia	11 (34.4%)	9 (28.1%)	3 (9.4%)	3 (37.5%)	4 (50%)	0
Chills	14 (43.8%)	9 (28.1%)	0	3 (37.5%)	2 (25%)	0
Hypotension	5 (15.6%)	4 (12.5%)	6 (18.8%)	2 (25%)	4 (50%)	0
Nausea	6 (18.8%)	8 (25%)	1 (3.1%)	1 (12%)	4 (50%)	0
Vomiting	5 (15.6%)	9 (28.1%)	0	3 (37.5%)	0	0
Fatigue	0	7 (21.9%)	0	1 (12.5%)	1 (12.5%)	0

* ≥ 20% patients overall in Parts 1 and 3 ** Includes Injection Site Rash

- No ≥ Grade 4 treatment-related TEAEs reported
- No treatment-related TEAEs led to discontinuation
- CRS was reported in 4 patients (n=3 Grade 2 in Part 1, n=1 Grade 1 in Part 3); no ≥ Grade 3 CRS was reported
- There were 5 deaths on study, all related to PD, and not related to SBT6050.
- DLTs were all Grade 3 and in Part 1. DLTs at 0.6 mg/kg (DLT evaluable=11) were hypotension (n=1); 0.9 mg/kg (DLT evaluable=6) were hypotension (n=1), hypoxia (n=1), and fever (n=1); 1.2 mg/kg (DLT evaluable n=4) were hypotension (n=3) and ISR (n=1).
- All DLTs resolved with supportive care. Seven of the 8 patients who reported DLTs continued treatment at a reduced dose.

Time on study and tumor assessment for patients with breast cancer, GEA, and NSCLC



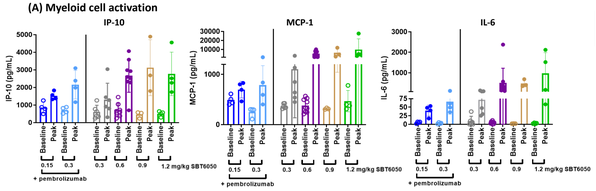
Part 1: SBT6050 monotherapy
0.3 mg/kg | 0.9 mg/kg | 0.6 mg/kg | 1.2 mg/kg

Part 3: SBT6050 monotherapy
0.15 mg/kg + 400 mg pembrolizumab | 0.30 mg/kg + 400 mg pembrolizumab

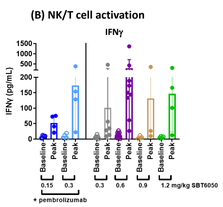
Figure includes efficacy evaluable patients with tumor types prioritized for expansion cohorts (breast, gastroesophageal, NSCLC). Each line represents one patient in the study with the bar ending at the time the decision is made to end all study treatments. Right arrow cap indicates that the patient is still in treatment.

SBT6050 induces myeloid and NK/T cell activation at all dose levels, with effects plateauing at 0.6 mg/kg

(A) Myeloid cell activation



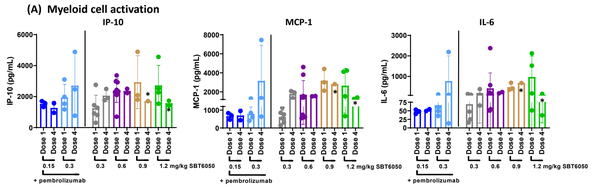
(B) NK/T cell activation



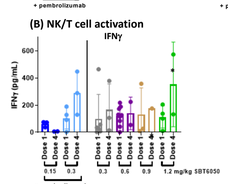
Pharmacodynamic markers of myeloid and NK/T cell activation were measured in patient serum samples collected prior to SBT6050 treatment (baseline) and at multiple timepoints after treatment initiation. Absolute levels of IP-10, MCP-1, IL-6 **(A)** and IFNγ **(B)** at baseline and for the timepoint with highest induction of pharmacodynamic activity after the first dose of SBT6050 (peak) are shown. No significant increase in IL-12p40 was observed (not shown). For MCP-1 and IP-10, peak levels were significantly higher (unpaired t-test, $p \leq 0.05$) at 0.6 mg/kg vs. lower dose levels, while no significant differences in peak levels were observed across the 0.6 to 1.2 mg/kg dose levels for any analyte.

Induction of pharmacodynamic activity is maintained with repeat dosing of SBT6050

(A) Myeloid cell activation



(B) NK/T cell activation

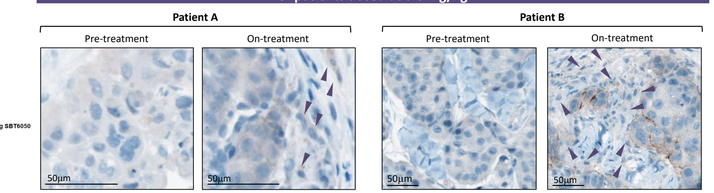


Pharmacodynamic markers of myeloid and NK/T cell activation were measured in patient serum samples collected at 24 hours after the first and fourth doses of SBT6050. Absolute levels of IP-10, MCP-1, IL-6 **(A)** and IFNγ **(B)** are shown. No statistically significant differences in the induction of pharmacodynamic markers after the first and fourth doses of SBT6050 were noted (paired t-test). Asterisk (*) denotes that patients in the 0.9 and 1.2 mg/kg cohorts received 0.6 mg/kg at dose 4.

Patient Case Studies

	NSCLC HER2 IHC 2+ Not amplified	Breast Cancer HER2 IHC 3+	Bladder Cancer HER2 IHC 2+ Amplification unknown	Breast Cancer HER2 IHC 3+	Breast Cancer HER2 IHC 3+	Gastric Cancer HER2 IHC 3+
Age, gender	67F	73F	60M	48F	40F	49M
Dose	0.3 mg/kg monotherapy	0.3 mg/kg monotherapy	0.6 mg/kg monotherapy	1.2 mg/kg monotherapy (decreased to 0.6 mg/kg at dose 3)	0.3 mg/kg plus pembro	0.3 mg/kg plus pembro
Treatment Duration	**26 weeks** (11 doses)	**33 weeks** (17 doses)	**>8 weeks** and remains on treatment	**>21 weeks** and remains on treatment, per investigator decision	**>8 weeks** and remains on treatment	**>8 weeks** and remains on treatment
Prior Lines of Therapy	**3 prior lines** with progression on prior PD-1 treatment	**7+ prior lines** including HER2-based cytotoxic ADC and HER2 targeted therapy	**2 prior lines** including anti-PD-L1 and cisplatin-gemcitabine	**4 prior lines** including HER2-based cytotoxic ADCs, anti-PD-L1, and HER2 targeted therapy	**3+ prior lines** including HER2-based cytotoxic ADC and HER2 targeted therapy	**1 prior line** including HER2 targeted therapy
Best Response	**Confirmed Partial Response** (-55%) Response ongoing at 36 weeks from first dose	**Stable Disease** (+2%) Maintained stable disease through 24-week scan	**Stable Disease** (-2.7%)	**Progressive Disease** (-3% in target lesions) PD based on new 5mm CNS lesion	**Stable Disease** (-20%)	**Stable Disease** (0%) Decreasing tumor marker (CA19-9 decrease from 135 to 64 U/mL)

SBT6050 payload is detected on tumor cells and in intratumoral macrophages of patients dosed at 0.6 mg/kg



Examples of SBT6050 payload-positive macrophage

Pre-treatment and on-treatment tumor biopsies (days 3-4 after the first dose) were collected from two patients with breast cancer treated with 0.6 mg/kg SBT6050. Samples were evaluated using an immunohistochemistry (IHC) assay developed for detection of the SBT6050 TLR8 agonist payload. Membrane and cytoplasmic staining of tumor cells, as well as cytoplasmic staining of tumor-resident macrophages, was observed, consistent with the mechanism of action of SBT6050. Macrophages with SBT6050 payload staining were identified in the on-treatment samples by an independent pathologist. Macrophages (not labeled) were detected in the pre-treatment biopsies. HER2 IHC status was determined on fresh baseline samples using Herceptest PharmDX IHC assay on pre-treatment samples (staining not shown): Patient A expressed HER2 at 1+ level while Patient B expressed HER2 at 3+ level.

Conclusions

- SBT6050 administered alone or in combination with pembrolizumab has a manageable safety profile.
  - » Common adverse events were similar between monotherapy and combination treatments and were consistent with immune activation.
  - » DLTs were observed at higher dose levels, were all Grade 3, and resolved with supportive care.
- Evaluation of pharmacodynamic activity in patients confirmed the preclinical profile of SBT6050, with induction of myeloid and NK/T cell activation markers observed at all dose levels.
- At the 0.6 mg/kg dose level, intratumoral SBT6050 payload is detectable, serum PK suggests HER2 target saturation, and pharmacodynamic markers indicative of myeloid, NK/T cell activation reach a plateau. Taken together, these data are supportive of selection of the 0.6 mg/kg dose for further evaluation.
- Preliminary data across all dose levels show early evidence of anti-tumor activity including a confirmed partial response and multiple patients with durable or decreasing volume stable disease.
- Enrollment into monotherapy and PD-1 inhibitor combination expansion cohorts is planned. The projected monotherapy RP2D is 0.6 mg/kg, and dose escalation in combination with pembrolizumab continues.
- The preliminary safety profile supports evaluation of SBT6050 in combination with other HER2-directed agents such as trastuzumab deruxtecan and trastuzumab-tucatinib.

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