COVER PAGE

Official Study Title:	An Open-label, Phase 1/2, Dose-escalation and Expansion Study of SBT6050 Combined With Other HER2-directed Therapies in Subjects With Pretreated Unresectable Locally Advanced and/or Metastatic HER2-expressing or HER2-amplified Cancers
NCT Number:	NCT05091528
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1 TITLE PAGE

PROTOCOL ADDENDUM 1

Study Title:	An Open-label, Phase 1/2, Dose-escalation and Expansion Study of SBT6050 Combined With Other HER2-directed Therapies in Subjects With Pretreated Unresectable Locally Advanced and/or Metastatic HER2-expressing or HER2-amplified Cancers
Investigational Product:	SBT6050
IND Number	[redacted]
Phase:	1/2
Protocol Number:	SBT6050-201
Addendum Date:	12 April 2022
Addendum Protocol Version	Amendment 1; 10 January 2022
Sponsor:	Silverback Therapeutics, Inc. 500 Fairview Avenue North Suite 600 Seattle, WA 98109
Medical Monitor:	[redacted]

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Summary of Changes for Protocol Addendum 1

Change	Rationale
End of treatment for subjects enrolled in the study or actively receiving study drug at the time of Sponsor's decision to prematurely terminate the study. Subjects who experience toxicity considered related to any component of study treatment should discontinue study treatment.	Subjects who experience toxicity related to any study drug should discontinue all study treatment.
Minimize study-related assessments for safety and efficacy for the duration of study treatment for subjects enrolled in the study or actively receiving study drug at the time of the Sponsor's decision to prematurely terminate the study. Remove requirement for collection of further research samples for subjects on treatment.	To minimize the extent of data collection following the Sponsor decision to terminate the SBT6050-201 study and reduce subject burden.
Study-related assessments in follow-up limited to safety and disease status per institutional standard of care.	To minimize the extent of data collection following the Sponsor decision to terminate the SBT6050-201 study and continue to ensure subject safety while on treatment.

3 SUMMARY

This is an addendum to the SBT6050-201 Protocol A01. This addendum provides further guidance to the Investigators regarding protocol modifications coming from the Sponsor decision to terminate the clinical trial.

This addendum describes changes to:

1. End of treatment for subjects enrolled in the study or actively receiving study drug at the time of Sponsor decision to prematurely terminate the clinical trial
2. Protocol-defined assessments in follow-up for treated subjects
3. Protocol-defined study assessments for safety and efficacy for subjects enrolled in the study actively receiving study drug

Refer to SBT6050-201 Protocol A01 for details regarding the original study design and schedule of assessments. A detailed summary of the nonclinical and clinical SBT6050 safety data is provided in the Investigator Brochure.

4 STUDY PLAN

4.1 Overall Design

This is a phase 1/2 open-label, multicenter, dose-escalation and expansion study designed to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and efficacy of SBT6050 in combination with trastuzumab deruxtecan (T-DXd; Part 1) or tucatinib and trastuzumab ± capecitabine (Part 2).

On 31 March 2022, the Sponsor decided to prematurely terminate the study and subject enrollment was terminated.

4.2 End of Treatment

Subjects enrolled in the screening period and those receiving active treatment at the time of the Sponsor decision may continue to receive treatment with SBT6050 in combination with T-DXd (Part 1) or tucatinib and trastuzumab ± capecitabine (Part 2) until any of the following reasons (whichever occurs first):

- completed 2 years of treatment with SBT6050
- progression of disease
- development of unacceptable toxicity
- confirmed pregnancy
- death
- withdrawal of consent
- subject decision

- lost to follow-up
- other reason (eg, Investigator decision)

Subjects who discontinue one of the study drugs due to toxicity considered related to that drug should discontinue all study treatment.

4.3 Follow-up and End of Study

Subject follow-up will continue after discontinuation of treatment through the required 30-day safety follow-up period until death, withdrawal of consent, lost to follow-up, or other reason.

End of study is defined as the time the last subject has completed the safety follow-up period after the last dose of study treatment (30 days), has died, is lost to follow-up, or has withdrawn consent.

4.4 Collection of Study Assessments

Subjects who have not received at least 2 cycles of study treatment at the time of the Sponsor decision will continue to have safety and response assessments captured as defined in Section 5 and Section 6 through completion of Cycle 2, including a tumor re-assessment at Week 6. Samples for research purposes will no longer be collected.

After Cycle 2, all subjects will have study assessments collected as outlined in the sections below.

4.4.1 Safety Measurements

Subjects who completed Cycle 2 and are continuing on study treatment will continue to be assessed for safety during treatment and follow-up per the institutional standard of care and the currently approved labeling for trastuzumab deruxtecan (Part 1) or the tucatinib combination (Part 2) and considering the safety profile of SBT6050 described in the Investigator Brochure.

The Sponsor will continue to collect data for serious adverse events (SAEs) for all subjects until the subject discontinues treatment through the required 30-day safety follow-up period unless the subject withdraws consent.

SAEs should be reported according to Section 6.9 of the protocol.

4.4.2 Efficacy Measurements

Disease progression will be evaluated per the institutional standard of care for all subjects. Disease status (progressed or not progressed) should be reported to the Sponsor following each tumor response assessment or every 3 months, whichever is sooner, and at discontinuation of treatment, unless the subject withdraws consent.

Subject status should also be reported to the Sponsor at each SBT6050 dosing visit and at discontinuation of treatment unless the subject withdraws consent.

4.4.3 Other Measurements

For all subjects, after Cycle 2 no further collection of study-related procedures or research samples per Section 6 of the protocol should be made.

5 SCHEDULE OF ASSESSMENTS FOR PART 1: SBT6050 COMBINED WITH TRASTUZUMAB DERUXTECAN

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days								Follow-up[a]
		Cycle 1					Cycle 2		Cycle 3+	
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	30 days post last dose
	Visit window			(24 ± 2 hrs)	(72–96 hrs ±2 hrs)	(±1 day)	(±2 day)	(±1 day)	(±2 day)	(±7 days)
		Pre	Post							
Informed consent	X									
Eligibility criteria	X									
Confirmation of HER2 status[b]	X									
Physical examination	X	X[c]					X			
Medical history and current medical conditions	X									
Pregnancy test[d]	X									
HIV, Hepatitis B and C screening	X									
Urinalysis	X									
Hematology panel[e]	X	X[c]			X	X	Predose	X		
Chemistry panel[f]	X	X[c]			X	X	Predose	X		
Thyroid panel[g]	X									
Coagulation panel[h]	X									
12-lead ECG	X				X					
ECHO/MUGA	X	Per institutional standard of care while on treatment								
EGOG Performance Status	X	X[c]					X			
SpO^2	X	X					X			
Vital signs	X	X[i]		X	X	X	X[i]	X		
MRI of brain[j]	X									
Administer SBT6050[k]		X					X		X	
Administer T-DXd[k]		X					X		X	
AE/concomitant medication review	X	Collect from consent through Cycle 2, then per institutional standard of care while on treatment								
SAE review	X	Collect from consent to 30 days post last dose								
Tumor assessment[l]	X						Week 6 then per institutional standard of care while on treatment			
Survival status										X

Abbreviations: AE = adverse event; CRC = colorectal cancer; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HR = hour; IV = intravenously; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small-cell lung cancer; SAE = serious adverse event; SPO^2 = oxygen saturation; SC = subcutaneously; T-DXd = trastuzumab deruxtecan.

[a]Subjects will be followed 30 days after the last dose for survival, disease status, and SAEs until death, withdrawal of consent, lost to follow-up, or other reason.

[b]The most recent result to confirm HER2 status should be used. If documentation of a previous HER2 result is not available, archived tissue, slides, fresh tissue or blood sample must be submitted to either a local laboratory or a Sponsor-designated central laboratory to confirm HER2 expression or amplification.

Confirmatory HER2 testing may be obtained greater than 28 days prior to Cycle 1 Day 1, if separate consent for confirmatory HER2 pre-testing is signed (see Section 6.1 of the protocol).

[c]Assessments do not need to be repeated if performed within 72 hours of first dose of SBT6050.

[d]For subjects of childbearing potential; to be performed within 14 days of Cycle 1 Day 1.

[e]Hematology panel consists of erythrocytes, hemoglobin, hematocrit, platelets, leucocytes and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes, as percentages and absolute values, if available); analyses for complete blood count, white blood cell differential, and reticulocyte count will also be performed.

[f]Chemistry panel consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, calcium, phosphate, magnesium, creatinine, total protein, albumin, glucose, total and direct bilirubin, amylase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, γ glutamyl transferase, lipase, triglycerides, and troponin. Creatinine clearance, only required for eligibility criteria at Screening/Baseline, will be calculated using the Cockcroft-Gault formula.

[g]Thyroid panel consists of triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

[h]Coagulation panel consists of PT/international normalized ratio (INR) and PTT (or, depending on institutional standard, aPTT).

[i]Vital signs will be taken predose SBT6050 and postdose 15, 30, 45, 60 minutes (+/-15 minutes) SBT6050 and then immediately following the end of the T-DXD infusion (+15 minutes) on dosing days.

[j]Required for all subjects with breast cancer or NSCLC and for subjects with gastric or GEJ cancer or CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis.

[k]See Protocol Section 5.1 for a description of treatments to be administered during the study. SBT6050 should be administered first, followed by T-DXd. T-DXd infusion should begin at least 15 minutes after the injection of SBT6050.

[l]Tumor assessment by CT, PET/CT (if diagnostic-quality CT scan included), or MRI.

6 SCHEDULE OF ASSESSMENTS FOR PART 2: SBT6050 COMBINED WITH TUCATINIB PLUS TRASTUZUMAB WITH OR WITHOUT CAPECITABINE

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days								FU[a]
		Cycle 1					Cycle 2		Cycle 3+	
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	30 days post last dose
	Visit window			(24 ± 2 hrs)	(72–96 hrs ±2 hrs)	(±1 day)	(±2 day)	(±1 day)	(±2 day)	(±7 days)
		Pre	Post							
Informed consent	X									
Eligibility criteria	X									
Confirmation of HER2 status[b]	X									
Physical examination	X	X[c]					X			
Medical history and current medical conditions	X									
Pregnancy test[d]	X									
HIV, Hepatitis B and C screening	X									
Urinalysis	X									
Hematology panel[e]	X	X[c]			X	X	Predose	X		
Chemistry panel[f]	X	X[c]			X	X	Predose	X		
Thyroid panel[g]	X									
Coagulation panel[h]	X									
12-lead ECG	X				X					
ECHO/MUGA	X	Per institutional standard of care while on treatment								
EGOG Performance Status	X	X[c]					X			
SpO^2	X	X					X			
Vital signs	X	X[i]		X	X	X	X[i]	X		
MRI of brain[j]	X									
Administer SBT6050[k]		X					X		X	
Administer trastuzumab[k]		X					X		X	
Administer tucatinib[k]		PO BID throughout the duration of the study								
Administer capecitabine, if applicable[k]		PO BID on Days 1–14 of every 21-day cycle							X	
AE/concomitant medication review	X	Collect from consent through Cycle 2, then per institutional standard of care while on treatment								
SAE review	X	Collect from consent to 30 days post last dose								
Tumor assessment[l]	X						Week 6 then per institutional standard of care while on treatment			
Survival status										X

Abbreviations: AE = adverse event; CRC = colorectal cancer; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HR = hour; IV = intravenously; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small-cell lung cancer; SAE = serious adverse event; SPO^2 = oxygen saturation; SC = subcutaneously.

[a]Subjects will be followed 30 days after the last dose for survival, disease status, and SAEs until death, withdrawal of consent, lost to follow-up, or other reason.

[b]The most recent result to confirm HER2 status should be used. If documentation of a previous HER2 result is not available, archived tissue, slides, fresh tissue or blood sample must be submitted to either a local laboratory or a Sponsor-designated central laboratory to confirm HER2 expression or amplification. Confirmatory HER2 testing may be obtained greater than 28 days prior to Cycle 1 Day 1, if separate consent for confirmatory HER2 pre-testing is signed (see Section 6.1 of the protocol).

[c]Assessments do not need to be repeated if performed within 72 hours of first dose of SBT6050.

[d]For subjects of childbearing potential; to be performed within 14 days of Cycle 1 Day 1.

[e]Hematology panel consists of erythrocytes, hemoglobin, hematocrit, platelets, leucocytes and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes, as percentages and absolute values, if available); analyses for complete blood count, white blood cell differential, and reticulocyte count will also be performed.

[f]Chemistry panel consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, calcium, phosphate, magnesium, creatinine, total protein, albumin, glucose, total and direct bilirubin, amylase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, γ glutamyl transferase, lipase, triglycerides, and troponin. Creatinine clearance, only required for eligibility criteria at Screening/Baseline, will be calculated using the Cockcroft-Gault formula.

[g]Thyroid panel consists of triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

[h]Coagulation panel consists of PT/international normalized ratio (INR) and PTT (or, depending on institutional standard, aPTT).

[i]Vital signs will be taken predose SBT6050 and postdose 15, 30, 45, 60 minutes (+/-15 minutes) SBT6050 and then immediately following the end of the T-DXD infusion (+15 minutes) on dosing days.

[j]Required for all subjects with breast cancer or NSCLC and for subjects with gastric or GEJ cancer or CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis.

[k]See Protocol Section 5.1 for a description of treatments to be administered during the study. SBT6050 should be administered first, followed by trastuzumab. Trastuzumab infusion should begin at least 15 minutes after the injection of SBT6050. At Cycle 1/Day 1, tucatinib and capecitabine (if applicable) should also be taken after SBT6050 and trastuzumab in the clinic. On Day 1 of each cycle, study staff should review tucatinib and capecitabine (if applicable) compliance from previous cycle.

[l]Tumor assessment by CT, PET/CT (if diagnostic-quality CT scan included), or MRI.

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Version:	Amendment 1; 10 January 2022
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Investigational Product:	SBT6050
Brief Title:	A Safety and Activity Study of SBT6050 in Combination with Other HER2-directed therapies for HER2-positive Cancers
Phase:	1/2
IND Number	[redacted]
Sponsor:	Silverback Therapeutics, Inc. 500 Fairview Avenue North, Suite 600 Seattle, WA 98109
Medical Monitor:	[redacted] Silverback Therapeutics, Inc. Tel: [redacted] E-mail: [redacted]
SAE Email or Fax:	Refer to SAE form

PROTOCOL SYNOPSIS

Protocol Number SBT6050-201	**Product Name** SBT6050
Version Amendment 1; 10-Jan-2022	**Sponsor** Silverback Therapeutics, Inc. 500 Fairview Avenue North, Suite 600 Seattle, WA 98109
Phase 1/2	

Protocol Title

An Open-label, Phase 1/2, Dose-escalation and Expansion Study of SBT6050 Combined With Other HER2-directed Therapies in Subjects With Pretreated Unresectable Locally Advanced and/or Metastatic HER2-expressing or HER2-amplified Cancers

Study Objectives

Part 1: Phase 1 Dose Escalation Cohorts:

Primary

- To estimate the maximum tolerated dose (MTD), if reached, and determine the recommended phase 2 dose (RP2D) of SBT6050 when combined with trastuzumab deruxtecan (T-DXd)
- To evaluate the safety and tolerability of SBT6050 and T-DXd

Secondary

- To assess preliminary efficacy of SBT6050 and T-DXd

[redacted]

Part 1: Phase 2 Dose Expansion Cohorts:

Primary

- To assess efficacy of SBT6050 and T-DXd

Secondary

- To evaluate the safety and tolerability of SBT6050 and T-DXd
- To further assess efficacy of SBT6050 and T-DXd

[redacted]

Part 2: Phase 1 Dose Escalation Cohorts:

Primary

- To estimate the MTD, if reached, and determine the RP2D of SBT6050 when combined with tucatinib plus trastuzumab ± capecitabine
- To evaluate the safety and tolerability of SBT6050 and tucatinib plus trastuzumab ± capecitabine

Secondary

- To assess preliminary efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine

[redacted]

Part 2: Phase 2 Dose Expansion Cohorts:

Primary

- To assess efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine

Secondary

- To evaluate the safety and tolerability of SBT6050 and tucatinib plus trastuzumab ± capecitabine
- To further assess efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine

[redacted]

Study Population

Inclusion Criteria:

Subjects must meet all the following criteria to be enrolled in the study:

1. Age 18 years or older
2. a.) **For Part 1**, subjects must have locally advanced (unresectable) and/or metastatic human epidermal growth factor receptor 2 (HER2)-expressing or HER2-amplified cancer as noted below and previously received the following therapies (unless ineligible to receive or refused to receive or therapy is unavailable in the region):
   - Breast cancer (dose escalation cohorts [1a] and dose expansion Cohort A): HER2-positive expression ($HER2^{pos}$) (immunohistochemistry [IHC] 3+ or IHC 2+/HER2 amplified)
     - ≥1 prior lines of HER2-targeted therapy in the advanced setting and received taxane, trastuzumab, and pertuzumab in the early stage or advanced setting
   - Colorectal cancer (CRC; Kirsten rat sarcoma viral oncogene homolog gene [KRAS], neuroblastoma RAS viral [v-ras] oncogene homolog [NRAS], and v-raf murine sarcoma viral oncogene homolog B1 [BRAF] wild type) (dose escalation cohorts [1a] and dose expansion Cohort B): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified) or HER2 amplified/IHC unknown
     - ≥1 prior line of therapy and must have received chemotherapy with a fluoropyrimidine and oxaliplatin or irinotecan
   - Non-small-cell lung carcinoma (NSCLC) without targetable genetic alterations (eg, alterations of epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], ROS1, BRAF, mitogen-activated extracellular signal-regulated kinase [MEK], and neurotrophic tyrosine receptor kinase [NTRK], etc.) (dose escalation cohorts [1a] and dose expansion Cohort C): HER2-expressing ($HER2^{exp}$) (IHC 3+ or IHC 2+) or HER2-amplified
     - ≥1 prior line of therapy, which must include a platinum-based chemotherapy, and a programmed cell death-1 (PD 1)/programmed death-ligand 1 (PD-L1) inhibitor
   - Gastric or gastroesophageal junction (GEJ) cancer (dose escalation cohorts [1b] and dose expansion Cohort D): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified)
     - ≥1 prior line of therapy and must have received a fluoropyrimidine, a platinum agent, and trastuzumab
   - **Subjects in all Part 1 cohorts** must not have received prior T-DXd for treatment of metastatic cancer

   b.) **For Part 2**, subjects must have locally advanced (unresectable) and/or metastatic $HER2^{exp}$ or HER2-amplified cancer as noted below and previously received the following therapies (unless ineligible to receive or refused to receive or therapy is unavailable in the region):
   - Breast cancer (dose escalation cohorts [2a] and dose expansion Cohorts E and G): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified)
     - ≥1 prior line of HER2-targeted therapy in the advanced setting and received taxane, trastuzumab, and pertuzumab in either the early stage or advanced setting
   - CRC (KRAS, NRAS, and BRAF wild type) (dose escalation cohorts [2b] and dose expansion Cohort F): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified) or HER2 amplified/IHC unknown
     - ≥1 prior line of therapy and must have received chemotherapy with fluoropyrimidine and oxaliplatin or irinotecan
   - **Subjects in all Part 2 cohorts** must not have received prior tucatinib for treatment of metastatic cancer
3. Histologic confirmation of cancer and HER2 expression and/or amplification should be performed in a Clinical Laboratory Improvement Amendments (CLIA) (or local equivalent) certified laboratory:
   - Assessment of HER2 expression in subjects with breast and gastroesophageal cancer should follow guidelines published by the American Society of Clinical Oncology (ASCO), the College of American Pathologists (CAP), and the American Society for Clinical Pathologists (ASCP)

- If documentation of a previous HER2 result is not available, tumor tissue (archival tissue or slides or fresh tissue) or a blood sample must be submitted to a local CLIA-certified (or local equivalent) laboratory or a Sponsor-designated central laboratory to confirm HER2 expression and/or HER2 amplification prior to enrollment

4. Subjects must have a tumor lesion amenable for fresh biopsy, or be able to submit an adequate recent archived tumor tissue for baseline testing as follows; variations from tissue requirements must be discussed with the medical monitor:
   - Breast cancer and CRC: archival biopsy tissue obtained after the last HER2-directed therapy (excluding trastuzumab and pertuzumab), or a fresh biopsy
   - Gastric or GEJ cancer and NSCLC: archival biopsy tissue taken within the past 12 months and after completion of last HER2-directed therapy, or a fresh biopsy
5. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
6. a) For **Part 1**, subjects must not have history of allergic reaction, including hypersensitivity reactions, to the following therapies: pertuzumab, trastuzumab, or T-DXd

   b.) For **Part 2**, subjects must not have history of allergic reaction, including hypersensitivity reactions, to the following therapies: pertuzumab, tucatinib, trastuzumab, or capecitabine (for relevant cohorts)
7. A brain magnetic resonance imaging (MRI) at baseline is required for
   - All subjects with breast cancer or NSCLC or
   - Subjects with gastric or GEJ cancer or CRC who have a history of central nervous system (CNS) metastases or have signs or symptoms suggestive of CNS metastases
8. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Section 11.5)
9. Adequate cardiac function with left ventricular ejection fraction (LVEF) ≥50%
10. Adequate hematologic function, including:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 100 \times 10^9$/L (platelet transfusions are not allowed within 1 week before screening visit)
    - Hemoglobin ≥9 g/dL (red blood cell transfusions are not allowed within 2 weeks before screening visit)
11. Adequate blood clotting function with prothrombin time (PT) and activated partial thromboplastin time/partial thromboplastin time (aPTT/PTT) <1.5 × upper limit of normal (ULN)
12. Adequate hepatic function with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (if liver or bone metastases are present, ≤4 × ULN) and total bilirubin ≤1.5 × ULN or <3 × ULN in the presence of Gilbert's syndrome
13. Adequate renal function with estimated glomerular filtration rate (eGFR) ≥45 mL/minute based on Cockcroft-Gault equation (see Section 11.6)
14. Female subjects of childbearing potential and fertile male subjects with partners who are of childbearing potential must agree to use highly effective contraception during the study and for up to 7 months (for females) or 2 months (for males) after the last dose of SBT6050 (see Section 11.7).

    Subjects must agree not to breastfeed, starting at the time of informed consent and continuing through 7 months after the last dose of SBT6050 or 4 months after the last dose of T-DXd (Part 1) or tucatinib plus trastuzumab with or without capecitabine (Part 2), whichever is later.

    A female subject is considered of childbearing potential if she is anatomically and physiologically capable of becoming pregnant and will be or could possibly be sexually active with a male partner while undergoing study treatment with the possibility of posing harm to a fetus.

    A male subject is considered of sexual reproductive potential if he is anatomically and physiologically capable of causing a pregnancy in a female partner and will be or could possibly be sexually active with a female partner (who is or may become pregnant) while undergoing study treatment with the possibility of posing harm to a fetus.
15. Subjects must have completed treatment with other systemic cancer therapy, including completing

monoclonal antibody (mAb) therapy at least 4 weeks prior to first dose of study treatment, and completing chemotherapy or therapy with small molecules at least 2 weeks prior to first dose of study treatment. Local radiation therapy must have been completed at least 2 weeks prior to the first dose of study treatment.

16. The subject or the subject's legally acceptable representative must provide written informed consent.

Exclusion Criteria:

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Prior lifetime exposure to anthracyclines exceeding:
   - Doxorubicin 360 mg/m^2
   - Epirubicin 720 mg/m^2
   - Mitoxantrone 120 mg/m^2
   - Idarubicin 90 mg/m^2
   - Liposomal doxorubicin 550 mg/m^2
2. Untreated brain metastases; subjects with treated brain metastases who are asymptomatic, have completed radiation therapy, and completed corticosteroid therapy at least 2 weeks prior to first dose of study treatment may participate
3. Subjects requiring an equivalent of >10 mg/day of prednisone
4. Active autoimmune disease or a documented history of autoimmune disease or syndrome that required systemic steroids (>10 mg/day prednisone or equivalent) or immunosuppressive agents within the past 2 years. Subjects are permitted to enroll if they have vitiligo, type 1 diabetes, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or resolved childhood asthma/atopy
5. Uncontrolled or clinically significant renal, pancreas, or liver disease
6. Subjects who are currently taking a medication which moderately induces cytochrome P450 family 2 subfamily C (CYP2C), a medication which strongly inhibits cytochrome P450 family 2 subfamily C member 8 (CYP2C8), or if they are taking medications that interact with both enzymes: cytochrome P450 family 3 subfamily A (CYP3A) and CYP2C8 (see Section 11.8)
7. Uncontrolled or clinically significant interstitial lung disease (ILD)/pneumonitis that required systemic corticosteroid (>10 mg prednisone per day or equivalent) treatment or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
8. Positive for human immunodeficiency virus (HIV), hepatitis B (positive by surface antigen [HBsAg]), or hepatitis C infection (positive by ribonucleic acid polymerase chain reaction [HCV RNA PCR])
9. History of another primary invasive malignancy that has not been definitively treated and in remission for at least 1 year, except:
   a. Subjects with a history of prostate cancer (tumor/node/metastasis stage) of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention
   b. Subjects who have been adequately treated for a malignancy with a low potential risk for recurrence (eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin).

10. History of symptomatic congestive heart failure (New York Heart Association classes II–IV), unstable angina, myocardial infarction, serious cardiac arrhythmia, or cerebral vascular accident within 6 months prior to first dose of study treatment
11. Corrected QT interval using Fridericia's formula (QTcF) >470 msec (females) or >450 msec (males)
12. Other medical or psychiatric illness or organ dysfunction which, in the opinion of the Investigator, would either compromise the subject's safety or interfere with the evaluation of the safety of the study treatment
13. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months after final dose of SBT6050 or 4 months after final dose of T-DXd (Part 1) or tucatinib plus trastuzumab with or without capecitabine (Part 2), whichever is later
14. Life expectancy ≤3 months, in the opinion of the Investigator

Number of Planned Subjects

Up to approximately 328 subjects will be enrolled across this 2-part study. Up to approximately 184 people will be enrolled in Part 1 and up to approximately 144 people will be enrolled in Part 2.

Study Design

This is a phase 1/2 open-label, multicenter, dose-escalation and expansion study designed to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and efficacy of SBT6050 in combination with T-DXd (Part 1) or tucatinib and trastuzumab ± capecitabine (Part 2).

The study is designed to determine the MTD, if reached, of SBT6050 when combined with two dose levels of T-DXd (Part 1) or with tucatinib and trastuzumab ± capecitabine (Part 2). In dose escalation, two dose levels of SBT6050 are planned (0.45 mg/kg and 0.6 mg/kg). The MTD is defined as the dose just below the dose level with at least 2 out of 6 subjects (≥33%) experiencing dose-limiting toxicities (DLTs). The DLT evaluation period is 21 days.

Dose expansion will be initiated once the Safety Monitoring Committee (SMC) has determined the SBT6050 RP2D from dose escalation of each respective part. The SBT6050 RP2D may be different for each of the four regimens. Dose expansion cohorts are designed to confirm the safety and tolerability of the RP2D for each combination regimen and to evaluate efficacy and pharmacodynamic effects of SBT6050 when combined with T-DXd (Part 1) or tucatinib and trastuzumab ± capecitabine (Part 2). Subjects will be enrolled into parallel expansion cohorts based on tumor type and HER2 expression level. Throughout dose expansion, the Sponsor will continually monitor safety data to assess benefit versus risk for subjects.

Investigational Product, Dose, and Mode of Administration

SBT6050 will be administered via subcutaneous (SC) injection as a single dose administered every 21 days (every 3 weeks [Q3W]). SBT6050 should not be administered as an intravenous (IV) bolus or infusion. Refer to the Pharmacy Manual for detailed instructions regarding SC administration of SBT6050.

In both **Part 1** and **Part 2**, during dose escalation, the starting dose of SBT6050 is 0.45 mg/kg and the next dose level is 0.6 mg/kg.

In both **Part 1** and **Part 2**, the SBT6050 RP2D for subjects during dose expansion will be determined based on safety, PK, pharmacodynamic, and clinical activity results from dose escalation.

Combination Product, Dose, and Mode of Administration

Part 1

For subjects with breast cancer, CRC, or NSCLC, T-DXd will be administered at 5.4 mg/kg via IV infusion over 90 minutes (Cycle 1) or over 30 minutes (subsequent cycles) on Day 1 of every 21-day cycle.

For subjects with gastric/GEJ cancer, T-DXd will be administered at 6.4 mg/kg via IV infusion over 90 minutes (Cycle 1) or over 30 minutes (subsequent cycles) on Day 1 of every 21-day cycle.

Part 2

Tucatinib 300 mg will be taken orally (PO) twice daily (BID) by all subjects starting on Cycle 1 Day 1 and for the duration of study treatment.

Trastuzumab 8 mg/kg will be administered to all subjects on Cycle1 Day 1 by IV infusion over 90 minutes. For subsequent cycles (Cycle 2 Day 1 and beyond), trastuzumab 6 mg/kg will be administered to all subjects by IV infusion over 30–90 minutes.

Capecitabine 1000 mg/m2 PO BID will be taken by subjects in Part 2a of dose escalation and Cohort E of dose expansion, on Days 1–14 of each cycle.

Duration of Treatment

Subjects will continue to be contacted for survival, disease status, and subsequent anticancer therapies until death, withdrawal of consent, lost to follow-up, study termination by Sponsor, or 1 year after the last dose of study treatment has been administered to the last subject. Subjects who discontinue one of the study drugs due to toxicity considered related to that drug may continue therapy with the other agent(s), respectively, for up to 2 years at the discretion of the Investigator after discussion with the medical monitor.

Antitumor Assessments

Antitumor assessments include radiographic imaging. Activity will be based on RECIST Version 1.1 (see Section 11.4).

Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and antidrug antibody (ADA) analyses will be collected and dose-related PK parameters to be estimated may include, but not be limited to, area under the concentration-time curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), apparent terminal half-life ($t_{1/2}$), and trough concentration (C_{trough}).

[redacted]

Safety Assessments

Safety assessments consist of the surveillance and recording of adverse events (AEs) and measurements of physical examination findings and laboratory tests. Adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0 and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (see Section 11.3). Laboratory results were also graded per NCI CTCAE, Version 5.0 when applicable.

Statistical Methodology

During dose expansion in both Part 1 and Part 2, for each tumor-specific cohort, objective response rate (ORR) along with the corresponding two-sided 80% confidence intervals (CI) will be evaluated to assess proof-of-concept for SBT6050 when combined with two dose levels of T-DXd (Part 1) or tucatinib plus trastuzumab ± capecitabine (Part 2). Other signs of potential activity, including duration of response and clinical benefit rate (CBR), as well as the overall benefit/risk will also be factored into the final efficacy conclusions. Because the study is evaluating SBT6050 in combination with approved therapies, no early futility analyses are planned.

All efficacy analyses will be performed for all treated subjects by cohort. Summary analyses will be performed in subjects treated at the RP2D for the given cohort; listings will be produced for subjects treated at other dose levels.

Safety evaluations will be based on the incidence, intensity, and type of treatment-emergent adverse event (TEAE) or serious adverse event (SAE), as well as changes in safety assessments. DLTs will be summarized by dose level in dose escalation phase and identified in listings; TEAEs leading to treatment discontinuation will be summarized in both the dose escalation and dose expansion phases of the study.

Extensive PK sampling will be done to appropriately characterize the PK of SBT6050, total antibody (tAb), and free payload (S-00193). Standard noncompartmental PK method will be used to calculate PK parameters. All estimated PK parameters will be summarized with mean, geometric mean, standard error of the mean, standard deviation, coefficient of variation (CV), and geometric mean CV, as data permit.

[redacted]

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SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT A01

Section(s)	Change	Rationale
Synopsis, Figure 1, 3.1.1.1, 3.1.1.2, 4.1, 5.1, 5.3	Treatment with T-DXd for subjects with NSCLC lowered from 6.4 mg/kg to 5.4 mg/kg.	To update the dose of T-DXd in NSCLC.
Synopsis, 4.1, Table 6	Cohort C (NSCLC) and Cohort D (gastric or GEJ cancer) revised to reflect the appropriate population description.	Correction.
1.1.2.3, Table 6	Updated confirmed response results from the recently published DESTINY-Gastric02 study.	To reflect the updated response rates for the combination therapy.
3.1.3	Removed reference to the Sponsor being part of the voting members of the ILD Adjudication Committee	Correction.
5.4.1	Added the following statement for tucatinib dose and administration: Tucatinib should be taken after administration of SBT6050 and trastuzumab in the clinic on Cycle 1 Day 1. On Day 1 of each subsequent cycle, study staff should review tucatinib compliance from previous cycle.	Clarification.
5.4.3	Added the following statement for capecitabine dose and administration: Capecitabine should be taken after administration of SBT6050 and trastuzumab in the clinic on Cycle 1 Day 1. On Day 1 of each subsequent cycle, study staff should review capecitabine compliance from previous cycle.	Clarification.
5.5.1	Added the following language regarding required premedications: In Part 1, subjects are required to receive • Ondansetron (or equivalent) 16 mg IV once at least 30 minutes prior to the dose of SBT6050 and then 8 mg PO every 8 hours as needed (PRN) for nausea and/or vomiting starting 8 hours after the prior dose of ondansetron • Dexamethasone (or equivalent) 8 mg PO every day for 3 days, beginning the day prior to Day 1 of each cycle, on Day 1 of each cycle at least 30-60 minutes prior to SBT6050 dosing, and ending on Day 2 of each cycle In Part 2, subjects are required to receive • Dexamethasone (or equivalent) 8 mg PO on Day 1 of each cycle at least 30-60 minutes prior to SBT6050 dosing • Ondansetron (or equivalent) 8 mg PO every 8 hours PRN for nausea and/or vomiting	To better conform with standard oncology premedication regimens.

Section(s)	Change	Rationale
5.5.2	Added the following language regarding recommended supportive medications: • Systemic corticosteroid as needed to treat ≥Grade 3 hypotension (not responding to IV fluid infusion)~~, or~~ ≥Grade 3 hypoxia, or ≥Grade 2 CRS, such as o methylprednisolone 1 mg/kg IV or equivalent, given as a single dose o dexamethasone 8-12 mg IV/PO given as a single dose	To better conform with standard oncology premedication regimens.
Table 2	Revised table column headings to reflect dose level rather than disease diagnosis for T-DXd dose reductions.	Correction.
6.4.3	Added the following language to skin biopsies: Photographs of the subject's injection site in the abdomen and the surrounding body areas may be taken by the study staff to assess any side effects. The photographs are for research purposes only and will be de-identified.	To allow for collection of photographs of subjects in the event of a skin reaction.
6.6.5, 11.1, 11.2	Added language to ECHO/MUGA scans stating that they will be obtained every 12 weeks as determined from Cycle 1 Day 1.	Clarification.
[redacted]	[redacted]	[redacted]
11.1, 11.2	Added the following to footnote "f": Creatinine clearance, only required for eligibility criteria at Screening/Baseline, will be calculated using the Cockcroft-Gault formula.	Clarification.
11.2	Revised the footnote for treatments to be administered during the study in Part 2 to include trastuzumab.	Clarification.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-FU	fluorouracil
5-FU/LV	fluorouracil plus leucovorin
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALP	alkaline phosphatase
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCP	American Society for Clinical Pathologists
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CAP	College of American Pathologists
CBR	clinical benefit rate
CLIA	Clinical Laboratory Improvement Amendments
CI	confidence interval
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
[redacted]	[redacted]
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
C_{trough}	trough concentration
CV	coefficient of variation

Abbreviation	Definition
CYP2C	cytochrome P450 family 2 subfamily C
CYP2C8	cytochrome P450 family 2 subfamily C member 8
CYP3A	cytochrome P450 family 3 subfamily A
DC	dendritic cell
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
eCRF	electronic case report form
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
FIH	first-in-human
FOLFIRI	fluorouracil, leucovorin, and irinotecan
FOLFOX	fluorouracil, leucovorin, and oxaliplatin
FT3	free tri-iodothyronine
FT4	free thyroxine
GEJ	gastroesophageal junction
GCP	Good Clinical Practice
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
$HER2^{exp}$	human epidermal growth factor receptor 2 expression
$HER2^{pos}$	human epidermal growth factor receptor 2 positive expression
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee

Abbreviation	Definition
IFN	interferon
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IRB	institutional review board
ISH	in situ hybridization
ISR	injection site reaction
IUD	intrauterine device
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
LVEF	left ventricular ejection fraction
LTFU	long-term follow-up
mAb	monoclonal antibody
MCP	monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated extracellular signal-regulated kinase pathway
MIP	macrophage inflammatory protein
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
[redacted]	[redacted]
NK	natural killer
NOAEL	no observed adverse effect level
NRAS	neuroblastoma RAS viral [v-ras] oncogene homolog
NSCLC	non-small cell lung carcinoma
NTRK	neurotrophic tyrosine receptor kinase
ORR	objective response rate
OR	objective response
OS	overall survival
[redacted]	[redacted]
PCR	polymerase chain reaction
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography

Abbreviation	Definition
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	by mouth (orally)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	corrected QT interval using Fridericia's formula
QW	every week
Q2W	every 2 weeks
Q3W	every 3 weeks
RAS	rat sarcoma viral oncogene homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS1	receptor tyrosine kinas encoded by the gene ROS1
RP2D	recommended phase 2 dose
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease
SIRPα	signal-regulatory protein alpha
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reactions
T3	tri-iodothyroinine
$t_{1/2}$	apparent terminal half-life
tAb	total antibody
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TEAE	treatment-emergent adverse event
TLR8	toll-like receptor 8
T_{max}	time to maximum concentration
[redacted]	[redacted]
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

Abbreviation	Definition
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor

1. INTRODUCTION

SBT6050 is a novel therapeutic comprising a selective small molecule toll-like receptor 8 (TLR8) agonist linked to the HER2-directed monoclonal antibody (mAb) 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 natural killer (NK) and T cells, inducing a broad spectrum of antitumor immune mechanisms. SBT6050 is currently being tested as a single agent and in combination with programmed cell death-1 (PD-1) inhibitors (NCT04460456). SBT6050 was well tolerated at a dose of 0.6 mg/kg, induced cytokines indicating myeloid cell and NK/T cell activation, and demonstrated early signs of antitumor activity.

Trastuzumab deruxtecan (T-DXd) (ENHERTU 2021) is an antibody-drug conjugate (ADC) composed of an anti-HER2 antibody, a cleavable linker, and a cytotoxic topoisomerase I inhibitor. T-DXd has demonstrated favorable outcomes in patients with previously treated HER2-expressing ($HER2^{exp}$) solid tumors, including breast cancer, gastric/gastroesophageal junction (GEJ) cancer, colorectal cancer (CRC), and non-small-cell lung carcinoma (NSCLC), leading to multiple regulatory approvals in the United States (US) and other regions. T-DXd is generally well tolerated; adverse events (AEs) of note include interstitial lung disease (ILD) and neutropenia, which may require dose interruption or reduction.

Tucatinib (TUKYSA 2020) is a potent and selective oral HER2 inhibitor that has recently received regulatory approval in the US and other regions based on improved progression-free survival (PFS) and overall survival (OS) in patients with previously treated HER2-positive ($HER2^{pos}$) breast cancer, when given in combination with trastuzumab and capecitabine. Improved outcomes were also observed in the subset of patients with breast cancer and a history of brain metastases, a challenging treatment setting with few options. Additionally, tucatinib plus trastuzumab in patients with $HER2^{pos}$ CRC has demonstrated encouraging results, with a substantial rate of durable responses. Tucatinib and trastuzumab with or without (±) capecitabine, is well tolerated with significant AEs including diarrhea and hepatotoxicity, which may require dose reductions or interruptions.

Strong scientific rationale supports the combination of SBT6050 with either T-DXd or trastuzumab plus tucatinib ± capecitabine. Both treatment regimens drive immunogenic 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. Thus, SBT6050 combined with T-DXd or trastuzumab plus tucatinib ± capecitabine is postulated to drive broad antitumor T cell responses. SBT6050 enhances the antibody-dependent cell mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) supported by trastuzumab and T-DXd. SBT6050 activates myeloid cells to secrete cytokines that amplify ADCC by NK cells. Additionally, SBT6050 activation downmodulates signal-regulatory protein alpha (SIRPα) on the surface of myeloid cells, which increases ADCP through attenuation of the CD47-SIRPα interaction. Consistent with this, in preclinical studies in mice, the combination of trastuzumab and a mouse surrogate of SBT6050 led to enhanced activity in the $HER2^{pos}$ NCI-N87 human tumor xenograft model compared to either agent alone.

1.1 Background

1.1.1 HER2-expressing Cancer

HER2 is an oncogenic driver and established therapeutic target in breast and gastric/GEJ cancers. HER2 overexpression or amplification has been reported in approximately 20% of breast and gastric/GEJ cancers and is also described in NSCLC, CRC, and multiple other tumor types. Guidelines for clinical testing for HER2 overexpression using Food and Drug Administration (FDA)-approved diagnostic tests have been established in breast and gastric/GEJ tumors (Ruschoff 2012) (Wolff 2013). Similar methods have been used to screen for HER2 expression in clinical trials for patients with CRC and NSCLC (Valtorta 2015) (Doi 2017) (Shen 2019).

HER2 overexpression refers to detection of the HER2 protein by immunohistochemistry (IHC). HER2 gene amplification is detected by in situ hybridization (ISH), differential polymerase chain reaction (PCR), or next-generation sequencing (NGS). Breast and gastric cancer are defined as $HER2^{pos}$ if they are either IHC 3+ or IHC 2+ and gene amplified. Similar terminology has been applied in clinical trials for patients with CRC and NSCLC.

1.1.2 Therapeutic Options for HER-expressing Cancer

HER2 is a validated target for treatment of advanced cancers, and several HER2-directed therapies have obtained regulatory approval in the US and globally. However, most patients with advanced $HER2^{pos}$-solid tumors eventually relapse and require additional therapeutic options.

1.1.2.1 $HER2^{pos}$ Metastatic Breast Cancer

Trastuzumab plus pertuzumab in combination with a taxane is the standard-of-care first-line therapy for patients with $HER2^{pos}$ metastatic breast cancer, increasing the time to progression and OS (Slamon 2001) (Baselga 2012). HER2 overexpression persists and remains relevant beyond progression, and strategies to overcome resistance have been developed; for example, changing the HER2-directed agent or switching chemotherapies in subsequent lines of treatment. Trastuzumab emtansine (T-DM1), an antibody-drug conjugate (ADC) comprising the cytotoxic agent DM1 linked to trastuzumab, has demonstrated positive outcomes (PFS; median, 6.2 months versus 3.3 months; hazard ratio [HR] 0.53, 95% confidence interval (CI) 0.42–0.66, and OS; median, 22.7 versus 15.8 months; HR 0.68, 95% CI 0.54–0.85) in patients with $HER2^{pos}$ breast cancer previously treated with trastuzumab and a taxane, and is a standard-of-care second-line therapy for metastatic breast cancer (Verma 2012) (Krop 2014) (Robert 2006) (Pegram 2004).

Tucatinib plus trastuzumab and capecitabine demonstrated improved PFS (median 7.8 months versus 5.6 months) and OS (median 21.9 months versus 17.4 months) compared to trastuzumab and capecitabine alone in patients with metastatic breast cancer who had received prior therapy and has received regulatory approval in multiple regions. Tucatinib plus trastuzumab and capecitabine has also demonstrated both a PFS benefit (9.9 months versus 4.2 months; HR 0.32, 95% CI 0.22–0.48 and a survival benefit (18 months versus 12 months; HR 0.58, 95% CI 0.40–0.85) in patients with central nervous system (CNS) metastases (Murthy 2020).

T-DXd recently demonstrated strong activity in a single arm study, with an objective response rate (ORR) of 61%, duration of response (DOR) of 14.8 months, and PFS of 16.4 months in patients with HER2^{pos} metastatic breast cancer who had received prior therapies (Modi 2020). Results from this study resulted in accelerated and conditional approval in the US and the European Union (EU), respectively, for treatment of patients with HER2^{pos} metastatic breast cancer who have received two or more prior HER2-directed therapies. T-DXd is also approved in Japan under accelerated approval in patients with HER2^{pos} unresectable or recurrent metastatic breast cancer who have received prior chemotherapy and are refractory or intolerant to standard treatments. Recently, it was reported that a phase 3 study comparing T-DXd to T-DM1 in patients with HER2^{pos} breast cancer who have received one prior therapy for metastatic disease met the primary endpoint of PFS, with T-DXd demonstrating superiority over T-DM1 (Astrazeneca 2021).

1.1.2.2 HER2^{pos} Colorectal Cancer

HER2 is overexpressed in 6–10% of patients with CRC and is often associated with gene amplification (Valtorta 2015) (Ross 2018) (Siena 2021). Regardless of HER2 status, standard of care first-line therapy for locally advanced, recurrent, or metastatic CRC is FOLFOX (fluorouracil [5-FU], leucovorin and oxaliplatin) or FOLFIRI (5-FU, leucovorin, and irinotecan), depending on prior adjuvant therapy regimens. FOLFOX and FOLFIRI are given with or without bevacizumab (vascular endothelial growth factor [VEGF] inhibitor), or with or without cetuximab or panitumumab (epidermal growth factor receptor [EGFR] inhibitor) if the tumor is wild-type for Kirsten rat sarcoma viral oncogene homolog gene (KRAS)/neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS)/v-raf murine sarcoma viral oncogene homolog B1 (BRAF). Capecitabine is sometimes substituted for 5-FU. For patients who cannot tolerate intensive chemotherapy, oxaliplatin or irinotecan may be omitted. Other options include nivolumab with or without ipilimumab or pembrolizumab for patients with tumors that are deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H), and encorafenib plus cetuximab or panitumumab for patients with tumors that are BRAFV600E-mutation positive.

A meta-analysis of 11 clinical trials analyzed the efficacy of FOLFIRI-bevacizumab as second-line chemotherapy in advanced CRC patients pretreated with oxaliplatin and not with bevacizumab. Overall, the pooled response rate (RR) (N=11 publications) was 26 %. Median PFS and OS (n=11 and 10 publications, respectively) were 8.3 months and 17.2 months. Studies of FOLFIRI alone in the second line setting demonstrated a PFS range of 3.4–11.2 months (Guiducci 2013) (Beretta 2013).

Although the standard recommendation for second-line therapy for metastatic CRC is additional chemotherapy, HER2-directed therapy may be an option for patients with HER2^{pos} CRC.

A phase 2 study demonstrated promising activity of HER2-targeted therapy with trastuzumab and lapatinib in CRC (Sartore-Bianchi 2016), with an ORR of 30% (95% CI 14, 50) and a DOR of 38 weeks (95% CI 24–94+).

Pertuzumab plus trastuzumab was evaluated as part of the phase 2a multicenter multiple basket study exploring targeted therapies with potentially predictive molecular alterations. In a cohort comprising 57 patients with treatment-refractory histologically confirmed HER2-amplified metastatic CRC with measurable or evaluable disease, ORR was 32% (95% CI, 20–45) with

combination pertuzumab and trastuzumab, with one patient (2%) achieving complete response (CR), and the regimen was well tolerated (Meric-Bernstam 2019).

T-DXd showed promising and durable activity in patients with HER2^{pos} metastatic CRC refractory to standard treatment, with a safety profile consistent with that reported in previous T-DXd trials. In the recently published interim results of the DESTINY-CRC01 phase 2 trial, for the 53 patients (68%) with HER2^{pos} tumors (cohort A), a confirmed objective response (OR) was reported in 24 patients (45.3%, 95% CI 31.6–59.6) with a median DOR of 7 months (95% CI 5.8–9.5) (Yoshino 2021).

An open-label, phase 2 study of trastuzumab plus tucatinib for patients with rat sarcoma viral oncogene homolog (RAS) wild type metastatic CRC in second-line and beyond is ongoing. Initial results in 45 patients have shown an ORR of 52%, median PFS of 8.1 months and OS of 18.7 months (Strickler 2021). An additional 70 patients were randomized in a 4:3 manner into 2cohorts (trastuzumab plus tucatinib or tucatinib alone, with the option to crossover to trastuzumab plus tucatinib).

Other available agents include regorafenib and trifluridine plus tipiracil and are associated with a PFS of approximately 2 months.

1.1.2.3 HER2^{pos} Metastatic Gastric/GEJ Cancer

The treatment landscape for HER2^{pos} gastric/GEJ cancer is rapidly changing. Trastuzumab in combination with FOLFOX is the established front-line standard of care in HER2^{pos}, locally advanced, recurrent or metastatic gastric/GEJ tumors based on OS benefit demonstrated in a phase 3 study (Bang 2010). 5FU-combination therapy with cisplatin or irinotecan may also be utilized in the first-line metastatic gastric/GEJ cancer population. Capecitabine can be interchanged for 5FU/LV (fluorouracil plus leucovorin), except when irinotecan is part of the regimen.

Recently, an interim analysis from a phase 3 randomized study comparing the addition of pembrolizumab versus placebo to trastuzumab plus chemotherapy in front-line therapy for patients with HER2^{pos} metastatic gastric/GEJ cancer (KEYNOTE 811) demonstrated an ORR of 74% (DOR of 10.5 months) for the pembrolizumab arm versus an ORR of 52% (DOR of 9.5 months) for the placebo arm. Pembrolizumab was granted FDA accelerated approval in the US for this indication, pending final analysis of the primary endpoint (PFS/OS).

Standard of care in the second line or beyond for HER2^{pos} metastatic gastric/GEJ cancer depends on prior therapy and performance status. Ramucirumab and paclitaxel are commonly used, with a response rate of approximately 10–30% and PFS of approximately 3–4 months (Wilke 2014) (Fuchs 2014). Single agent chemotherapy such as docetaxel is also used.

Treatment with T-DXd demonstrated superior outcomes compared to physician's choice chemotherapy (irinotecan or paclitaxel) in patients with relapsed or refractory HER2^{pos} metastatic gastric/GEJ cancer in a randomized phase 2 study, with a confirmed ORR of 41% versus 11%, an OS benefit of 12.5 months versus 8.4 months, and a DOR of 11.3 months versus 3.9 months, respectively (ENHERTU USPI). In a single arm study of T-DXd in patients with HER2^{pos} unresectable or metastatic gastric/GEJ cancer, the confirmed ORR was 38% and the median DOR was 8.1 months (van Cutsem 2021). T-DXd has subsequently received regulatory approval in multiple regions for the treatment of patients with HER2^{pos} metastatic gastric/GEJ cancer who have received prior therapies, including US FDA approval as a second-line agent.

1.1.2.4 HER2-expressing Non-Small-Cell Lung Carcinoma

Immune checkpoint inhibitor therapy alone or in combination with chemotherapy is the standard therapy for patients with NSCLC without other targetable genetic alterations, with response rates of 48–58%. Options are limited for second-line therapy in patients without specific genetic alterations who have already received checkpoint inhibitors, and include docetaxel or other chemotherapy, with response rates of approximately 10% and PFS of approximately 3–4 months (Herbst 2015) (Horn 2017).

HER2 is not routinely checked in patients with NSCLC. HER2 expression (IHC 2+ or 3+) has been reported in 10–30% of patients with NSCLC, and HER2 amplification occurs in up to 22% of patients with NSCLC. Currently, no HER2-directed therapy is approved for NSCLC.

Recently, T-DXd has demonstrated promising activity in patients with HER2-expressing (HER2^{exp}) NSCLC who had received prior therapy, with an ORR of 24.5%, DOR of 6 months, and PFS of 5.4 months (Nakagawa 2020). The Investigators defined HER2-expressing as patients with HER2-activating mutations, occurring in 1.7-3% of NSCLC, are not generally associated with HER2-expression (Pillai 2017) (Arcila 2012) (Mazieres 2013). Both T-DM1 and T-DXd have activity in tumors with HER2-activating mutations.

1.2 Study Treatments

1.2.1 SBT6050

SBT6050 is composed of a humanized, anti-HER2 mAb conjugated via a peptide linker to a proprietary small molecule agonist of TLR8. The amino acid sequence of the antibody component of SBT6050 is identical to pertuzumab. Conjugation of the TLR8 agonist to the anti-HER2 antibody backbone serves to enable systemic delivery of the payload while reducing the risk of limiting toxicities at effective antitumor doses.

TLR8 is an endosomal pattern recognition receptor with expression restricted to myeloid-lineage cells (monocytes, macrophages, and DCs). TLR8 activation directly and indirectly induces numerous immune-stimulating mechanisms, including macrophage-mediated tumor cell killing, reversal of tumor-mediated immune suppression, production of inflammatory cytokines/chemokines, T cell priming, and NK cell activation. [redacted] In addition, the antibody is capable of inducing ADCC

cytotoxicity and phagocytosis of HER2^{exp} tumor cells, which in combination with TLR8 agonism, serves to prime the antitumor adaptive immune response.

A detailed summary of the SBT6050 nonclinical and clinical development program is provided in the Investigator's Brochure. A summary of key information is provided below.

[redacted]

A more detailed summary of the SBT6050 nonclinical development program is provided in the Investigator's Brochure.

1.2.1.2 Clinical Safety Data

[redacted]

[redacted]

Additional information regarding SBT6050 clinical safety data is provided in the Investigator's Brochure.

[redacted]

- [redacted]

A more detailed summary of the nonclinical and clinical SBT6050 safety data is provided in the Investigator's Brochure.

1.2.2 Trastuzumab Deruxtecan

Trastuzumab deruxtecan (ENHERTU®) is a HER2-directed antibody and topoisomerase I inhibitor-drug conjugate with excellent response rates in multiple $HER2^{exp}$ malignancies. T-DXd has recently received regulatory approval in multiple regions to treat patients diagnosed with $HER2^{pos}$ metastatic breast cancer who have received two or more prior HER2 -directed therapies and in patients with $HER2^{pos}$ gastric/GEJ cancer who have received trastuzumab-based therapy in gastric cancer (US) and in patients with $HER2^{pos}$ unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy (Japan). T-DXd has also demonstrated encouraging preliminary activity in patients with $HER2^{exp}$ NSCLC and $HER2^{pos}$ CRC.

Identified safety risks as described in the regional labeling for T-DXd are (ENHERTU 2021):

- Interstitial lung disease(ILD)/pneumonitis: ILD occurred in 9% of patients with breast cancer treated with T-DXd at 5.4 mg/kg. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients. Median time to first onset was 4.1 months. ILD occurred in 10% of patients with gastric/GEJ cancer treated with T-DXd at 6.4 mg/kg. Median time to first onset was 2.8 months.
- Hematologic toxicity: Among patients with breast cancer treated with T-DXd at 5.4 mg/kg, 62% of patients had a decrease in neutrophil count (16% Grade 3–4). Febrile neutropenia was reported in 1.7% of patients. Among patients with gastric/GEJ cancer treated with T-DXd at 6.4 mg/kg, 72% of patients had a decrease in neutrophil count (51% Grade 3–4). Febrile neutropenia was reported in 4.8% of patients.
- Left ventricular dysfunction: Among patients with breast cancer treated with T-DXd at 5.4 mg/kg, 0.9% of patients developed an asymptomatic decrease in LVEF. Among patients with gastric/GEJ cancer treated with T-DXd at 6.4 mg/kg, no clinical AEs of heart failure were reported; however, on echocardiography, 8% were found to have asymptomatic Grade 2 decrease in left ventricular ejection fraction (LVEF).
- Embryo-fetal toxicity: Based on its mechanism of action, T-DXd can cause fetal harm when administered to a pregnant woman. In post marketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Based on its mechanism of action, the topoisomerase inhibitor component of T-DXd, deruxtecan, can also cause embryo-fetal harm when administered to a pregnant woman because it is genotoxic and targets actively dividing cells.

1.2.3 Tucatinib

Tucatinib (TUKYSA®) is a small molecule inhibitor of HER2 for the treatment of HER2^{pos} breast cancer. Tucatinib received approval in the US in combination with trastuzumab and capecitabine for the treatment of adults with locally-advanced, unresectable or metastatic HER2^{pos} breast cancer, including those with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Tucatinib plus trastuzumab ± capecitabine

In 2020, the FDA approved tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with advanced, unresectable or metastatic HER2^{pos} breast cancer, who had previously been treated with trastuzumab, pertuzumab (PERJETA®), and trastuzumab emtansine (KADCYLA®), based on the results of the HER2CLIMB study.

The median PFS in subjects who received tucatinib plus trastuzumab and capecitabine was 7.8 months (95% CI: 7.5, 9.6) compared to 5.6 months (95% CI: 4.2, 7.1) in those subjects who received placebo plus trastuzumab and capecitabine (HR 0.54; 95% CI: 0.42, 0.71; P<0.00001). The median OS in subjects who received tucatinib plus trastuzumab and capecitabine was 21.9 months (95% CI: 18.3, 31.0) compared to 17.4 months (95% CI: 13.6, 19.9) in subjects who received placebo plus trastuzumab and capecitabine (HR: 0.66; 95% CI: 0.50, 0.87; P=0.00480). The median PFS in subjects with brain metastases at baseline who received tucatinib plus trastuzumab and capecitabine was 7.6 months (95% CI: 6.2, 9.5) compared to 5.4 months (95% CI: 4.1, 5.7) in subjects who received placebo plus trastuzumab and capecitabine (HR: 0.48; 0.34, 0.69; P<0.00001) (Murthy 2020).

Tucatinib and trastuzumab has also been studied in patients with HER2^{pos}, RAS wild-type metastatic CRC who have progressed on first- and second-line therapy with FOLFOX and FOLFIRI. In the phase 1 MOUNTAINEER01 trial, the results were ORR 52%, PFS 8.1 months, OS 18.7 months, and DOR 10.4 months (Strickler 2021).

Identified safety risks as described in the regional labeling for tucatinib are (TUKYSA 2020):

- Gastrointestinal toxicity: including diarrhea, nausea and vomiting. In patients with breast cancer receiving tucatinib plus trastuzumab and capecitabine, diarrhea occurred in 81% of patients in the tucatinib plus trastuzumab and capecitabine arm, versus 53% of patients in the placebo plus trastuzumab and capecitabine arm.
- Hepatotoxicity: Hepatotoxicity occurred in 42% of patients with breast cancer receiving tucatinib plus trastuzumab and capecitabine, versus 24% of patients receiving placebo plus trastuzumab and capecitabine, respectively.
- Hematologic toxicity: Anemia occurred in 21% of patients receiving tucatinib plus trastuzumab and capecitabine, versus 13% of patients receiving placebo plus trastuzumab and capecitabine.
- Embryo-fetal toxicity: In rats, oral administration of tucatinib resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption) at doses ≥90 mg/kg/day. Fetal effects included reduced number of live fetuses, decreased fetal weight, and fetal abnormalities (increase in skeletal variations, incomplete ossification) at ≥90 mg/kg/day (approximately 3.5 times the human exposure at the recommended dose

based on area under the curve [AUC]). In rabbits, oral administration of tucatinib resulted in increased resorptions, decreased percentages of live fetuses, and skeletal, visceral, and external malformations in fetuses at doses ≥90 mg/kg/day (1.3 times the human exposure at the recommended dose based on AUC). Fetal abnormalities included domed head, brain dilation, incomplete ossification of frontal and parietal bones, and a hole in the parietal bone.

1.2.4 Trastuzumab

Trastuzumab is a humanized anti-HER2 antibody that binds to subdomain IV of the HER2-extracellular domain and exerts its antitumor effects by blocking HER2 cleavage, stimulating ADCC and inhibiting ligand-independent HER2-mediated mitogenic signaling.

Identified safety risks as described in the regional labeling for trastuzumab are (HERCEPTIN 2021):

- Cardiomyopathy: Trastuzumab administration can result in subclinical and clinical cardiac failure. An evaluation of metastatic breast cancer clinical trials showed that 5.0% of patients receiving trastuzumab plus chemotherapy compared to 1.1% of patients receiving chemotherapy alone had LVEF value below 50% with a >10% absolute decrease in LVEF from pretreatment values.
- Infusion reactions: Trastuzumab administration can result in serious and fatal infusion reactions. An evaluation of metastatic breast cancer clinical trials showed that approximately 40% of patients reported chills and fevers with their first infusion of trastuzumab.
- Pulmonary toxicity: Trastuzumab administration can result in serious and fatal pulmonary toxicity. Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving trastuzumab compared with 0.3% of those receiving chemotherapy alone.
- Exacerbation of chemotherapy-induced neutropenia: In randomized controlled clinical trials in the adjuvant setting, the incidence of selected National Cancer Institute Common Terminology Criteria (NCI-CTC) Grade 4–5 neutropenia (1.7% versus 0.8%) and of selected Grade 2–5 neutropenia (6.4% versus 4.3%) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone.
- Anemia: In randomized controlled clinical trials, the overall incidence of anemia (30% versus 21%), of selected NCI-CTC Grade 2–5 anemia (12.3% versus 6.7%), and of anemia requiring transfusions (0.1% versus no patients) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone.
- Embryo-fetal toxicity: In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

1.2.5 Capecitabine

Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form the active moiety fluorouracil. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, in turn interfering with deoxyribonucleic acid (DNA) and, to a lesser degree, ribonucleic acid (RNA) synthesis.

Identified safety risks as describing in the regional labeling for capecitabine are (XELODA 2021), (Murthy 2020):

- Skin disorders including plantar-palmar fasciitis (hand-foot syndrome) and rash: In a phase 3 study, hand-foot syndrome occurred in 63% of patients receiving tucatinib plus trastuzumab and capecitabine, versus 53% of patients receiving placebo plus trastuzumab and capecitabine. In an analysis of pooled phase 3 metastatic CRC trials, comparing capecitabine versus 5FU/LV, hand-foot syndrome occurred in 54% (all grades) of patients on the capecitabine arm versus 6% (all grades) of patients on the 5FU/LV arm.
- Gastrointestinal toxicity: In pooled phase 3 metastatic CRC trials, comparing capecitabine versus 5FU/LV, diarrhea occurred in 55% (all grades) of patients on the capecitabine arm versus 61% (all grades) of patients on the 5FU/LV arm.

1.3 Study Rationale

Despite the improvements in PFS and OS achieved with the addition of new agents to first-line therapy for advanced or metastatic HER2^{pos} cancers, nearly all patients will experience relapsed or progressive disease, and new treatment options are needed.

T-DXd is a trastuzumab-based ADC with robust activity across multiple HER2-expressing tumor types, that has received US regulatory approval for second-line therapy of HER2^{pos} gastric cancer. Additionally, it was recently reported that T-DXd demonstrated superior PFS compared to standard of care second line therapy with T-DM1 in HER2-positive breast cancer. In preliminary studies, T-DXd also has activity comparable to second-line standard of care treatment options for HER2^{pos} CRC and HER2-expressing NSCLC.

Tucatinib plus trastuzumab and capecitabine was recently granted US regulatory approval for second-line therapy of HER2^{pos} breast cancer, and in early-phase trials studies, tucatinib plus trastuzumab has demonstrated antitumor activity comparable to second-line standard of care options in HER2^{pos} CRC.

The addition of immunotherapy to cytotoxic regimens could improve response rates or duration of response. Subjects with the tumor types eligible for this study are expected to have a low response rate with PD-(L)1 checkpoint inhibition, either due to relative insensitivity of the tumor type (HER2+ breast cancer, HER2+ colorectal cancer) or due to having already received a PD-(L)1 inhibitor as part of initial therapy (gastric cancer and NSCLC). However, these tumors are often replete with myeloid cells, which may be contributing to an immune-tolerant tumor microenvironment. The addition of an innate immune activator, such as a TLR8 agonist, could reprogram these immunosuppressive myeloid cells into immune effectors, inducing inflammatory cytokines, activating DCs, and recruiting T cells into the tumor. Additionally,

activation of macrophages enhances the antitumor ADCC and ADCP effects of trastuzumab and T-DXd. SBT6050 is an ideal agent to combine with trastuzumab-based regimens, as there is extensive clinical experience combining the backbone antibody, pertuzumab, with trastuzumab.

Based on the strong clinical and preclinical rationale, this study will evaluate the antitumor activity, safety, pharmacokinetics (PK), and pharmacodynamics of SBT6050 in combination with T-DXd (Part 1) or tucatinib and trastuzumab ± capecitabine (Part 2).

2. STUDY OBJECTIVES AND ENDPOINTS

This study will evaluate the safety and efficacy of SBT6050 in combination with T-DXd or tucatinib and trastuzumab with or without (±) capecitabine in subjects with HER2^{pos} breast cancer, CRC, or gastric/GEJ cancer, or HER2^{exp} NSCLC. Specific objectives for the study are summarized below.

2.1.1 Part 1: SBT6050 Combined With Trastuzumab Deruxtecan

2.1.1.1 Phase 1 Dose Escalation Cohorts

Objectives	Endpoints
Primary	
• To estimate the maximum tolerated dose (MTD), if reached, and determine the recommended phase 2 dose (RP2D) of SBT6050 when combined with T-DXd	• Proportion of subjects experiencing dose limiting toxicities (DLTs)
• To evaluate the safety and tolerability of SBT6050 and T-DXd	• Incidence and severity of AEs graded according to NCI CTCAE Version 5.0 • Incidence of laboratory abnormalities
Secondary	
• To assess preliminary efficacy of SBT6050 and T-DXd	• ORR, defined as the proportion of subjects with confirmed complete response (CR) or partial response (PR) per RECIST Version 1.1 criteria
	• DOR, defined as the time from date of first response (CR or PR) to progression of disease or death, whichever occurs first
[redacted]	
• [redacted]	• [redacted]
	[redacted]
	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

2.1.1.2 Phase 2 Dose Expansion Cohorts

Objectives	Endpoints
Primary	
• To assess efficacy of SBT6050 and T-DXd	• ORR
Secondary	
• To evaluate the safety and tolerability of SBT6050 and T-DXd	• Incidence and severity of AEs graded according to NCI CTCAE Version 5.0
• To further assess efficacy of SBT6050 and T-DXd	• DOR • CBR
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	[redacted]

2.1.2 Part 2: SBT6050 Combined With Tucatinib and Trastuzumab ± Capecitabine

2.1.2.1 Phase 1 Dose Escalation Cohorts

Objectives	Endpoints
Primary	
• To estimate the MTD, if reached, and determine the RP2D of SBT6050 when combined with tucatinib plus trastuzumab ± capecitabine	• Proportion of subjects experiencing DLTs
• To evaluate the safety and tolerability of SBT6050 and tucatinib plus trastuzumab ± capecitabine	• Incidence and severity of AEs graded according to NCI CTCAE Version 5.0 • Incidence of laboratory abnormalities
Secondary	
• To assess preliminary efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine	• ORR • DOR
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.1.2.2 Phase 2 Dose Expansion Cohorts

Objectives	Endpoints
Primary	
• To assess efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine	• ORR
Secondary	
• To evaluate the safety and tolerability of SBT6050 and tucatinib plus trastuzumab ± capecitabine	• Incidence and severity of AEs graded according to NCI CTCAE Version 5.0
• To further assess efficacy of SBT6050 and tucatinib plus trastuzumab ± capecitabine	• DOR • CBR
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3. INVESTIGATIONAL PLAN

3.1 Summary of Study Design

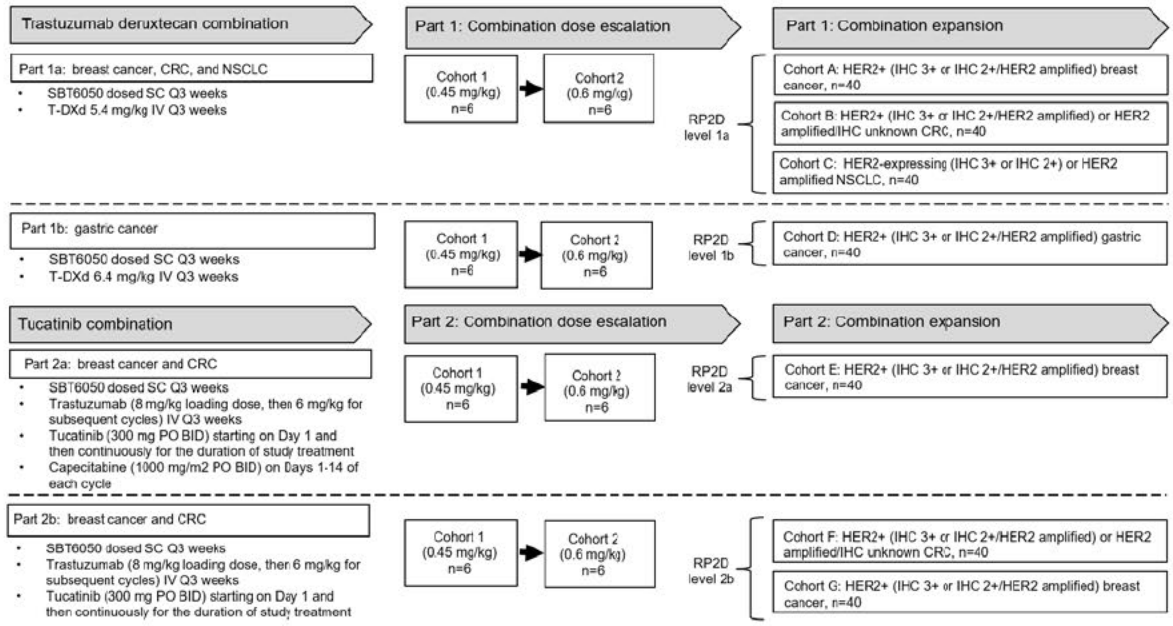
This is a phase 1/2 open-label, multicenter, dose-escalation and expansion study designed to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and efficacy of SBT6050 in combination with T-DXd (**Part 1**) or tucatinib and trastuzumab ± capecitabine (**Part 2**).

The study is designed to determine the MTD, if reached, of SBT6050 when combined with T-DXd (**Part 1**) or tucatinib and trastuzumab ± capecitabine (**Part 2**). In dose escalation, two dose levels of SBT6050 are planned (0.45 mg/kg and 0.6 mg/kg). The MTD is defined as the dose just below the dose level with 2 or more out of 6 subjects (≥33%) experiencing DLTs. The DLT evaluation period is 21 days.

Dose expansion will be initiated once the SMC has determined the SBT6050 RP2D from dose escalation of each respective part. The SBT6050 RP2D may be different for each of the four regimens. Dose expansion cohorts are designed to confirm the safety and tolerability of the RP2D and to evaluate efficacy and pharmacodynamic effects of SBT6050 when combined with T-DXd (**Part 1**) or tucatinib and trastuzumab ± capecitabine (**Part 2**). Subjects will be enrolled into parallel expansion cohorts based on tumor type and HER2 expression level. Throughout dose expansion, the Sponsor will continually monitor safety data to assess benefit versus risk for subjects.

Cohorts in dose escalation and expansion may enroll subjects in parallel based on eligibility. See Figure 1 for the study schema.

Figure 1: Overall Study Schema



BID =twice daily; CRC = colorectal cancer; IHC = immunohistochemistry; IV = intravenously; NSCLC = non-small cell lung cancer; PO = by mouth; Q3 = every 3; RP2D = recommended phase 2 dose; SC = subcutaneously

Antitumor assessments include radiographic imaging. Activity will be based on RECIST Version 1.1.

Safety assessments include the surveillance and recording of AEs including serious adverse events (SAEs), recording of concomitant medication, and measurements of physical examination findings and laboratory tests.

Blood samples for PK and ADA analyses will be collected and dose-related PK parameters to be estimated may include, but not be limited to, area under the concentration-time curve (AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), apparent terminal half-life ($t_{1/2}$), and trough concentration (C_{trough}).

[redacted]

3.1.1 Part 1: SBT6050 Combined With Trastuzumab Deruxtecan

3.1.1.1 Dose Escalation Cohorts

- Part 1a (5.4 mg/kg T-DXd, subjects with breast cancer, CRC, or NSCLC):
  - Cohort 1 (0.45 mg/kg SBT6050)
  - Cohort 2 (0.6 mg/kg SBT6050)
- Part 1b (6.4 mg/kg T-DXd, subjects with gastric or GEJ cancer):

- Cohort 1 (0.45 mg/kg SBT6050)
- Cohort 2 (0.6 mg/kg SBT6050)

3.1.1.2 Dose Expansion Cohorts

- Part 1a (5.4 mg/kg T-DXd):
  - Cohort A: subjects with breast cancer
  - Cohort B: subjects with CRC
  - Cohort C: subjects with NSCLC
- Part 1b (6.4 mg/kg T-DXd):
  - Cohort D: subjects with gastric or GEJ cancer

3.1.2 Part 2: SBT6050 Combined With Tucatinib and Trastuzumab With or Without Capecitabine

3.1.2.1 Dose Escalation Cohorts

- Part 2a (tucatinib and trastuzumab + capecitabine, subjects with breast cancer or CRC):
  - Cohort 1 (0.45 mg/kg SBT6050)
  - Cohort 2 (0.6 mg/kg SBT6050)
- Part 2b (tucatinib and trastuzumab without capecitabine, subjects with breast cancer or CRC):
  - Cohort 1 (0.45 mg/kg SBT6050)
  - Cohort 2 (0.6 mg/kg SBT6050)

3.1.2.2 Dose Expansion Cohorts

- Part 2a (tucatinib plus trastuzumab with capecitabine):
  - Cohort E: subjects with breast cancer
- Part 2b (tucatinib plus trastuzumab without capecitabine):
  - Cohort F: subjects with CRC
  - Cohort G: subjects with breast cancer

3.1.3 Dose Escalation

Two dose levels of SBT6050 are planned (0.45 mg/kg and 0.6 mg/kg). A minimum of three and up to approximately six subjects will be enrolled at the starting dose of SBT6050. The DLT evaluation period is 21 days. The following rules will be applied:

- If 0 of 3 patients experience a DLT in the evaluation period, the next 3 subjects will be enrolled at the next higher dose of SBT6050. If the current dose is SBT6050 0.6 mg/kg, then this will be the RP2D.
- If 1 of 3 patients experience a DLT in the evaluation period, 3 additional patients will be enrolled at the same dose of SBT6050.
    - If 1 of 6 subjects experience a DLT, and if the current dose is the starting dose level of SBT6050 (0.45 mg/kg), then the next 3 subjects will be enrolled at the next higher dose of SBT6050. If the current dose is SBT6050 0.6 mg/kg, then this will be the RP2D.
    - If ≥2 of 6 subjects experience a DLT, the MTD has been exceeded. Dose escalation will stop, and this dose level will be declared the maximum tolerated dose. If the current dose is SBT6050 0.6 mg/kg, 3 additional subjects will be evaluated at the prior dose level if only 3 were treated at that dose previously.
- If 2 of 3 patients experience a DLT in the evaluation period, the MTD has been exceeded. Dose escalation will stop, and this dose level will be declared the maximum administered dose. If the current dose is SBT6050 0.6 mg/kg, 3 additional subjects will be evaluated at the prior dose level if only 3 were treated at that dose previously.
- If the starting dose level of SBT6050 (0.45 mg/kg) exceeds the MTD, dose escalation will be stopped; the Safety Monitoring Committee (SMC) may recommend evaluation of a lower dose level of SBT6050 or other interventions to improve tolerability.

The SMC will consist of Investigators and Sponsor personnel who will review DLTs and available safety information to determine if enrollment may then commence at the next dose level of SBT6050 (0.6 mg/kg). The SMC will select the RP2D level to be used for the dose expansion tumor-specific cohorts based on an integrated analysis of safety, PK, pharmacodynamic, and clinical activity data from Part 1 and Part 2 dose escalation. There will be an ILD Adjudication Committee, consisting of disease experts who will review available clinical data, radiologic images, and pathology information for suspected cases of ILD.

3.1.3.1 Dose Limiting Toxicity

A DLT is defined as one of the following toxicities that occur during the 21-day DLT observation period in Part 1 or Part 2 dose escalation and is considered by the Investigator to be related to the combination of SBT6050 and T-DXd or tucatinib and trastuzumab ± capecitabine.

Part 1: SBT6050 Combined With Trastuzumab Deruxtecan

- Any death not clearly due to the underlying disease or extraneous causes
- Any Hy's law case
- Grade 4 neutropenia that lasts ≥7 days or with a fever ≥39°C (febrile neutropenia not meeting these criteria is not a DLT unless agreed upon by the SMC)
- Grade 4 thrombocytopenia lasting >7 days
- Grade ≥3 thrombocytopenia with bleeding
- Grade 4 anemia

- Grade ≥3 nausea/vomiting or diarrhea lasting >72 hours with adequate antiemetic and other supportive care
- Grade 3 fatigue lasting ≥1 week
- Grade 4 fever and/or chills
- Grade ≥3 electrolyte or serum chemistry abnormality lasting >72 hours, unless the subject has clinical symptoms in which case all Grade ≥3 abnormalities are considered a DLT regardless of duration; Note: Grade ≥3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis should not be considered a DLT.
    - For subjects with hepatic or bone metastases, confirmed aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >8 × upper limit of normal (ULN), or AST or ALT >5 × ULN lasting for ≥14 days
- Grade 3 hypersensitivity or allergic reaction requiring hospitalization, or Grade 4 hypersensitivity or allergic reaction
- Grade 3 ILD/pneumonitis confirmed by the ILD Adjudication Committee
- Any other non-hematologic AE Grade ≥3 not clearly and incontrovertibly due to the underlying disease or extraneous causes

Part 2: SBT6050 Combined With Tucatinib and Trastuzumab ± Capecitabine

- Any death not clearly due to the underlying disease or extraneous causes
- Any Hy's law case
- Grade ≥3 neutropenia with fever ≥39°C (febrile neutropenia not meeting these criteria is not a DLT unless agreed upon by the SMC)
- Grade 4 thrombocytopenia lasting >7 days
- Grade ≥3 thrombocytopenia with bleeding
- Grade 4 anemia
- Grade ≥3 nausea/vomiting, decreased appetite, or diarrhea lasting >72 hours with adequate antiemetic and other supportive care
- Grade 3 fatigue lasting ≥1 week
- Grade 4 fever and chills
- Grade ≥3 electrolyte or serum chemistry abnormality lasting >72 hours (excluding ALT and AST elevations; see below) unless the subject has clinical symptoms in which case all Grade ≥3 abnormalities are considered a DLT regardless of duration. Grade ≥3 amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis should not be considered a DLT
- Grade 4 hepatotoxicity including ALT and AST elevations
- Grade 3 hypersensitivity or allergic reaction requiring hospitalization, or Grade 4 hypersensitivity or allergic reaction

- Any other non-hematologic AE Grade ≥3 not clearly and incontrovertibly due to the underlying disease or extraneous causes

3.1.4 Replacement of Subjects

During dose escalation, subjects who are not evaluable for the assessment of DLTs may be replaced to ensure the study design requirements are met. Subjects who are not evaluable for a DLT that discontinue due to study drug toxicity will remain in the safety population and continue to be followed per study requirements.

Additional subjects may be enrolled for evaluation of alternative dosing regimens, or for further exploring safety, PK/pharmacodynamics, or preliminary activity used to guide the selection of the RP2D.

3.1.5 End of Study

End of study is defined as the time when the last subject has completed approximately 1 year of follow-up after the last dose of study treatment, has died, is lost to follow-up, or has withdrawn consent, whichever occurs first. In addition, the Sponsor may terminate the study at any time (Section 9.3.2).

4. STUDY POPULATION

Subjects must meet all the enrollment criteria to be eligible for this study.

4.1 Inclusion Criteria

Subjects must meet all the following criteria to be enrolled in the study:

1. Age 18 years or older
2. For **Part 1**, subjects must have locally advanced (unresectable) and/or metastatic HER2-expressing or HER2-amplified cancer as noted below and previously received the following therapies (unless ineligible to receive or refused to receive or therapy is unavailable in the region):
    - Breast cancer (dose escalation cohorts [1a] and dose expansion Cohort A): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified)
        - ≥1 prior lines of HER2-targeted therapy in the advanced setting and received taxane, trastuzumab, and pertuzumab in the early stage or advanced setting
    - CRC (KRAS, NRAS, and BRAF wild type) (dose escalation cohorts [1a] and dose expansion Cohort B): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified) or HER2 amplified/IHC unknown
        - ≥1 prior line of therapy and must have received chemotherapy with a fluoropyrimidine and oxaliplatin or irinotecan
    - NSCLC without targetable genetic alterations (eg, alterations of EGFR, anaplastic lymphoma kinase [ALK], ROS1, BRAF, MEK, and NTRK, etc.) (dose escalation cohorts [1a] and dose expansion Cohort C): $HER2^{exp}$ (IHC 3+ or IHC 2+) or HER2-amplified
        - ≥1 prior line of therapy, which must include a platinum-based chemotherapy, and a PD-1/PD-L1 inhibitor
    - Gastric or GEJ cancer (dose escalation cohorts [1b] and dose expansion Cohort D): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified)
        - ≥1 prior line of therapy and must have received a fluoropyrimidine, a platinum agent, and trastuzumab
    - **Subjects in all Part 1 cohorts** must not have received prior T-DXd for treatment of metastatic cancer

    b) **For Part 2**, subjects must have locally advanced (unresectable) and/or metastatic $HER2^{exp}$ or HER2-amplified cancer as noted below and previously received the following therapies (unless ineligible to receive or refused to receive or therapy is unavailable in the region):
    - Breast cancer (dose escalation cohorts [2a] and dose expansion Cohorts E and G): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified)

    - ≥1 prior line of HER2-targeted therapy in the advanced setting and received taxane, trastuzumab, and pertuzumab in either the early stage or advanced setting
- CRC (KRAS, NRAS, and BRAF wild type) (dose escalation cohorts [2b] and dose expansion Cohort F): $HER2^{pos}$ (IHC 3+ or IHC 2+/HER2 amplified) or HER2 amplified/IHC unknown
    - ≥1 prior line of therapy and must have received chemotherapy with fluoropyrimidine and oxaliplatin or irinotecan
- **Subjects in all Part 2 cohorts** must not have received prior tucatinib for treatment of metastatic cancer

3. Histologic confirmation of cancer and HER2 expression and/or amplification should be performed in a Clinical Laboratory Improvement Amendments (CLIA) (or local equivalent) certified laboratory:
    - Assessment of HER2 expression in subjects with breast and gastroesophageal cancer should follow guidelines published by the American Society of Clinical Oncology (ASCO), the College of American Pathologists (CAP), and the American Society for Clinical Pathologists (ASCP)
    - If documentation of a previous HER2 result is not available, tumor tissue (archival tissue or slides or fresh tissue) or a blood sample must be submitted to a local CLIA-certified (or local equivalent) laboratory or a Sponsor-designated central laboratory to confirm HER2 expression and/or HER2 amplification prior to enrollment
4. Subjects must have a tumor lesion amenable for fresh biopsy, or be able to submit an adequate recent archived tumor tissue for baseline testing as follows; variations from tissue requirements must be discussed with the medical monitor:
    - Breast cancer and CRC: archival biopsy tissue obtained after the last HER2-directed therapy (excluding trastuzumab and pertuzumab), or a fresh biopsy
    - Gastric or GEJ cancer and NSCLC: archival biopsy tissue taken within the past 12 months and after completion of last HER2-directed therapy, or a fresh biopsy
5. Measurable disease per RECIST Version 1.1.
6. a) For **Part 1**, subjects must not have history of allergic reaction, including hypersensitivity reactions, to the following therapies: pertuzumab, trastuzumab, or T-DXd

    b) For **Part 2**, subjects must not have history of allergic reaction, including hypersensitivity reactions, to the following therapies: pertuzumab, tucatinib, trastuzumab, or capecitabine (for relevant cohorts)
7. A brain magnetic resonance imaging (MRI) at baseline is required for
    - All subjects with breast cancer or NSCLC or

- Subjects with gastric or GEJ cancer or CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis

8. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Section 11.5)
9. Adequate cardiac function with LVEF ≥50%
10. Adequate hematologic function, including:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 100 \times 10^9$/L (platelet transfusions are not allowed within 1 week before screening visit)
    - Hemoglobin ≥9 g/dL (red blood cell transfusions are not allowed within 2 weeks before screening visit)
11. Adequate blood clotting function with prothrombin time (PT) and activated partial thromboplastin time/partial thromboplastin time (aPTT/PTT) <1.5 × ULN
12. Adequate hepatic function with aspartate aminotransferase (AST) and ALT ≤2.5 × ULN (if liver or bone metastases are present, ≤4 × ULN) and total bilirubin ≤1.5 × ULN or <3 × ULN in the presence of Gilbert's syndrome
13. Adequate renal function with estimated glomerular filtration rate (eGFR) ≥45 mL/minute based on Cockcroft-Gault equation
14. Female subjects of childbearing potential and fertile male subjects with partners who are of childbearing potential must agree to use highly effective contraception during the study and for up to 7 months (for females) or 2 months (for males) after the last dose of SBT6050 (see Section 11.7).

    Subjects must agree not to breastfeed, starting at the time of informed consent and continuing through 7 months after the last dose of SBT6050 or 4 months after the last dose of T-DXd (**Part 1**) or tucatinib plus trastuzumab with or without capecitabine (**Part 2**), whichever is later.

    A female subject is considered of childbearing potential if she is anatomically and physiologically capable of becoming pregnant and will be or could possibly be sexually active with a male partner while undergoing study treatment with the possibility of posing harm to a fetus.

    A male subject is considered of sexual reproductive potential if he is anatomically and physiologically capable of causing a pregnancy in a female partner and will be or could possibly be sexually active with a female partner (who is or may become pregnant) while undergoing study treatment with the possibility of posing harm to a fetus.
15. Subjects must have completed treatment with other systemic cancer therapy, including completing mAb therapy at least 4 weeks prior to first dose of study treatment, and completing chemotherapy or therapy with small molecules at least 2 weeks prior to first dose of study treatment. Local radiation therapy must have been completed at least 2 weeks prior to the first dose of study treatment.

16. The subject or the subject's legally acceptable representative must provide written informed consent.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Prior lifetime exposure to anthracyclines exceeding:
    - Doxorubicin 360 mg/m2
    - Epirubicin 720 mg/m2
    - Mitoxantrone 120 mg/m2
    - Idarubicin 90 mg/m2
    - Liposomal doxorubicin 550 mg/m2
2. Untreated brain metastases; subjects with treated brain metastases who are asymptomatic, have completed radiation therapy, and completed corticosteroid therapy at least 2 weeks prior to first dose of study treatment may participate
3. Subjects requiring an equivalent of >10 mg/day of prednisone
4. Active autoimmune disease or a documented history of autoimmune disease or syndrome that required systemic steroids (>10 mg/day prednisone or equivalent) or immunosuppressive agents within the past 2 years. Subjects are permitted to enroll if they have vitiligo, type 1 diabetes, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or resolved childhood asthma/atopy
5. Uncontrolled or clinically significant renal, pancreas, or liver disease
6. Subjects who are currently taking a medication which moderately induces CYP2C, a medication which strongly inhibits CYP2C8, or if they are taking medications that interact with both enzymes: CYP3A and CYP2C8 (see Section 11.8)
7. Uncontrolled or clinically significant ILD/pneumonitis that required systemic corticosteroid (>10 mg prednisone per day or equivalent) treatment or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
8. Positive for human immunodeficiency virus (HIV), hepatitis B (positive by surface antigen [HBsAg]), or hepatitis C infection (positive by ribonucleic acid polymerase chain reaction [HCV RNA PCR])
9. History of another primary invasive malignancy that has not been definitively treated and in remission for at least 1 year, except:
    a. Subjects with a history of prostate cancer (tumor/node/metastasis stage) of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention

b. Subjects who have been adequately treated for a malignancy with a low potential risk for recurrence (eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin).

10. History of symptomatic congestive heart failure (New York Heart Association classes II-IV), unstable angina, myocardial infarction, serious cardiac arrhythmia, or cerebral vascular accident within 6 months prior to first dose of study treatment
11. Corrected QT interval using Fridericia's formula (QTcF) >470 msec (females) or >450 msec (males)
12. Other medical or psychiatric illness or organ dysfunction which, in the opinion of the Investigator, would either compromise the subject's safety or interfere with the evaluation of the safety of the study treatment
13. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months after final dose of SBT6050 or 4 months after final dose of T-DXd (**Part 1**) or tucatinib plus trastuzumab with or without capecitabine (**Part 2**), whichever is later
14. Life expectancy ≤3 months, in the opinion of the Investigator

4.3 Criteria for Discontinuation from Study Treatment and Withdrawal of Subjects

Subjects are allowed to withdraw from the study at any time for any reason, without prejudice, and without having to justify their decision. Silverback or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and electronic case report form (eCRF).

4.3.1 Discontinuation of Study Treatment

Subjects may be discontinued from study treatment for any of the following reasons:

- Completed 2 years of treatment
- Progression of disease
- Development of unacceptable toxicity
- Confirmed pregnancy
- Death
- Withdrawal of consent
- Subject decision
- Lost to follow-up
- Study termination by Sponsor
- Other reason (eg, Investigator decision)

Subjects who discontinue one of the study drugs due to toxicity considered related to that drug may continue therapy with the other agent(s), respectively, for up to 2 years at the discretion of the Investigator after discussion with the medical monitor.

Subjects who present equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions) or suspected pseudoprogression (temporary increase in size of tumor lesions due to inflammation), may be allowed to continue the study treatment with approval of the medical monitor and if, in the opinion of the Investigator, the subject is deemed clinically stable. Subjects with progressive disease based on small or equivocal lesions or lesions amenable to local therapy (eg, radiation therapy) may be allowed to continue the study treatment with approval of the medical monitor and if, in the opinion of the Investigator, the subject is deemed clinically stable. If, at the next scheduled assessment progression is confirmed, the date of progression should be the date when progression was initially suspected.

Subjects who discontinue from study treatment prior to radiographic evidence of progressive disease will continue to be contacted for disease progression (eg, tumor response assessments/scans) until radiographic evidence of disease progression, treatment with another anticancer therapy, or withdrawal of consent. Long-term follow-up will continue for all subjects until death, withdrawal of consent, lost to follow-up, study termination by Sponsor, end of study, or other reason.

4.3.2 Discontinuation From the Study

Subjects may be discontinued from the study for any of the following reasons:

- Death
- Withdrawal of consent
- Lost to follow-up
- Study termination by Sponsor
- End of study
- Other

5. STUDY TREATMENTS

5.1 Treatments Administered

The planned dose levels of SBT6050 in this study are based on the initial results from the ongoing dose-escalation phase 1/1b clinical study Protocol SBT6050-101 (NCT04460456).

T-DXd dose levels are based on the approved doses for $HER2^{pos}$ breast cancer and gastric or GEJ cancer (ENHERTU 2021) and on clinical trial data for NSCLC and CRC. Tucatinib, trastuzumab, and capecitabine dose levels are based on approved doses for $HER2^{pos}$ breast cancer (TUKYSA 2020) and clinical trial data for CRC. See the national prescribing information (PI) for details.

Biosimilar or therapeutic equivalents of the drugs of the study drug (eg, trastuzumab) are acceptable.

In **Part 1**, the following treatments will be administered (see Figure 1):

- Subjects with breast cancer, CRC, and NSCLC:
    1. SBT6050 (0.3–0.6 mg/kg or RP2D) will be administered by SC injection on Day 1 of each 21-day cycle
    2. T-DXd (5.4 mg/kg) will be administered by IV infusion on Day 1 of each 21-day cycle
- Subjects with gastric/GEJ cancer:
    1. SBT6050 (0.3–0.6 mg/kg or RP2D) will be administered by SC injection on Day 1 of each 21-day cycle
    2. T-DXd (6.4 mg/kg) will be administered by IV infusion on Day 1 of each 21-day cycle

In **Part 2**, the following treatments will be administered to subjects with breast cancer and CRC (see Figure 1):

1. SBT6050 (0.3–0.6 mg/kg or RP2D) will be administered by SC injection on Day 1 of each 21-day cycle
2. Trastuzumab (8 mg/kg loading dose; 6 mg/kg subsequent cycles) will be administered by IV infusion on Day 1 of each 21-day cycle
3. Tucatinib (300 mg PO twice daily [BID]) starting on Day 1 of the first cycle and for the duration of study treatment
4. If applicable based on cohort enrollment: Capecitabine (1000 mg/m^2 PO BID) on Days 1–14 of each cycle

5.2 Investigational Product: SBT6050

Detailed information describing the preparation, administration, and storage of SBT6050 is provided in the Pharmacy Manual.

5.2.1 Description of SBT6050

[redacted]

5.2.2 Dose and Administration of SBT6050

SBT6050 will be administered via SC injection as a single dose administered every 21 days (every 3 weeks [Q3W]). SBT6050 should not be administered as an IV bolus or infusion. Refer to the Pharmacy Manual for detailed instructions regarding SC administration of SBT6050.

In both **Part 1 and Part 2**, during dose escalation, the starting dose of SBT6050 is 0.45 mg/kg and the next dose level is 0.6 mg/kg (Table 1).

In both **Part 1 and Part 2**, the SBT6050 RP2D for subjects during dose expansion will be determined based on safety, PK, pharmacodynamic, and clinical activity results from dose escalation.

Table 1: Recommended SBT6050 dose levels

Dose Level	SBT6050 Dose
-1	0.3 mg/kg
1	0.45 mg/kg
2	0.6 mg/kg

In the event a subject is unable to tolerate his/her dose level, additional treatment cycles (Cycle 2 or later) may be administered at a lower dose level upon approval by the medical monitor.

Dose administration should be performed at a clinical site properly equipped and staffed to manage anaphylaxis should it occur. Premedications should be administered prior to dosing of SBT6050 as outlined in Section 5.5.

All subjects should be observed at least 4 hours following Cycle 1 Dose 1. During this observation period, an IV line should remain open to allow administration of IV drugs if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use (see Section 5.5.2). All supportive measures consistent with optimal patient care should be provided throughout the study, according to institutional standards.

5.2.3 Storage and Handling of SBT6050

[redacted]

Refer to the Pharmacy Manual for further details regarding the storage and handling of SBT6050.

5.2.4 Packaging and Labeling of SBT6050

Each vial of SBT6050 will be labeled in compliance with applicable regulatory requirements. Refer to the Pharmacy Manual for information regarding packaging and labeling of SBT6050.

5.2.5 Preparation of SBT6050

Detailed drug preparation instructions for SBT6050 are provided in the Pharmacy Manual.

5.3 Part 1: SBT6050 Combined With Trastuzumab Deruxtecan

For subjects with breast cancer, CRC, or NSCLC, T-DXd will be administered at 5.4 mg/kg via IV infusion over 90 minutes (Cycle 1) or over 30 minutes (subsequent cycles) on Day 1 of every 21-day cycle.

For subjects with gastric/GEJ cancer, T-DXd will be administered at 6.4 mg/kg via IV infusion over 90 minutes (Cycle 1) or over 30 minutes (subsequent cycles) on Day 1 of every 21-day cycle.

T-DXd infusion should begin at least 15 minutes after the injection of SBT6050. Infusion rates may be slowed if the subject develops an infusion-related symptom (see Section 5.6.1).

T-DXd should be prepared, administered, and stored, per instructions in the currently approved regional labeling and under the direction of the Investigator (eg, ENHERTU® USPI).

5.4 Part 2: SBT6050 Combined With Tucatinib and Trastuzumab ± Capecitabine

Part 2 of the study includes tucatinib and trastuzumab with capecitabine (Part 2a) or without capecitabine (Part 2b). Tucatinib, trastuzumab and capecitabine will be supplied as described in the Pharmacy Manual.

5.4.1 Tucatinib

Tucatinib 300 mg PO BID will be taken by all Part 2 subjects starting on Cycle 1 Day 1 and for the duration of study treatment. Tucatinib should be taken after administration of SBT6050 and trastuzumab in the clinic on Cycle 1 Day 1. On Day 1 of each subsequent cycle, study staff should review tucatinib compliance from previous cycle.

Tucatinib should be prepared, administered, and stored per instructions in the currently approved regional labeling and under the direction of the Investigator (eg, TUKYSA® USPI). Per the labeling, tucatinib can be taken with or without food.

5.4.2 Trastuzumab

Trastuzumab 8mg/kg will be administered to all Part 2 subjects on Cycle1 Day 1 by IV infusion over 90 minutes.

Trastuzumab 6 mg/kg will be administered to all Part 2 subjects on Cycle 2 Day 1 and Day 1 of all subsequent cycles, by IV infusion over 30–90 minutes.

Trastuzumab infusion should begin at least 15 minutes after the injection of SBT6050. Infusion rates may be slowed if the subject develops an infusion-related symptom (see Section 5.6.1).

Trastuzumab should be stored, prepared, and administered per instructions in the currently approved regional labeling and under the direction of the Investigator (eg, HERCEPTIN® USPI).

5.4.3 Capecitabine

Capecitabine 1000 mg/m^2 PO BID will be taken by subjects in Part 2a of dose escalation and Cohort E of dose expansion, on Day 1–14 of each cycle. Capecitabine should be taken after administration of SBT6050 and trastuzumab in the clinic on Cycle 1 Day 1. On Day 1 of each subsequent cycle, study staff should review capecitabine compliance from previous cycle.

The dose administered may not exactly match the calculated dose because capecitabine is an oral drug available in fixed doses. Local institutional practices should be followed to determine rounding of capecitabine doses for administration. Documentation of both the calculated and administered dose should be captured.

Capecitabine should be prepared, administered, and stored per instructions in the currently approved regional labeling and under the direction of the Investigator (eg, XELODA® USPI). Per its labeling, it is recommended that capecitabine be taken within 30 minutes of a meal.

5.5 Concomitant Medications

5.5.1 Required Premedication and Postmedication

All subjects should receive the following prophylactic medications with each subsequent dose of SBT6050 after the first dose, if needed. Contraindications or other exceptions for individual subjects, including subjects who discontinue one of the study drugs, should be discussed with the medical monitor.

In **Part 1**, subjects are required to receive

- Ondansetron (or equivalent) 16 mg IV once at least 30 minutes prior to the dose of SBT6050 and then 8 mg PO every 8 hours as needed (PRN) for nausea and/or vomiting starting 8 hours after the prior dose of ondansetron
- Dexamethasone (or equivalent) 8 mg PO every day for 3 days, beginning the day prior to Day 1 of each cycle, on Day 1 of each cycle at least 30-60 minutes prior to SBT6050 dosing, and ending on Day 2 of each cycle

In **Part 2**, subjects are required to receive

- Dexamethasone (or equivalent) 8 mg PO on Day 1 of each cycle at least 30-60 minutes prior to SBT6050 dosing
- Ondansetron (or equivalent) 8 mg PO every 8 hours PRN for nausea and/or vomiting

All subjects are required to receive

- Acetaminophen (or equivalent) 650–1000 mg PO within approximately 1 hour prior to the dose, and then every 4-6 hours for 2 days post dose (not to exceed 3250 mg in 24 hours) and then as needed for pyrexia or pain
- An antihistamine, given within approximately 1 hour prior to each dose and then as needed, such as:
    - diphenhydramine 25–50 mg PO or IV
    - cetirizine 10 mg PO or IV, or
    - loratadine 10 mg PO
- Intravenous fluid supplementation as appropriate prior to each dose, and the day after each dose, per the Investigator's assessment, to prevent dehydration and hypotension
- Topical high-potency corticosteroid applied to the area 5-10 cm around the planned injection site, at least one hour and, optimally, up to 24 hours prior to the injection, such as:
    - clobetasol proprionate 0.05% cream
    - halobetasol proprionate 0.05% cream
    - betamethasone dipropionate 0.05% cream, or an equivalent

5.5.2 Recommended Supportive Medications

Supportive medications that may be useful for some subjects include the following, which may be given as needed, or as pre-medication based on the treating physician's medical judgement:

- Anti-nausea medications including 5-HT3 inhibitors such as
    - ondansetron 8 mg PO twice daily as needed for nausea
    - palonosetron 0.25 mg IV or 0.5 mg PO as a single dose, as needed for nausea
- Non-steroidal anti-inflammatory medication such as ibuprofen 400 mg PO every 4-6 hours or naproxen sodium 220 mg PO every 8-12 hours for pyrexia or pain
- Meperidine 25-50 mg IV as a single injection, as needed to treat shaking chills (rigors)
- Intravenous fluid, per institutional standards, to prevent dehydration
- Systemic corticosteroid as needed to treat ≥Grade 3 hypotension (not responding to IV fluid infusion), ≥Grade 3 hypoxia, or ≥Grade 2 CRS, such as
    - methylprednisolone 1 mg/kg IV or equivalent, given as a single dose
    - dexamethasone 8-12 mg IV/PO given as a single dose

5.5.3 Allowed Concomitant Therapy

Corticosteroids and other immunosuppressive therapies may be used to treat acute AEs; however, given that the mechanism of action of corticosteroids may interfere with SBT6050 activity, their use should be minimized in the context of best supportive care and carefully documented.

Non-systemic corticosteroids, including inhaled, topical, intranasal, intra-articular, and ophthalmic steroids are permitted.

All other concomitant medications, blood products, other non-drug therapies (eg, procedures), and radiotherapy administered will be recorded if new or ongoing from informed consent through the safety reporting period.

Standard supportive care medications will be permitted, including use of growth factors or blood product transfusions as required to treat AEs. Growth factors (eg, colony-stimulating factors or erythropoietin) should not be used prophylactically.

Subjects who are on a stable dose of luteinizing hormone-releasing hormone agonists for maintenance of postmenopausal endocrine state may continue therapy.

Supportive therapies for bone metastases, including bisphosphonates and RANK-ligand inhibitors (eg, denosumab) are allowed; however, initiation of these therapies during the first cycle of study treatment should be avoided to prevent confounding the assessment of safety.

Routine vaccination with inactivated, subunit, recombinant, polysaccharide, and conjugate vaccines are permitted but should not be administered within 5 days before or after SBT6050 and should be avoided during the first cycle of study treatment. Live attenuated viral vaccines such as the intranasal influenza vaccine are not permitted while on study drug.

Required premedication is described in Section 5.5.1. Other medication that is not specifically excluded will be allowed during the study to manage any subject clinical condition.

5.5.4 Prohibited Concomitant Therapy

Subjects requiring chronic immunosuppressive therapy at baseline (eg, requiring equivalent of >10 mg/day of prednisone) are not eligible for the study. Temporary immunosuppressive therapy (eg, corticosteroid premedication for imaging studies) should be completed at least 1 week prior to first dose of study treatment.

Anticancer agents (except study drugs), including chemotherapy, endocrine therapy (except as noted in Section 5.5.3), immunotherapy, and experimental therapies are prohibited. Palliative radiation therapy is generally not allowed but may be considered in select cases after discussion with the medical monitor.

In **Part 2**, subjects must avoid concomitant use of strong CYP3A inducers or moderate CYP2C inducers, strong CYP2C8 inhibitors, and CYP3A substrates; the Investigator should also consider reducing the dose of P-glycoprotein (P-gp) substrate drug (see Section 11.8). Additionally, subjects in **Part 2** must avoid using tanning lights and booths and should cover their skin and use sunscreen when in the sun (or exposed to UV radiation) as much as possible.

5.6 Dose Modifications

5.6.1 Dose Modifications for SBT6050 and T-DXd

In both **Part 1 and Part 2**, subjects who experience DLT during the DLT assessment period should not receive SBT6050 or T-DXd unless the toxicity resolves to Grade 1 or baseline, and the Investigator judges the subject may benefit from further therapy. Subsequent doses will be

defined by the medical monitor in discussion with the site Investigator in the context of the type of AE observed. In the event a subject is unable to tolerate their dose level, additional treatment cycles (Cycle 2 or later) may be administered at a lower dose level upon approval by the medical monitor.

Slow or interrupt the T-DXd infusion rate if the subject develops infusion-related symptoms. Permanently discontinue T-DXd in case of severe infusion-related reactions.

LVEF should be assessed prior to initiation of SBT6050 and at regular intervals (ie, every 12 weeks) during treatment. Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of T-DXd and SBT6050 as described in Table 1, Table 2, and Table 3.

Table 2: T-DXd dose reduction schedule

Dose reduction schedule	Dose level	Dose level
Recommended starting dose	5.4 mg/kg	6.4 mg/kg
First dose reduction (DL-1)	4.4 mg/kg	5.4 mg/kg
Second dose reduction (DL-2)	3.2 mg/kg	4.4 mg/kg
Requirement for further dose reduction	Discontinue treatment	Discontinue treatment

Table 3: Recommended dose modifications for SBT6050 and T-DXd

Adverse Reaction	Severity	Action to be taken for SBT6050	Action to be taken for T-DXd
Interstitial lung disease/pneumonitis	Grade 1 (asymptomatic)	Interrupt SBT6050 until resolved to Grade 0, then:	Interrupt T-DXd until resolved to Grade 0, then:
		• If resolved in 28 days or less from date of onset, maintain dose	
		• If resolved in greater than 28 days from date of onset, maintain SBT6050 dose (see Table 1)	• If resolved in greater than 28 days from date of onset, reduce T-DXd dose 1 level (see Table 2)
		• Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected	
	≥Grade 2 (symptomatic)	• Permanently discontinue SBT6050	• Permanently discontinue T-DXd
		• Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected	
Neutropenia	Grade 3	• Interrupt study treatment until resolved to ≤ Grade 2, then maintain dose	
	Grade 4	• Interrupt study treatment until resolved to ≤ Grade 2	
		• Maintain dose for SBT6050 (see Table 1)	• Reduce T-DXd dose 1 level (see Table 2)
Thrombocytopenia	Grade 3	• Interrupt study treatment until resolved to ≤ Grade 1, then maintain dose	
	Grade 4	• Interrupt study treatment until resolved to ≤ Grade 1	
		• Maintain SBT6050 dose (see Table 1)	• Reduce T-DXd dose 1 level (see Table 2)
LVEF	>45% AND absolute decrease from baseline is 10%–20%	• Continue treatment	

Adverse Reaction	Severity		Action to be taken for SBT6050	Action to be taken for T-DXd
	40%–45%	AND absolute decrease from baseline is <10%	• Continue treatment • Repeat LVEF assessment in 3 weeks	
		AND absolute decrease from baseline is 10%–20%	• Interrupt treatment • Repeat LVEF assessment in 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue treatment • If LVEF recovers to within 10% from baseline, resume treatment at the same dose level	
	<40% or absolute decrease from baseline is >20%		• Interrupt treatment • Repeat LVEF assessment in 3 weeks • If LVEF of <40% or absolute decrease of baseline of >20% is confirmed, permanently discontinue treatment	
	Symptomatic congestive heart failure		• Permanently discontinue treatment	
Other adverse events	Grade 3		• Hold SBT6050 until recovery to ≤ Grade 1, then resume SBT6050 at the same or reduced dose level if related to SBT6050 as per the Investigator.	Hold T-DXd until recovery to ≤ Grade 1, then resume SBT6050 at the same or reduced dose level if related to T-DXd as per the Investigator.
	Grade 4		Permanently discontinue SBT6050.	Permanently discontinue T-DXd.

Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v.4.03).

Refer to the currently approved regional labeling (eg, ENHERTU® USPI) for T-DXd-related dose modifications.

Subsequent doses of SBT6050 should be held for ≥Grade 3 AEs or toxicities until resolved to Grade 1 or baseline. Doses of study drugs may be held for toxicity for up 21 days; delays of >21 days must be discussed with the medical monitor.

5.6.2 Dose Modifications for Tucatinib plus Trastuzumab ± Capecitabine

Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of SBT6050, tucatinib-, trastuzumab-, and capecitabine (if applicable)-related dose modifications as described in Table 1, Table 4, and Table 5.

Table 4: Tucatinib dose reduction schedule

Dose reduction schedule	Tucatinib dosing
Recommended starting dose	300 mg orally twice daily
First dose reduction (DL-1)	250 mg orally twice daily
Second dose reduction (DL-2)	200 mg orally twice daily
Third dose reduction (DL-3)	150 mg orally twice daily

Table 5: Recommended dose modifications for SBT6050, tucatinib, trastuzumab, and capecitabine

Adverse Reaction	Severity		Action to be Taken With SBT6050	Action to be Taken With Tucatinib	Action to be Taken With Trastuzumab	Action to be Taken With Capecitabine
LVEF	>45% AND absolute decrease from baseline is 10%–20%		• Continue treatment			
	40%–45%	AND absolute decrease from baseline is <10%	• Continue treatment • Repeat LVEF assessment in 3 weeks			
		AND absolute decrease from baseline is 10%–20%	• Interrupt treatment • Repeat LVEF assessment in 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue treatment • If LVEF recovers to within 10% from baseline, resume treatment at the same dose level			
	<40% or absolute decrease from baseline is >20%		• Interrupt treatment • Repeat LVEF assessment in 3 weeks • If LVEF of <40% or absolute decrease of baseline of >20% is confirmed, permanently discontinue treatment			
	Symptomatic congestive heart failure		• Permanently discontinue treatment			
Diarrhea	Grade 3 (without anti-diarrheal treatment)		• Initiate or intensify appropriate medical therapy. Hold treatment until recovery to ≤Grade 1, then resume treatment at the same dose level			
	Grade 3 (with anti-diarrheal treatment)		• Initiate or intensify appropriate medical therapy. Hold SBT6050 until recovery to ≤ Grade 1, then resume SBT6050 at the same dose level	• Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level	• Initiate or intensify appropriate medical therapy. Hold treatment until recovery to ≤ Grade 1, then resume treatment at the same dose level	

Adverse Reaction	Severity	Action to be Taken With SBT6050	Action to be Taken With Tucatinib	Action to be Taken With Trastuzumab	Action to be Taken With Capecitabine
	Grade 4	• Permanently discontinue treatment			
Hepatotoxicity	Grade 2 bilirubin	• Hold treatment until recovery to ≤ Grade 1, then resume treatment at the same dose level.			
	Grade 3 ALT or AST, OR Grade 3 bilirubin	• Hold SBT6050 until recovery to ≤ Grade 1, then resume SBT6050 at the same dose level.	• Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level.	• Hold treatment until recovery to ≤ Grade 1, then resume treatment at the same dose level.	
	Grade 4 ALT or AST OR Grade 4 bilirubin	• Hold SBT6050 until recovery to ≤ Grade 1, then resume SBT6050 at the same or reduced dose level if related to SBT 6050 as per Investigator	• Permanently discontinue tucatinib, regardless of relationship.	• Hold trastuzumab until recovery to ≤ Grade 1, then resume treatment at the same dose level.	• Hold capecitabine until recovery to ≤ Grade 1, then resume capecitabine at the same or reduced dose level as per Investigator
	ALT or AST >3xULN AND bilirubin >2xULN	• Permanently discontinue treatment.			
Other adverse events	Grade 3	• Hold SBT6050 until recovery to ≤ Grade 1, then resume SBT6050 at the same or reduced dose level if related to SBT 6050 as per Investigator.	• Hold tucatinib until recovery to ≤ Grade 1, then resume tucatinib at the next lower dose level if related to tucatinib as per Investigator.	• Hold trastuzumab until recovery to ≤ Grade 1, then resume trastuzumab at same or reduced dose level if related to trastuzumab as per Investigator.	• Hold capecitabine until recovery to ≤ Grade 1, then resume capecitabine at reduced dose level if related to capecitabine as per Investigator
	Grade 4	• Permanently discontinue treatment.			

ULN=upper limit of normal
Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v.4.03)

Refer to the currently approved regional labeling (eg, TUKYSA® USPI) for additional tucatinib-, trastuzumab-, and capecitabine (if applicable)-related dose modifications.

Subsequent doses of SBT6050 should be held for ≥ Grade 3 AEs or toxicities until resolved to Grade 1 or baseline. Doses of study drugs may be held for toxicity for up to 21 days; delays of >21 days must be discussed with the medical monitor.

5.7 Management of Overdose

Overdose is defined as the administration of a quantity of study drug given per administration or cumulatively that is above the maximum dose according to the protocol. Overdoses will be collected as part of investigational product dosing information and/or as a protocol violation, as required. Any AE associated with an overdose should be recorded on the AE eCRF with the diagnosis of the AE.

5.8 Treatment Compliance

Data regarding the administration and dose of T-DXd and trastuzumab, as well as the number of tablets of tucatinib and capecitabine taken will also be collected by the site after each cycle. Dose modifications and interruptions of any study drug will be documented in the source documents and the electronic case report form (eCRF).

5.9 Study Drug Accountability

SBT6050 used during the course of the study should be handled according to the Pharmacy Manual. Accountability for SBT6050 at the study site is the responsibility of the Investigator. The Investigator will ensure that SBT6050 is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a licensed pharmacist or other appropriate individual. SBT6050 will be tracked and documented from the time of receipt at the site, through subject dosing, until the Sponsor approves of the final return or destruction.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to the Sponsor or its designee (or disposal of the drug, if approved by the Sponsor). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from the Sponsor. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during site visits.

Sites will also be required to provide accountability for administration of T-DXd, trastuzumab, tucatinib and capecitabine for entry into the eCRF.

All unused and used study drug should be handled according to the Sponsor's instructions in the Pharmacy Manual.

6. STUDY ASSESSMENTS AND PROCEDURES

The study assessments and procedures will be performed at the time points provided in the Schedule of Assessments (Section 11.1 and Section 11.2). Blood and serum samples will be collected, processed, and stored based on procedures presented in the Laboratory Manual.

6.1 Screening/Baseline Procedures

The following will be collected or performed at screening/baseline:

- Informed consent (see Section 9.1).
- Study eligibility per inclusion/exclusion criteria (see Section 4.1 and Section 4.2). Only subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in this study.
- Confirmation of HER2-expressing cancer (HER2 2+ or 3+ by IHC) and/or HER2-amplified cancer as determined by in situ hybridization (ISH) or molecular profiling from a CLIA-certified (or local equivalent) laboratory. The most recent results should be used.
    - If documentation of a previous HER2 result is not available, archived tumor tissue (formalin-fixed and paraffin-embedded [FFPE] block or slides), or fresh tumor tissue, or a blood sample for molecular profiling must be submitted to confirm HER2 expression by either a local laboratory or a Sponsor-designated central laboratory prior to enrollment. Confirmatory HER2 testing may be obtained more than 28 days prior to Screening/Baseline if a separate consent for confirmatory HER2 pre-testing is signed.
- [redacted]
- Medical history, which includes a thorough review of relevant past medical history, current medical conditions, type of underlying malignancy, any treatment for prior malignancies and response to prior treatment.
- Urine sample for urinalysis. Urinalysis analytes will include dipstick for pH, glucose, blood, protein, ketones, and bilirubin. If there is a clinically significant positive result (ie, confirmed by a positive repeated sample), urine samples will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick result (eg, menses), then microscopy and culture need not to be performed but the reason should be documented.
- Blood samples for the following:
    - Hepatitis B, hepatitis C, and HIV screening; only subjects with negative results for hepatitis B virus (HBV), HCV, and HIV will be eligible for the study (see Section 4.2 for specific requirements). Note: for hepatitis C, only the RNA PCR test will be acceptable (eg, the antibody test is not acceptable).
    - Thyroid panel, which will include tri-iodothyronine (T3) or free tri-iodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

    - Coagulation panel, which will include PT/international normalized ratio (INR) and PTT (or, depending on institutional standard, aPTT).
    - Genomic DNA. If this sample is not collected during Screening, it can be obtained during any future clinical visit.
    - Peripheral blood for PK and biomarker analyses (see Section 6.4.2)
    - Hematology and chemistry panels
- Baseline tumor assessment by computed tomography (CT), positron emission tomography (PET)/CT (if diagnostic-quality CT scan included) or MRI of chest, abdomen, and pelvis, as well as other appropriate imaging of known sites of disease (eg, bone scan).
- A brain MRI is required at baseline for all subjects with breast cancer or NSCLC, or subjects with gastric/GEJ cancer or CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis.
- Physical examination (including height and weight)
- Pregnancy test for subjects of childbearing potential
- Vital sign measurements, which include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is either seated or supine.
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO)/multi-gated acquisition (MUGA) scan
- ECOG performance status
- Saturated oxygen (SpO^2) levels by pulse oximetry
- Collection of prior and concomitant medications and AEs

6.2 Efficacy Measurements

Tumor response will be evaluated as specified in the Schedule of Assessments (Section 11.1 and Section 11.2) using radiographic evidence of progressive disease according to RECIST Version 1.1 using unidimensional measurement such as CT, PET/CT scan (if diagnostic-quality CT scan included), or MRI. At a minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (eg, bone scan or MRI in case of previously documented brain metastases).

Subjects who experience an objective response (ie, tumor reduction) should have a confirmatory assessment performed approximately 4 weeks after the initial response.

6.3 Pharmacokinetic Measurements

Blood samples for measurements of SBT6050, tAb, and free payload (S-00193) will be collected at time points specified in the Schedule of Assessments (Section 11.1 and Section 11.2). Samples will be collected, processed, and stored based on procedures presented in the Laboratory Manual.

Collection of samples for PK assessments will not be required for subjects who discontinue SBT6050 and continue treatment with the combination therapy only.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4.4 Immunogenicity Measurements

Serum samples will be analyzed for the presence of ADA using a validated method.

[redacted]

[redacted]

[redacted]

6.6 Safety Assessments on Cycle 1, Day 1 and Beyond

Safety assessments will be collected at protocol-specified timepoints in the Schedule of Assessments (Section 11.1 and Section 11.2).

6.6.1 Physical Examination

The physical examination will include assessment of the head, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes, extremities, and weight. Height will be collected at the Baseline visit only.

6.6.2 Pregnancy Testing

Subjects of childbearing potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Pregnancy tests may also be repeated as requested per institutional review board (IRB)/independent ethics committee (IEC) or if required by local regulations.

6.6.3 Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is either seated or supine.

6.6.4 12-Lead Electrocardiogram

A single 12-lead ECG will be obtained following 3 minutes of recumbency or semi recumbency. Any clinically significant ECG finding should be evaluated by a cardiologist.

6.6.5 Echocardiogram or Multigated Acquisition Scan

An ECHO or MUGA scan will be obtained every 12 weeks as determined from Cycle 1 Day 1 to assess the subject's cardiac function and to identify any structural abnormalities. For comparison, the testing modality used in screening should be used for all subsequent cardiac assessments throughout the study.

6.6.6 Eastern Cooperative Oncology Group Performance Status

The ECOG performance status scales are used to assess how a subject's disease is progressing and assess how the disease affects the activity of daily living of the subject. The ECOG performance status scales are available in Section 11.5.

6.6.7 Oxygen Saturation

Oxygen saturation (SpO^2) will be obtained to assess the subjects' amount of oxygen in blood hemoglobin and to identify hypoxemia and/or hypoxia.

6.6.8 Clinical Laboratory Tests

Blood and urine samples will be collected and processed according to the instructions from the local laboratories. Samples will be reported by the local laboratories against their normal reference ranges.

Hematology analytes will include erythrocytes, hemoglobin, hematocrit, platelets, leucocytes and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes, as percentages and absolute values, if available). Analyses for complete blood count, white blood cell differential, and reticulocyte count will also be performed.

Clinical chemistry analytes will include: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, calcium, phosphate, magnesium, creatinine, total protein, albumin, glucose, total and direct bilirubin, amylase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, γ-glutamyl transferase, lipase, triglycerides, thyroid-stimulating hormone, and troponin. Creatinine clearance will be calculated using the Cockcroft-Gault formula.

Cholesterol (total, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol) is only required at baseline.

[redacted]

6.7 Long-term Follow-up (Every 3 Months After 30-day Follow-up Visit)

Approximately every 3 months after the 30-day follow-up visit, subjects will be followed for survival, disease status, and subsequent anticancer therapies until death, withdrawal of consent, lost to follow-up, study termination by Sponsor, or 1 year after the last dose of study treatment has been administered to the last subject. Reasonable efforts should be made to follow subjects who are lost to follow-up either by direct contact or collecting public records (eg, death certificates) as allowed by local and/or regional laws.

6.8 End of Study/End of Follow-up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded.

6.9 Adverse Events

Monitoring of AEs will be conducted throughout the study. Adverse events will be recorded in the eCRF from time of signing informed consent through 30 days after the last dose of study drug (SBT6050, T-DXd, tucatinib, trastuzumab, or capecitabine).

All SAEs will be recorded in the eCRF from the initiation of study drug through 30 days after the last dose of study drug (SBT6050, T-DXd, tucatinib, trastuzumab, or capecitabine). If an SAE occurs between the time of signing informed consent but prior to the initiation of study drug, it should only be recorded in the eCRF if caused by a protocol-mandated intervention.

In addition, SAEs that are assessed as related to study treatment that occur >30 days after the last dose of study treatment are also to be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

6.9.1 Definitions

Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), clinically significant ECG change, symptom, complications that occur as a result of protocol-mandated procedures, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (eg, off label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse Event Severity

Severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI CTCAE Version 5.0 (see Section 11.3). Adverse events not listed by the CTCAE will be graded as follows:

- Mild: The event is noticeable to the subject but does not interfere with routine activity.
- Moderate: The event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: The event significantly limits the subject's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: An event in which the subject was at risk of death at the time of the event.
- Fatal: An event that results in the death of the subject.

Relationship of the Adverse Event to Study Treatment

Relationship to study drug administration will be determined by the Investigator according to the criteria listed below. Where study treatment is a combination therapy, assessment of causality should be to each individual product administered as part of the regimen as follows:

- Not Related: Exposure to the study treatment did not occur, or the occurrence of the AE is not reasonably related in time, or the AE is considered unlikely to be related to the study treatment.
- Related: A clinical event occurs in a plausible time relationship to treatment administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of nontreatment-related factors that are known to be associated with the occurrence of the event.

Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.

Unexpected Adverse Event

An unexpected AE is one for which the nature or severity of the event is not consistent with the applicable product reference safety information (eg, the Investigator's Brochure).

Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the opinion of either the Investigator or Sponsor, it results in any of the following:

- Death (ie, the AE actually causes or leads to death).
- Life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalizations solely for the purpose of receiving supportive care treatment, observation following dosing, or hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did

not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment by the Investigator or the Sponsor, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

6.9.2 Procedures for Eliciting and Recording Adverse Events

Each subject must be carefully monitored for the development of any AEs. This information should be obtained in the form of nonleading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from subjects.

Eliciting Adverse Events

All AEs (serious and nonserious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF.

Any clinically relevant deterioration in laboratory assessments (see Section 6.9.2) for capturing abnormal laboratory findings as AEs) or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event except for AEs associated with study treatment administration (see Section 6.9.4).

Recording Adverse Events

All AEs, whether serious or not, will be described in the source documents and on the AE page of the eCRF. All new events that occur after signing the informed consent, including those that worsen in severity or frequency relative to baseline, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 30-day follow up visit. Serious adverse events felt by the Investigator to be related to study treatment, however, must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 30 days after the last dose of study treatment.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded).
- The date and time of onset of the event.
- The date and time of resolution of the event.
- Whether the event is serious or not.
- Severity of the event (see below for definitions).
- Relationship of the event to study treatment (see below for definitions).
- Action taken with study treatment: dose not changed; dose reduced; drug interrupted; drug withdrawn; not applicable (eg, AE occurred prior to the first dose of study medication; unknown; information in the medical record should include drug treatment and non-drug treatment and diagnostic procedures performed related to the event, if applicable.
- Outcome: not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; recovering/resolving; died; unknown.
- The subject was discontinued from study treatment due to the AE
- Treatment was administered
- The event met the criteria of a DLT

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF and avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field on the AE eCRF.

Recording Serious Adverse Events

All SAEs and follow-up to previously reported SAEs that occur during the study must be promptly reported by the Investigator. Deaths and AEs assessed as life-threatening are to be reported immediately and SAEs that meet other criteria are to be reported within 24 hours from the time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not they are considered causally related to study treatment (SBT6050, T-DXd, tucatinib, trastuzumab, and/or capecitabine). Serious adverse event forms will be completed, and the information collected will include subject number, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relationship to study drug. Follow-up information on the SAE may be requested by the Sponsor or medical monitor.

If there are serious, unexpected adverse drug reactions associated with the use of study treatment, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. The local institutional review board/independent ethics committee (IRB/IEC) will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected adverse drug reactions involving risk to human subjects.

Progression of the Underlying Cancer

Disease progression or death due to the primary disease under study should not be reported as an AE (or an SAE) if clearly consistent with the suspected progression of the underlying cancer as

defined by RECIST Version 1.1 (see Section 11.4); however, disease progression or death will be collected as an outcome or reason for discontinuation, as appropriate. Adverse events (or SAEs) considered to be complications of disease progression should be reported.

Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the subject's underlying disease or does not fit the expected pattern of progression for the disease. The specific disease or clinical manifestation of the progression (eg, malignant pleural effusion, spinal bone metastases, lymphadenopathy from underlying malignancy, brain metastases) should be recorded.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Adverse Events Associated with SBT6050 Administration

For AEs suspected to be associated with the study drug, each sign and symptom should be recorded as an individual AE (including in instances where multiple signs or symptoms occur). If signs and symptoms are consistent with a specific syndrome (eg, "cytokine release syndrome"), this should be reported in addition to individual signs and symptoms.

6.9.3 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (eg, dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

If a clinically significant laboratory abnormality is a sign of a disease (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), record only the diagnosis (ie, cholecystitis), if known, on the AE eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating if the test result is above or below the normal range.

Pregnancy

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (eg, spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or partner of a male subject occurring while the subject is on study treatment, or within 30 days of the subject's last dose of study treatment, are considered immediately reportable events. If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female subjects, study treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately using the Pregnancy Report form. The Investigator must follow-up and document the course and outcome of all pregnancies even if the subject was discontinued from the study or if the subject has completed the study. The female subject or partner of a male subject should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female subject or the sexual partner of a male subject) must be reported by the Investigator to the Sponsor or medical monitor on a Pregnancy Outcome Report form within 30 days after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

6.9.4 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 30 days after the last dose of study treatment. However, all AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the Investigator should also be reported to the Sponsor.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the Investigator, or the subject dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

6.9.5 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, Investigators are to report the event to the Sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

The completed SAE form is to be emailed or faxed to the Sponsor within 24 hours (see email or fax number specified on the SAE form), unless otherwise instructed on the Sponsor's SAE form.

Relevant follow-up information is to be submitted to the Sponsor as soon as it becomes available.

6.9.6 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the Sponsor (see Section 6.9.5). The Sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local legislation or regulatory reporting requirements.

6.10 Appropriateness of Measurements

The safety measures that will be used in this research study are considered standard procedures for evaluating the potential adverse effects of study medications.

Efficacy endpoints in this study are recommended by FDA (FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics") for approval of anticancer drugs. Response will be assessed according to RECIST Version 1.1, which are standardized criteria for evaluating response and progression in the disease(s) under study. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity (ADA) is commonly assessed for biologic therapeutics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to SBT6050. PK assessments are also common in clinical studies to help characterize dose level-exposure-response relationships.

[redacted]

7. DATA QUALITY CONTROL AND QUALITY ASSURANCE

7.1 Site Training and Monitoring Procedures

The study will be conducted in accordance with GCP, ICH guidelines, and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol, Investigator's Brochure, and pharmacy manual. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

The study will be monitored by the Sponsor or its designee. Monitoring will be done virtually or on site by the Sponsor or designee and will include review of the source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, e-mail, and fax).

All unused study drug and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed, as directed by the Sponsor.

7.2 Data Management Procedures

Source documents and eCRFs will be completed for each study subject, including subjects who provide informed consent but do not meet study eligibility. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source documents and eCRF. The source document and eCRF should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be provided for all missing data.

Paper and digital source documents are to be retained to enable reconstruction and evaluation of the clinical study. Source documents include the hospital subject files and any study-related worksheets provided by the Sponsor.

The Investigator must sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

7.3 Access to Source Data

Regulatory authorities, the IEC/IRB, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for

an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

7.4 Accuracy and Reliability of Data

To assure the accuracy and reliability of data, steps to be taken include:

- The selection of qualified Investigators and appropriate study sites/centers.
- Review of protocol procedures with Investigators and associated personnel prior to the study.
- Periodic monitoring visits by designated monitor(s) (see Section 7.1).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study sites/centers. Any discrepancies will be resolved with the Investigator or designees as appropriate.

7.5 Quality Assurance Procedures

The Sponsor or its designee may conduct audits at the clinical site/center or other study-related facilities and organizations. Audit reports will be retained by the Sponsor as part of the written record.

7.6 Data Handling and Record Keeping

7.6.1 Data Handling

All data for the subjects recruited for the trial will be entered onto the eCRFs via an electronic data capture (EDC) system provided by the Sponsor or designee. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Electronic CRFs (eCRFs) will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Data entry will be reviewed with programmed logic checks and electronic data queries will be generated to verify potential discrepancies in the eCRF system. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

7.6.2 Investigator Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

8. STATISTICAL CONSIDERATIONS

A brief description of key analyses is provided below; a full description of the statistical evaluations, general considerations, and procedures for handling missing data will be provided in the Statistical Analysis Plan (SAP). All analyses will be performed by cohort within each part (dose escalation and dose expansion).

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (eg, adding safety assessments to further define the course of TEAEs). The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

8.1 Determination of Sample Size

Up to approximately 328 subjects will be enrolled across this 2-part study as described in Section 3.1 and presented in Figure 1 (approximately 12 subjects in each of the four dose-escalation plans and approximately 40 subjects in each of the seven expansion cohorts). The expansion cohort sample size is consistent with FDA Guidance for Industry, Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics, 2018. Accessed: Aug 19, 2021.

During dose expansion in both Part 1 and Part 2, for each tumor-specific cohort, the ORR along with the corresponding two-sided 80% confidence intervals will be evaluated to assess proof-of-concept for SBT6050 when combined with two dose levels of T-DXd (**Part 1**) or tucatinib and trastuzumab ± capecitabine (**Part 2**). Other signs of potential activity, including duration of response and clinical benefit rate (CBR), as well as the overall benefit/risk will also be factored into the final efficacy conclusions. Because the study is evaluating SBT6050 in combination with approved therapies, no early futility analyses are planned.

Table 6 provides the ORR estimates that must be observed in each tumor-specific cohort in **Part 1** so that the lower 80% confidence bound will rule out the response rate associated with T-DXd alone. For each cohort, the power to observe the ORR estimate is also shown under a 15% absolute improvement in ORR for SBT6050 with T-DXd relative to the historical ORR for T-DXd

Table 6: Historical and target ORR estimates with associated precision and power calculations under varying response probabilities for SBT6050 combined with T-DXd

Cohort	Historical ORR for T-DXd alone (p0)	SBT6050 with T-DXd ORR (p1)	Lower CI bound approximately above p0	Power under assumed true SBT6050 with T-DXd ORR (π1)	
				π1[a]	Power
Cohort A (HER2$^+$ BC)	61% (Modi 2020)	29/40 (73%)	80% CI: (62%, 82%)	76%	76%
Cohort B (HER2$^+$ CRC)	45.3% (Yoshino 2021)	23/40 (58%)	80% CI: (46%, 68%)	60%	69%
Cohort C (HER2-expressing NSCLC)	24.5% (Nakagawa 2020)	14/40 (35%)	80% CI: (25%, 46%)	40%	79%
Cohort D (HER2$^+$ gastric/GEJ cancer)	38% (van Cutsem 2021)	20/40 (50%)	80% CI: (39%, 61%)	53%	71%

CI = confidence interval; CRC = colorectal cancer; BC = breast cancer; GEJ = gastroesophageal junction; NSCLC = non-small-cell lung cancer; ORR = objective response rate; T-DXd = trastuzumab deruxtecan
[a]True SBT6050 with T-DXd ORR is assumed to be 15% greater than historical ORR for T-DXd alone (absolute difference).

Table 7 provides the ORR estimates that must be observed in each dose expansion cohort in (**Part 2**) so that the lower 80% confidence bound will rule out the response rate associated with tucatinib and trastuzumab ± capecitabine. For each cohort, the power to observe the ORR estimate is also shown under a 15% absolute improvement in ORR for the SBT6050 combination regimen relative to the historical ORR for the backbone regimen.

Table 7: Historical and target ORR estimates with associated precision and power calculations under varying response probabilities for SBT6050 combined with tucatinib and trastuzumab ± capecitabine

Cohort	Historical ORR for tucatinib and trastuzumab + capecitabine (p0)	Historical ORR for tucatinib and trastuzumab (p0)	SBT6050 with T-DXd ORR (p1)	Lower CI bound approximately above p0	Power under assumed true SBT6050 with tucatinib and trastuzumab ± capecitabine ORR (π1)	
					π1[a]	Power
Cohort E (HER2$^+$ BC)	41% (Murthy 2020)	N/A	21/40 (53%)	80% CI: (41%, 64%)	56%	73%
Cohort F (HER2$^+$ BC)	N/A	40%	21/40 (53%)	80% CI: (41%, 64%)	55%	68%
Cohort G (HER2$^+$ CRC)	N/A	52%	26/40 (65%)	80% CI: (54%, 75%)	67%	67%

CI = confidence interval; CRC = colorectal cancer; BC = breast cancer; N/A = not applicable
[a]True SBT6050 combined with tucatinib and trastuzumab ± capecitabine ORR is assumed to be 15% greater than historical ORR for tucatinib and trastuzumab ± capecitabine (absolute difference).

8.2 Analysis Populations

The following subject populations will be analyzed:

- Enrolled population: all subjects who sign informed consent
- All-Treated population: all subjects who receive at least one dose of study treatment
- PK-Evaluable population: all subjects who receive at least one dose of study treatment and have concentration-time data available
- DLT-Evaluable population: all subjects who receive at least one dose of study treatment and have completed the 21-day DLT evaluation period or discontinue study drug due to AEs meeting DLT criteria.
- Efficacy-Evaluable population: all subjects who receive at least 1 dose of the study treatment and have an evaluable baseline and post baseline response assessment per RECIST Version 1.1 or who discontinue prior to disease assessment due to clinical progression of disease.
- Per Protocol population (for sensitivity analysis only): all subjects who receive at least one dose of study treatment, have an evaluable baseline and post baseline response assessment per RECIST Version 1.1, and have no major protocol deviations that would exclude them from the population

Additional analysis sets of subjects may be defined in the SAP.

8.3 Efficacy Analyses

All efficacy analyses will be performed for all treated subjects by cohort. Summary analyses will be performed in subjects treated at the RP2D for the given cohort; listings will be produced for subjects treated at other dose levels.

8.3.1 Dose Expansion Cohorts

ORR is defined as the proportion of treated subjects who achieve a best response of CR or PR. To evaluate proof-of-concept for an efficacy signal, a two-sided 80% exact CI as well as a 95% exact CI will be calculated for ORR using the Clopper-Pearson method. Best response will be summarized by response category.

CBR is defined as the proportion of treated subjects who achieve a best response of CR or PR or have a best response of SD with a duration of ≥ 6 months from initiation of study treatment. CBR will also contribute to evaluation of efficacy proof-of-concept. A two-sided 80% exact CI as well as a 95% exact CI will be calculated for CBR using the Clopper-Pearson method.

PFS is defined as the time from the first dose of study therapy to the date of documented progression or death, whichever occurs first. Subjects who are alive and progression-free will be censored on the date of last evaluable efficacy assessment. Subjects who receive subsequent anti-cancer therapy prior to documented progression will be censored on the date of the last evaluable efficacy assessment on or prior to the subsequent anti-cancer therapy start date.

OS is defined as the time from first dose of study therapy to the date of death due to any cause. Subjects who are alive will be censored on the date of last contact.

DOR is measured from the time of initial response until documented tumor progression or death, whichever occurs first. Subjects who are alive and progression-free will be censored on the date of last evaluable efficacy assessment. Subjects who receive subsequent anti-cancer therapy prior to documented progression will be censored on the date of the last evaluable efficacy assessment on or prior to the subsequent anti-cancer therapy start date.

DOR, PFS, and OS will be estimated using the Kaplan-Meier (KM) product limit method. For subjects treated at the RP2D for a given cohort, the KM estimate of the medians for each of these endpoints will be reported, and the corresponding 95% CI will be computed using Brookmeyer and Crowley's method (log-log transformation). KM estimates of PFS and OS rates at milestone time points will be reported along with two-sided 95% CIs using Greenwood's formula, provided the minimum follow-up in subjects exceeds the time point to support stable estimation of the rate.

8.4 Safety Analyses

Safety evaluations will be based on the incidence, intensity, and type of TEAE or SAE, as well as changes in safety assessments. DLTs will be summarized by dose level in dose escalation phase and identified in listings; TEAEs leading to treatment discontinuation will be summarized in both the dose escalation and dose expansion phases of the study.

Safety outcomes including TEAEs and laboratory evaluations will be summarized using descriptive statistics for all subjects who received at least one dose of study therapy. AEs will be assessed for severity according to the CTCAE Version 5.0 (see Section 11.3); verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization.

8.5 Pharmacokinetic Analyses

Extensive PK sampling will be done to appropriately characterize the PK of SBT6050, tAb, and S-00193. Standard noncompartmental PK method will be used to calculate PK parameters. All estimated PK parameters will be summarized with mean, geometric mean, standard error of the mean, standard deviation, coefficient of variation (CV), and geometric mean CV, as data permit.

[redacted]

8.7 Timing of Analysis

There are no formal interim analyses planned for this study.

The SMC will review available data following the DLT evaluation period for each dose escalation cohort and recommend the RP2D selection.

A given expansion cohort will be reviewed when approximately 40 subjects have received at least one dose of study therapy and have at least one post-baseline efficacy evaluation. The Sponsor will assess whether the efficacy and safety data support proof-of-concept for the cohort. The Sponsor may also periodically evaluate available data during the expansion enrollment.

A primary analysis for the study may be conducted after a minimum follow-up of 4 months after the last subject's first visit or when the last subject has progressed, whichever occurs sooner among the last dose expansion cohort to fully enroll. The primary analysis will be the basis for the CSR.

Subjects may continue to be followed for long-term efficacy and safety after the primary analysis. In this case, the final analysis will be conducted at the end of the trial and will be summarized in a CSR addendum.

8.7.1 Interim Analyses

During dose escalation in Part 1 and Part 2, an SMC will convene periodically during the study to monitor the trial for safety. An ongoing review of SAEs in both parts of the study and all cohorts will also be conducted by the Sponsor.

Because no formal statistical inference is planned, adjustment to type 1 error is not required.

9. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6(R2), Good Clinical Practice: Integrated addendum to ICH E6(R1), 2018. Accessed: Aug 19, 2021; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2003), and all applicable regulatory requirements.

9.1 Informed Consent

The Investigator at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation.

The subject's signed and dated informed consent must be obtained before conducting any study related procedures. The Investigator must maintain the original, signed consent form. A copy of the signed form must be given to the subject.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

9.2 Ethical Review

The Investigator must obtain the IRB/IEC approval for the investigation and must submit written documentation of the approval to the Sponsor before he or she can enroll any subject into the study. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and wellbeing of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions are to be provided to the IRB/IEC according to local regulations and guidelines.

9.3 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

9.3.1 Investigator Information

The contact information and qualifications of the principal Investigator and subinvestigators and the name and address of the research facilities are included in the Investigator file.

9.3.2 Protocol Amendments and Study Termination

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

Any Investigator-initiated changes to the protocol (except for changes to eliminate an immediate hazard to a study subject) must be approved by the Sponsor prior to seeking approval from the IRB/IEC and prior to implementation. Any departures from the protocol must be fully documented in the source documents/eCRF.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

9.4 Study Documentation, Privacy, and Records Retention

To maintain subject privacy, all source documents/eCRFs, study drug accountability records, study reports and communications will identify the subject by the assigned Subject Number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

All information regarding SBT6050 supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without written consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of SBT6050 and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

Details regarding payments by the Sponsor to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical study agreement.

10. REFERENCES

Arcila, M. E., J. E. Chaft, K. Nafa, S. Roy-Chowdhuri, C. Lau, M. Zaidinski, P. K. Paik, M. F. Zakowski, M. G. Kris, and M. Ladanyi. 2012. 'Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas', *Clin Cancer Res*, 18: 4910-8.

Astrazeneca. 2021. 'Enhertu significantly improved progression-free survival in destiny-breast03 head-to-head trial vs. Trastuzumab emtansine (t-dm1) in patients with her2-positive metastatic breast cancer.', *Press Release. https://www.astrazeneca.com/media-centre/press-releases/2021/enhertu-head-to-head-trial-meets-primary-endpoint.html*.

Bang, Y. J., E. Van Cutsem, A. Feyereislova, H. C. Chung, L. Shen, A. Sawaki, F. Lordick, A. Ohtsu, Y. Omuro, T. Satoh, G. Aprile, E. Kulikov, J. Hill, M. Lehle, J. Ruschoff, Y. K. Kang, and G. A. Trial Investigators To. 2010. 'Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial', *Lancet*, 376: 687-97.

Baselga, J., J. Cortes, S. B. Kim, S. A. Im, R. Hegg, Y. H. Im, L. Roman, J. L. Pedrini, T. Pienkowski, A. Knott, E. Clark, M. C. Benyunes, G. Ross, S. M. Swain, and Cleopatra Study Group. 2012. 'Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer', *N Engl J Med*, 366: 109-19.

Beretta, G. D., F. Petrelli, S. Stinco, M. Cabiddu, M. Ghilardi, M. Squadroni, K. Borgonovo, and S. Barni. 2013. 'FOLFIRI + bevacizumab as second-line therapy for metastatic colorectal cancer pretreated with oxaliplatin: a pooled analysis of published trials', *Med Oncol*, 30: 486.

Doi, T., K. Shitara, Y. Naito, A. Shimomura, Y. Fujiwara, K. Yonemori, C. Shimizu, T. Shimoi, Y. Kuboki, N. Matsubara, A. Kitano, T. Jikoh, C. Lee, Y. Fujisaki, Y. Ogitani, A. Yver, and K. Tamura. 2017. 'Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study', *Lancet Oncol*, 18: 1512-22.

Eisenhauer, E. A., P. Therasse, J. Bogaerts, L. H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, and J. Verweij. 2009. 'New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)', *Eur J Cancer*, 45: 228-47.

ENHERTU. 2021. 'ENHERTU Prescribing Information', *Daiichi Sankyo, Inc.*

Fuchs, C. S., J. Tomasek, C. J. Yong, F. Dumitru, R. Passalacqua, C. Goswami, H. Safran, L. V. Dos Santos, G. Aprile, D. R. Ferry, B. Melichar, M. Tehfe, E. Topuzov, J. R. Zalcberg, I. Chau, W. Campbell, C. Sivanandan, J. Pikiel, M. Koshiji, Y. Hsu, A. M. Liepa, L. Gao, J. D. Schwartz, J. Tabernero, and Regard Trial Investigators. 2014. 'Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial', *Lancet*, 383: 31-39.

Guiducci, C., M. Gong, A. M. Cepika, Z. Xu, C. Tripodo, L. Bennett, C. Crain, P. Quartier, J. J. Cush, V. Pascual, R. L. Coffman, and F. J. Barrat. 2013. 'RNA recognition by human TLR8 can lead to autoimmune inflammation', *J Exp Med*, 210: 2903-19.

Herbst, R. S., D. R. Gandara, F. R. Hirsch, M. W. Redman, M. LeBlanc, P. C. Mack, L. H. Schwartz, E. Vokes, S. S. Ramalingam, J. D. Bradley, D. Sparks, Y. Zhou, C. Miwa, V. A. Miller, R. Yelensky, Y. Li, J. D. Allen, E. V. Sigal, D. Wholley, C. C. Sigman, G. M. Blumenthal, S. Malik, G. J. Kelloff, J. S. Abrams, C. D. Blanke, and V. A. Papadimitrakopoulou. 2015. 'Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400', *Clin Cancer Res*, 21: 1514-24.

HERCEPTIN. 2021. 'HERCEPTIN Prescribing Information', *Genentech, Inc.*

Horn, L., S. Gettinger, D. R. Camidge, E. F. Smit, Y. Y. Janjigian, V. A. Miller, W. Pao, M. Freiwald, J. Fan, B. Wang, V. K. Chand, and H. J. M. Groen. 2017. 'Continued use of afatinib with the addition of cetuximab after progression on afatinib in patients with EGFR mutation-positive non-small-cell lung cancer and acquired resistance to gefitinib or erlotinib', *Lung Cancer*, 113: 51-58.

Krop, I. E., S. B. Kim, A. Gonzalez-Martin, P. M. LoRusso, J. M. Ferrero, M. Smitt, R. Yu, A. C. Leung, H. Wildiers, and Th Resa study collaborators. 2014. 'Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial', *Lancet Oncol*, 15: 689-99.

Mazieres, J., S. Peters, B. Lepage, A. B. Cortot, F. Barlesi, M. Beau-Faller, B. Besse, H. Blons, A. Mansuet-Lupo, T. Urban, D. Moro-Sibilot, E. Dansin, C. Chouaid, M. Wislez, J. Diebold, E. Felip, I. Rouquette, J. D. Milia, and O. Gautschi. 2013. 'Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives', *J Clin Oncol*, 31: 1997-2003.

Meric-Bernstam, F., A. M. Johnson, E. E. I. Dumbrava, K. Raghav, K. Balaji, M. Bhatt, R. K. Murthy, J. Rodon, and S. A. Piha-Paul. 2019. 'Advances in HER2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast and Gastric Cancer', *Clin Cancer Res*, 25: 2033-41.

Modi, S., C. Saura, T. Yamashita, Y. H. Park, S. B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S. A. Im, K. S. Lee, S. A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, I. Krop, and D. ESTINY-Breast01 Investigators. 2020. 'Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer', *N Engl J Med*, 382: 610-21.

Murthy, R. K., S. Loi, A. Okines, E. Paplomata, E. Hamilton, S. A. Hurvitz, N. U. Lin, V. Borges, V. Abramson, C. Anders, P. L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S. S. Shachar, V. Muller, S. Braga, F. P. Duhoux, R. Greil, D. Cameron, L. A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M. C. Palanca-Wessels, L. Walker, W. Feng, and E. P. Winer. 2020. 'Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer', *N Engl J Med*, 382: 597-609.

Nakagawa, K., NM, Felip E., et al. . 2020. 'Trastuzumab deruxtecan in her2-overexpressing metastatic non-small cell lung cancer: Interim results of destiny-lung01.', *Presented at: 2020 World Conference on Lung Cancer Singapore(Virtual).*

Pegram, M. D., G. E. Konecny, C. O'Callaghan, M. Beryt, R. Pietras, and D. J. Slamon. 2004. 'Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer', *J Natl Cancer Inst*, 96: 739-49.

Pillai, R. N., M. Behera, L. D. Berry, M. R. Rossi, M. G. Kris, B. E. Johnson, P. A. Bunn, S. S. Ramalingam, and F. R. Khuri. 2017. 'HER2 mutations in lung adenocarcinomas: A report from the Lung Cancer Mutation Consortium', *Cancer*, 123: 4099-105.

Ponce, R. 2011. 'ICH S9: Developing anticancer drugs, one year later', *Toxicol Pathol*, 39: 913-5.

Robert, N., B. Leyland-Jones, L. Asmar, R. Belt, D. Ilegbodu, D. Loesch, R. Raju, E. Valentine, R. Sayre, M. Cobleigh, K. Albain, C. McCullough, L. Fuchs, and D. Slamon. 2006. 'Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer', *J Clin Oncol*, 24: 2786-92.

Ross, J. S., M. Fakih, S. M. Ali, J. A. Elvin, A. B. Schrock, J. Suh, J. A. Vergilio, S. Ramkissoon, E. Severson, S. Daniel, D. Fabrizio, G. Frampton, J. Sun, V. A. Miller, P. J. Stephens, and L. M. Gay. 2018. 'Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3', *Cancer*, 124: 1358-73.

Rostoker, G., P. Andrivet, I. Pham, M. Griuncelli, and S. Adnot. 2007. 'A modified Cockcroft-Gault formula taking into account the body surface area gives a more accurate estimation of the glomerular filtration rate', *J Nephrol*, 20: 576-85.

Ruschoff, J. 2012. 'Adenocarcinoma of the GEJ: gastric or oesophageal cancer?', *Recent Results Cancer Res*, 196: 107-13.

Sartore-Bianchi, A., L. Trusolino, C. Martino, K. Bencardino, S. Lonardi, F. Bergamo, V. Zagonel, F. Leone, I. Depetris, E. Martinelli, T. Troiani, F. Ciardiello, P. Racca, A. Bertotti, G. Siravegna, V. Torri, A. Amatu, S. Ghezzi, G. Marrapese, L. Palmeri, E. Valtorta, A. Cassingena, C. Lauricella, A. Vanzulli, D. Regge, S. Veronese, P. M. Comoglio, A. Bardelli, S. Marsoni, and S. Siena. 2016. 'Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial', *Lancet Oncol*, 17: 738-46.

Shen, Y., T. Fujii, N. T. Ueno, D. Tripathy, N. Fu, H. Zhou, J. Ning, and L. Xiao. 2019. 'Comparative efficacy of adjuvant trastuzumab-containing chemotherapies for patients with early HER2-positive primary breast cancer: a network meta-analysis', *Breast Cancer Res Treat*, 173: 1-9.

Siena, S., M. Di Bartolomeo, K. Raghav, T. Masuishi, F. Loupakis, H. Kawakami, K. Yamaguchi, T. Nishina, M. Fakih, E. Elez, J. Rodriguez, F. Ciardiello, Y. Komatsu, T. Esaki, K. Chung, Z. Wainberg, A. Sartore-Bianchi, K. Saxena, E. Yamamoto, E. Bako, Y. Okuda, J. Shahidi, A. Grothey, T. Yoshino, and Destiny-Crc investigators. 2021. 'Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial', *Lancet Oncol*, 22: 779-89.

Slamon, D. J., B. Leyland-Jones, S. Shak, H. Fuchs, V. Paton, A. Bajamonde, T. Fleming, W. Eiermann, J. Wolter, M. Pegram, J. Baselga, and L. Norton. 2001. 'Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2', *N Engl J Med*, 344: 783-92.

Strickler, John H., Kimmie Ng, Andrea Cercek, Christos Fountzilas, Federico Augusto Sanchez, Joleen M. Hubbard, Christina Wu, Salvatore Siena, Josep Tabernero, Eric Van Cutsem, Adel Kardosh, Anwaar Saeed, Thierry Andre, Michael Stecher, Maria Corinna Palanca-Wessels, and Tanios S. Bekaii-Saab. 2021. 'MOUNTAINEER: open-label, phase II study of tucatinib combined with trastuzumab for HER2-positive metastatic colorectal cancer (SGNTUC-017, trial in progress)', *Journal of Clinical Oncology*, 39: TPS153-TPS53.

TUKYSA. 2020. 'TUKYSA Prescribing Information', *Seagen Inc.*

Valtorta, E., C. Martino, A. Sartore-Bianchi, F. Penaullt-Llorca, G. Viale, M. Risio, M. Rugge, W. Grigioni, K. Bencardino, S. Lonardi, V. Zagonel, F. Leone, J. Noe, F. Ciardiello, C. Pinto, R. Labianca, S. Mosconi, C. Graiff, G. Aprile, B. Frau, C. Garufi, F. Loupakis, P. Racca, G. Tonini, C. Lauricella, S. Veronese, M. Truini, S. Siena, S. Marsoni, and M. Gambacorta. 2015. 'Assessment of a HER2 scoring system for colorectal cancer: results from a validation study', *Mod Pathol*, 28: 1481-91.

Van Cutsem, E., di Bartolomeo, M., Smyth, E., Chau, I., Park, H., Siena, S., Lonardi, S., Wainberg, Z. A., Ajani, J., Chao, J., Seraj, J., Kawaguchi, Y., Qin, A., Singh, J. Meinhardt, G., and Ku, G. Primary analysis of a phase 2, open-label, single arm trial of trastuzumab deruxtecan in Western patients with HER2-positive unresectable or metastatic gastric or gastroesophageal junction cancer on or after a trastuzumab-containing regimen. Presented at: European Society for Medical Oncology; Sep 17, 2021; Virtual Congress.

Verma, S., D. Miles, L. Gianni, I. E. Krop, M. Welslau, J. Baselga, M. Pegram, D. Y. Oh, V. Dieras, E. Guardino, L. Fang, M. W. Lu, S. Olsen, K. Blackwell, and Emilia Study Group. 2012. 'Trastuzumab emtansine for HER2-positive advanced breast cancer', *N Engl J Med*, 367: 1783-91.

Wilke, H., K. Muro, E. Van Cutsem, S. C. Oh, G. Bodoky, Y. Shimada, S. Hironaka, N. Sugimoto, O. Lipatov, T. Y. Kim, D. Cunningham, P. Rougier, Y. Komatsu, J. Ajani, M. Emig, R. Carlesi, D. Ferry, K. Chandrawansa, J. D. Schwartz, A. Ohtsu, and Rainbow Study Group. 2014. 'Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial', *Lancet Oncol*, 15: 1224-35.

Wolff, H. A., C. R. Wolff, C. F. Hess, K. Jung, S. Sennhenn-Kirchner, M. Hinterthaner, A. Muller-Dornieden, W. Korber, K. Marten-Engelke, R. Roedel, H. Christiansen, and C. Engelke. 2013. 'Second primary malignancies in head and neck cancer patients: high prevalence of curable-stage disease', *Strahlenther Onkol*, 189: 874-80.

XELODA. 2021. 'XELODA Prescribing Information', *Genentech, Inc.*

Yoshino, T. Di Bartolomeo, M. Raghav KPS, Masuishi T, Loupakis F, Kawakami H, Yamaguchi K, Nishina T, Wainberg ZA, Elez E, Rodriguez J, Fakih M, Ciardiello F, Saxena K, Kobayashi K, Bako E, Okuda Y, Meinhardt G, Grothey A and Siena S. 2021. 'Trastuzumab deruxtecan (t-dxd; ds-8201) in patients (pts) with her2-expressing metastatic colorectal cancer (mcrc): Final results from a phase 2, multicenter, open-label study (destiny-crc01).', *Journal of Clinical Oncology*, 39: 3505-05.

11. APPENDICES

11.1 Schedule of Assessments for Part 1: SBT6050 Combined With Trastuzumab Deruxtecan

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days												FU	LTFU[a]
		Cycle 1					Cycle 2		Cycle 3				Cycle 4+		
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	Day 2	Day 4 or Day 5	Day 8	Day 1	30 days post last dose	Every 3 months after 30-day FU
	Visit window			(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±1 d)	(±2 d)	(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±7 d)	
		Pre	Post												
Informed consent	X														
Eligibility criteria	X														
Confirmation of HER2 status[b]	X														
Physical examination	X	X[c]					X		X				X	X	
Medical history and current medical conditions	X														
Pregnancy test[d]	X														
HIV, Hepatitis B and C screening	X														
Urinalysis	X														
Hematology panel[e]	X	X[c]			X	X	Predose	X	Predose		X	X	Predose	X	
Chemistry panel[f]	X	X[c]			X	X	Predose	X	Predose		X	X	Predose	X	
Thyroid panel[g]	X														
Coagulation panel[h]	X														
[redacted]															
12-lead ECG	X				X						X			X	
ECHO/MUGA	X			Every 12 weeks from Cycle 1 Day 1 (±7 days) while on treatment										X[i]	
EGOG Performance Status	X	X[c]					X		X				X	X	
SpO^2	X	X					X		X				X	X	
Vital signs	X	X[j]		X	X	X	X[j]	X	X[j]	X	X		X[j]	X	
MRI of brain[k]	X														
[redacted]															
SBT6050 PK sampling[o]		X	X[m]	X	X	X	Predose		Predose	X	X	X	Predose		
ADA sample		X					Predose		Predose				Predose	X	

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days												FU	LTFU[a]
		Cycle 1					Cycle 2		Cycle 3				Cycle 4+		
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	Day 2	Day 4 or Day 5	Day 8	Day 1	30 days post last dose	Every 3 months after 30-day FU
	Visit window			(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±1 d)	(±2 d)	(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±7 d)	
		Pre	Post												
Administer SBT6050[p]		X					X		X				X		
Administer T-DXd[p]		X					X		X				X		
AE/SAE review	X	Collect from consent to 30 days post last dose													
Concomitant medication review	X	Collect from consent to 30 days post last dose													
Tumor assessment[q]	X						Week 6, Week 12, Week 18, Week 24, and every 9 weeks (-7 days) thereafter while on treatment						X[r]	
[redacted]															
Survival status															X

Abbreviations: AE = adverse event; CRC = colorectal cancer; [redacted] CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; FU = follow-up; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HR = hour; IHC = immunohistochemistry; IV = intravenously; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small-cell lung cancer; [redacted] PK = pharmacokinetic; SAE = serious adverse event; SPO^2 = oxygen saturation; SC = subcutaneously; [redacted]

[a]Subjects will be followed for survival, disease status, and subsequent anticancer therapies until death, withdrawal of consent, lost to follow-up, study termination by Sponsor, or 1 year after the last dose of study treatment has been administered to the last subject.

[b]The most recent result to confirm HER2 status should be used. If documentation of a previous HER2 result is not available, archived tissue, slides, fresh tissue or blood sample must be submitted to either a local laboratory or a Sponsor-designated central laboratory to confirm HER2 expression or amplification. Confirmatory HER2 testing may be obtained greater than 28 days prior to Cycle 1 Day 1, if separate consent for confirmatory HER2 pre-testing is signed (see Section 6.1).

[c]Assessments do not need to be repeated if performed within 72 hours of first dose of SBT6050.

[d]For subjects of childbearing potential; to be performed within 14 days of Cycle 1 Day 1.

[e]Hematology panel consists of erythrocytes, hemoglobin, hematocrit, platelets, leucocytes and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes, as percentages and absolute values, if available); analyses for complete blood count, white blood cell differential, and reticulocyte count will also be performed.

[f]Chemistry panel consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, calcium, phosphate, magnesium, creatinine, total protein, albumin, glucose, total and direct bilirubin, amylase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, γ glutamyl transferase, lipase, triglycerides, thyroid-

stimulating hormone, and troponin. Creatinine clearance, only required for eligibility criteria at Screening/Baseline, will be calculated using the Cockcroft-Gault formula.

[g]Thyroid panel consists of triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

[h]Coagulation panel consists of PT/international normalized ratio (INR) and PTT (or, depending on institutional standard, aPTT).

[i]Required only if not performed in the previous 12 weeks.

[j]Vital signs will be taken predose SBT6050 and postdose 15, 30, 45, 60 minutes (+/-15 minutes) SBT6050 and then immediately following the end of the T-DXD infusion (+15 minutes) on dosing days.

[k]Required for all subjects with breast cancer or NSCLC and for subjects with gastric or GEJ cancer or CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis.

[redacted]

[m]Postdose measurements should be taken 4 hours ±30 minutes after SBT6050 dosing.

[n]Collect Day 1 predose at Cycles 4, 6, 8, 11 and every 3 cycles thereafter.

[o]If a subject stops treatment with SBT6050, no further PK sample is needed.

[p]See Section 5.1 for a description of treatments to be administered during the study. SBT6050 should be administered first, followed by T-DXd. T-DXd infusion should begin at least 15 minutes after the injection of SBT6050.

[q]Tumor assessment by CT, PET/CT (if diagnostic-quality CT scan included), or MRI. Subjects who experience an objective response (ie, tumor reduction) should have a confirmatory assessment performed approximately 4 weeks after the initial response.

[r]If not performed in the previous 6 weeks.

[s]An archived tumor tissue may be submitted for baseline/screening tests for some subjects (see Section 6.1).

[redacted]

11.2 Schedule of Assessments for Part 2: SBT6050 Combined With Tucatinib Plus Trastuzumab With or Without Capecitabine

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days												FU	LTFU[a]
		Cycle 1					Cycle 2		Cycle 3				Cycle 4+		
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	Day 2	Day 4 or Day 5	Day 8	Day 1	30 days post last dose	Every 3 months after 30-day FU
	Visit window			(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±1 d)	(±2 d)	(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±7 d)	
		Pre	Post												
Informed consent	X														
Eligibility criteria	X														
Confirmation of HER2 status[b]	X														
Physical examination	X	X[c]					X		X				X	X	
Medical history and current medical conditions	X														
Pregnancy test[d]	X														
HIV, Hepatitis B and C screening	X														
Urinalysis	X														
Hematology panel[e]	X	X[c]			X	X	Predose	X	Predose		X	X	Predose	X	
Chemistry panel[f]	X	X[c]			X	X	Predose	X	Predose		X	X	Predose	X	
Thyroid panel[g]	X														
Coagulation panel[h]	X														
[redacted]															
12-lead ECG	X				X						X			X	
ECHO/MUGA	X	Every 12 weeks from Cycle 1 Day 1 (±7 days) while on treatment												X[i]	
EGOG Performance Status	X	X[c]					X		X				X	X	
SpO2	X	X					X		X				X	X	
Vital signs	X	X[j]		X	X	X	X[j]	X	X[j]	X	X		X[j]	X	
MRI of brain[k]	X														
[redacted]															
SBT6050 PK sampling[o]		X	X[m]	X	X	X	Predose		Predose	X	X	X	Predose		
ADA sample		X					Predose		Predose				Predose	X	

Procedure	Screening/ Baseline	Each Treatment Cycle is 21 Days											FU	LTFU[a]
		Cycle 1				Cycle 2		Cycle 3				Cycle 4+		
	D-28 to D1	Day 1		Day 2	Day 4 or Day 5	Day 8	Day 1	Day 8	Day 1	Day 2	Day 4 or Day 5	Day 8	Day 1	30 days post last dose	Every 3 months after 30-day FU
	Visit window			(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±1 d)	(±2 d)	(24 ±2 hr)	(72–96 hr ±2 hr)	(±1 d)	(±2 d)	(±7 d)	
		Pre	Post												
Administer SBT6050[p]		X					X		X				X		
Administer trastuzumab[p]		X					X		X				X		
Administer tucatinib[p]		PO BID throughout the duration of the study													
Administer capecitabine, if applicable[p]		PO BID on Days 1–14 of every 21-day cycle													
AE/SAE review	X	Collect from consent to 30 days post last dose													
Concomitant medication review	X	Collect from consent to 30 days post last dose													
Tumor assessment[q]	X						Week 6, Week 12, Week 18, Week 24, and every 9 weeks (-7 days) thereafter while on treatment						X[r]	
[redacted]															
Survival status															X

Abbreviations: AE = adverse event; CRC = colorectal cancer; [redacted] CT = computed tomography; D = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; FU = follow-up; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HR = hour; IHC = immunohistochemistry; IV = intravenously; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small-cell lung cancer; [redacted] PK = pharmacokinetic; SAE = serious adverse event; SPO^2 = oxygen saturation; SC = subcutaneously; [redacted]

[a]Subjects will be followed for survival, disease status, and subsequent anticancer therapies until death, withdrawal of consent, lost to follow-up, study termination by Sponsor, or 1 year after the last dose of study treatment has been administered to the last subject.

[b]The most recent result to confirm HER2 status should be used. If documentation of a previous HER2 result is not available, archived tissue, slides, fresh tissue or blood sample must be submitted to either a local laboratory or a Sponsor-designated central laboratory to confirm HER2 expression or amplification. Confirmatory HER2 testing may be obtained greater than 28 days prior to Cycle 1 Day 1, if separate consent for confirmatory HER2 pre-testing is signed (see Section 6.1).

[c]Assessments do not need to be repeated if performed within 72 hours of first dose of SBT6050.

[d]For subjects of childbearing potential; to be performed within 14 days of Cycle 1 Day 1.

[e]Hematology panel consists of erythrocytes, hemoglobin, hematocrit, platelets, leucocytes and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes, as percentages and absolute values, if available); analyses for complete blood count, white blood cell differential, and reticulocyte count will

also be performed.

[f]Chemistry panel consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, calcium, phosphate, magnesium, creatinine, total protein, albumin, glucose, total and direct bilirubin, amylase, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase, γ glutamyl transferase, lipase, triglycerides, thyroid-stimulating hormone, and troponin. Creatinine clearance, only required for eligibility criteria at Screening/Baseline, will be calculated using the Cockcroft-Gault formula.

[g]Thyroid panel consists of triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).

[h]Coagulation panel consists of PT/international normalized ratio (INR) and PTT (or, depending on institutional standard, aPTT).

[i]Required only if not performed in the previous 12 weeks.

[j]Vital signs will be taken predose SBT6050 and postdose 15, 30, 45, 60 minutes (+/-15 minutes) SBT6050 and then immediately following the end of the trastuzumab infusion (+15 minutes) on dosing days.

[k]Required for all subjects with breast cancer and for subjects with CRC who have a history of CNS metastases or have signs or symptoms suggestive of CNS metastasis.

[redacted]

[m]Postdose measurements should be taken 4 hours ±30 minutes after SBT6050 dosing.

[n]Collect Day 1 predose at Cycles 4, 6, 8, and 11, then every 3 cycles thereafter.

[o]If a subject stops treatment with SBT6050, no further PK sample is needed.

[p]See Section 5.1 for a description of treatments to be administered during the study. SBT6050 should be administered first, followed by trastuzumab. Trastuzumab infusion should begin at least 15 minutes after the injection of SBT6050. At Cycle 1/Day 1, tucatinib and capecitabine (if applicable) should also be taken after SBT6050 and trastuzumab in the clinic. On Day 1 of each cycle, study staff should review tucatinib and capecitabine (if applicable) compliance from previous cycle.

[q]Tumor assessment by CT, PET/CT (if diagnostic-quality CT scan included), or MRI. Subjects who experience an objective response (ie, tumor reduction) should have a confirmatory assessment performed approximately 4 weeks after the initial response.

[r]If not performed in the previous 6 weeks.

[s]An archived tumor tissue may be submitted for baseline/screening tests for some subjects (see Section 6.1).

[redacted]

11.3 Common Terminology Criteria for Adverse Events

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

11.4 Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1

Response assessment for this protocol will be performed according to RECIST Version 1.1 (Eisenhauer 2009) as described below.

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease	At least 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute of at least 5 mm. Note that the appearance of one or more new lesions is also considered progressions.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference he smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-progressive disease	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference the smallest measurements recorded for progressive disease since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response[a]	Best Overall Response when Confirmation is Required[b]
CR	CR	No	CR	>4 weeks confirmation[c]
CR	Non-CR/ Non-progressive disease	No	PR	>4 weeks confirmation[c]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-progressive disease/ Not evaluated	No	PR	
Stable disease	Non-CR/Non-progressive disease/ Not evaluated	No	Stable disease	Documented at least once >4 weeks from baseline[c]
Progressive disease	Any	Yes or No	Progressive disease	No prior stable disease, PR, or CR
Any	Progressive disease[d]	Yes or No	Progressive disease	
Any	Any	Yes	Progressive disease	

[a] Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

[b] See RECIST Version 1.1 for further details for evidence of a new lesion.

[c] Only for non-randomized studies with response as primary endpoint.

[d] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

For Subjects with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-progressive disease	No	Non-CR/Non-progressive disease[a]
Not all evaluated	No	Not evaluated
Unequivocal progressive disease	Yes or No	Progressive disease
Any	Yes	Progressive disease

[a] Non-CR/non-progressive disease is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Duration of Response

Duration of overall response	The duration of overall response is measured from the time measurement criteria are met for CR and PR (whichever is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference the smallest measurements for progressive disease since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.
Duration of stable disease	Stable disease is measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including baseline measurements.

11.5 Eastern Cooperative Oncology Group Performance Status

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work	1
Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair or more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to be or chair	4

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5(6): 649-655.

11.6 Cockroft-Gault Equation

Cockcroft-Gault equation (Rostoker 2007) = [(140 – age) × weight in kg × (0.85 if female)] ÷ (72 × plasma creatinine in mg/dL)

11.7 Guidance on Contraception

Female Subjects

A female subject is considered of childbearing potential if she is anatomically and physiologically capable of becoming pregnant and will be or could possibly be sexually active with a male partner while undergoing study treatment with the possibility of posing harm to a fetus.

Female subjects of childbearing potential must agree to abstain from sexual intercourse or to use a highly effective form of contraception from the time of giving informed consent, during the study, and for up to 7 months following the last dose of study treatment.

Examples of highly effective contraceptive methods (methods with a failure rate of <1% per year) include bilateral tubal ligation; male sterilization; established, proper use of hormonal contraceptives that inhibit ovulation; hormone-releasing intrauterine device (IUD); and copper IUDs. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Male Subjects

A male subject is considered of sexual reproductive potential if he is anatomically and physiologically capable of causing a pregnancy in a female partner and will be or could possibly be sexually active with a female partner (who is or may become pregnant) while undergoing study treatment with the possibility of posing harm to a fetus.

Males with partners of reproductive potential must agree to commit to either continued abstinence from sexual intercourse, or that they or their partners will use at least 2 effective contraceptive methods (including 1 barrier method) when engaging in reproductive sexual activity throughout the study, and will avoid conceiving for up to 2 months after the last dose of study treatment.

11.8 Drug Interactions Table of Substrates, Inhibitors, and Inducers

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

11.9 Investigator Statement

I understand that all documentation provided to me by Silverback Therapeutics, Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board/Ethics Committee. No changes will be made to the study protocol without the prior written approval of Silverback Therapeutics, Inc. and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the subject.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Investigational site or name of institution and address (printed)

11.10 Document History

Version	Date
Amendment 1	10-Jan-2022
Original	30-Aug-2021