EUROPEAN UNION RISK MANAGEMENT PLAN

Product Name:	Tucatinib
Marketing Authorisation Applicant:	Seagen B.V.
Version:	0.3
Supersedes:	0.2
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Risk Management Plan (RMP) Version To Be Assessed as Part of This Application

RMP version number:	0.3
Data lock point of this RMP:	29 May 2020[a]
Date of final sign-off:	04 Nov 2020
Rationale for submitting an updated RMP:	Updated RMP submitted in parallel with EMA D180 Questions

[a]Data cutoff date for safety for studies ONT-380-004, ONT-380-005, ONT-380-206. Data cut-off for primary analysis is presented in Part II: Module SIII.

Summary of Significant Changes in This RMP

Not applicable, this is an initial EU RMP.

Other RMP versions under evaluation: RMP version number: Submitted on: Procedure number:	Not applicable
Details of the currently approved RMP: Version number: Approved with procedure: Date of approval (opinion date):	Not applicable
Qualified Person for Pharmacovigilance (QPPV) Name:	[redacted]
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ANNEXES

LIST OF ABBREVIATIONS

ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	area under the plasma concentration-time curve
BID	twice per day
BRCA1	breast cancer type 1
BRCA2	breast cancer type 2
CNS	central nervous system
CYP2C8	cytochrome P450 2C8
CRC	colorectal cancer
CYP2C9	cytochrome P450 2C9
CYP3A	cytochrome P450 3A
CYP3A4	cytochrome P450 3A4
CYP450	cytochrome P450
DDI	drug-drug interaction
EEA	European Economic Area
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ErbB1	human epidermal growth factor receptor-1, also abbreviated as HER1
ErbB2	human epidermal growth factor receptor-2, also abbreviated as HER2
ESMO	European Society for Medical Oncology
EU	European Union
GD	gestation day
GI	gastrointestinal
HER1	human epidermal growth factor receptor-1, also abbreviated as ErbB1
HER2	human epidermal growth factor receptor-2, also abbreviated as ErbB2
HER3	human epidermal growth factor receptor-3, also abbreviated as ErbB3
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HR	hazard ratio
INN	International Nonproprietary Name
IV	intravenous

LA/M	locally advanced/metastatic
LumA	luminal-A
LVEF	left ventricular ejection fraction
MA	marketing authorisation
MAH	marketing authorisation holder
MATE	multidrug and toxin extrusion
NCCN	National Comprehensive Cancer Network
OCT2	organic cation transporter 2
OR	odds ratio
P-gp	P-glycoprotein
pH	potential of hydrogen
PI	prescribing information
PIC	powder-in-capsule
PL	package leaflet
PO	oral dose
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	risk management plan
SC	subcutaneous
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
T-DM1	trastuzumab emtansine
TKI	tyrosine kinase inhibitor
UGT1A1	5'-diphospho-glucuronosyltransferase 1A1
UK	United Kingdom

PART I PRODUCT(S) OVERVIEW

Table 1: Product(s) Overview	
Active substance(s) (International Nonproprietary Name [INN] or common name)	Tucatinib
Pharmacotherapeutic group (Anatomical Therapeutic Chemical Classification System [ATC] Code)	Not yet assigned
Name of marketing authorisation holder (MAH) or applicant	Seagen B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	TUKYSA®
Marketing authorisation procedure	Centralised
Brief description of the product	Tucatinib is an orally administered, reversible human epidermal receptor type 2 (HER2)-targeted small molecule tyrosine kinase inhibitor (TKI). Tucatinib is a potent inhibitor of HER2 in vitro, and in cellular signaling assays is >1000-fold more selective for HER2 compared to the closely related kinase epidermal growth factor receptor (EGFR).
Hyperlink to the Product Information	The Summary of Product Characteristics (SmPC) and Package Leaflet is provided in Module 1.3.1.

Table 1: Product(s) Overview

Indication(s) in the EEA	
Current	Not applicable
Proposed (if applicable)	TUKYSA is indicated in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens.
Dosage in the EEA	
Current (if applicable)	Not applicable
Proposed (if applicable)	The recommended dose is 300 mg tucatinib (two 150 mg tablets) taken twice daily continuously in combination with trastuzumab and capecitabine, at doses described in the table below.

Treatment	**Dose**	**Treatment days**	**Timing relative to food intake**
Tucatinib	300 mg orally twice daily	Continuously	With or without a meal
Capecitabine	1000 mg/m^2 orally twice daily	Days 1 to 14 every 21 days	Within 30 minutes after a meal
Trastuzumab			
Intravenous (IV) dosing			
Initial dose	8 mg/kg IV	Day 1	
Subsequent doses	6 mg/kg IV	Every 21 days	NA
OR			
Subcutaneous (SC) dosing	600 mg SC	Every 21 days	

Pharmaceutical form(s) and strength(s)	
Current (if applicable)	Not applicable
Proposed (if applicable)	Tucatinib drug product is supplied as a round, yellow, film-coated, tablet in a 50 mg dosage strength and an oval-shaped, yellow, film-coated tablet in a 150 mg dosage strength for oral administration.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes

PART II SAFETY SPECIFICATION

Part II: Module SI. Epidemiology of the Indication(s) and Target Population(s)

Table 2: Summary of Epidemiology of HER2-Positive Breast Cancer

Incidence	Breast cancer is the most common form of cancer in women worldwide (Ferlay 2018), with approximately 2 million patients diagnosed globally with breast cancer in 2018 resulting in 626,000 deaths. Approximately 1% of breast cancer cases occur in men (Siegel 2019). Invasive breast cancer occurred in 234,190 new cases and there were approximately 40,730 breast cancer deaths in 2015 (Hurvitz 2013). The incidence rate is specifically high in North America, Western Europe and Australasia with an age standardised rate of more than 90 per 100,000 women. In the European Union (EU-28), 404,920 new cases of breast cancer and 98,755 deaths occurred in 2018. The highest age standardised incidence rate was observed in Belgium (113.2 per 100,000), while the highest mortality rate was observed in Croatia (18.2 per 100,000) (Ferlay 2019). Between 15% and 30% of breast cancers overexpress the HER2 receptor and are classified as HER2+ breast cancer (Slamon 1987; Owens 2004; Cronin 2010; Wolff 2014; Loibl 2017). Historically, HER2+ breast cancer tends to be more aggressive and more likely to recur than HER2-negative breast cancer (Slamon 1987; Loibl 2017; American Cancer Society (ACS) 2018a). HER2+ breast cancer also disproportionately affects younger patients, where the proportion of HER2 positivity is higher compared to older patients (Murphy 2019). The HER2+ breast cancers comprise about 10% to 20% of new breast cancer diagnoses in the United States and Europe and is more frequent in younger patients. In a study in Norway, 27% of subjects 20 to 39 years had HER2+ disease; this proportion decreased to 12.4% for ages 70 to 79 and 11.2% after age 80 (Johansson 2019). A study in Germany showed a higher proportion of HER2+ breast cancers in premenopausal women (21% versus 16% in postmenopausal women) (Inwald 2015). In the United States, 20.0% of breast cancer patients below age 50 have HER2+ disease (Howlader 2014), down to 10.7% in patients above age 75.
Prevalence	More than 2 million, or about 5 per 1,000, women in Europe are living with a previous breast cancer diagnosis (5 year prevalence) (Ferlay 2019).
Demographics of target population in the proposed indication	The incidence of breast cancer is higher in white women compared to South Asian and/or Black women (Gathani 2014; Wu 2017), however a study in the United Kingdom (UK) showed ethnic differences are mostly due to differences in known risk factors for the disease (American Cancer Society (ACS) 2018b).

Table 2: Summary of Epidemiology of HER2-Positive Breast Cancer

Risk factors for the disease	The risk factors associated with breast cancer (National Cancer Institute (NCI) 2019) include: • age • genetic alterations (eg, breast cancer type 1 [BRCA1], breast cancer type 2 [BRCA2], and others) • mammographic breast density • family history • personal history of breast cancer • radiation therapy • alcohol consumption • long-term hormone therapy • high body weight • low physical activity
The main existing treatment options	First-line treatment for most patients with HER2+ metastatic breast cancer is a combination of trastuzumab plus pertuzumab and chemotherapy. However, within 2 years, the majority of patients treated with this combination will progress (Baselga 2012; Swain 2013). After progression on trastuzumab, pertuzumab, and chemotherapy, standard of care treatment for patients with HER2+ metastatic breast cancer is T-DM1. Although T-DM1 is often given as a second line of metastatic treatment, when patients receive a pertuzumab-based regimen in the neoadjuvant or adjuvant setting and relapse quickly, T-DM1 may also be given as a first-line metastatic agent (Cardoso 2018; Giordano 2018). Treatment of patients after progression on T-DM1 remains a clinical challenge, and the prognosis of these patients remains poor. There is no single established standard of care (Verma 2012; Dieras 2017) and no approved therapies have demonstrated clinically meaningful improvements in progression free survival or overall survival (Geyer 2006; Blackwell 2012; Verma 2012). Preferred regimens based on American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines for these patients include continuation of HER2-targeted therapy with trastuzumab or lapatinib in combination with cytotoxic chemotherapy, such as capecitabine (Gradishar 2016; Cardoso 2018; Giordano 2018).

Table 2: Summary of Epidemiology of HER2-Positive Breast Cancer	
Natural history of the indicated condition in the population including mortality and morbidity	Seventy-seven (77%) to 86% of breast cancer patients in Europe survive up to 5 years after diagnosis. The rate varies by country but generally, the survival rate is higher in Western Europe compared to Central and Eastern Europe (American Cancer Society (ACS) 2018b). Five-year survival of breast cancer patients in different European countries has approached a ceiling of 85% (highest survival in northern Europe). While Sweden had a 5-year survival rate of 89% in 2014, Slovakia, Romania, and Poland had survival rates of 73% to 75% (Allemani 2018). Differences in survival between countries are probably due to differences in stage at diagnosis, access to good care, screening, and differences in cancer biology (De Angelis 2014). The HER2+ subtype has been shown to be more aggressive than other breast cancer subtypes. The HER2+ subtype are reported to be associated with bone metastasis (odds ratio [OR] = 1.6), brain metastasis (OR: 2.8 to 5), liver metastasis (OR: 3.4 to 5.4) and lung metastasis (OR: 2.0 to 3.0) and survival is much lower in patients with HER2+ disease compared with HER2-negative disease (hazard ratio [HR]: 5.65) (Wu 2017). In a study on Swiss cancer registries patients, the overall survival hazard ratio was 3.5 times higher (ie, poorer survival) in HER2-enriched patients than luminal A (LumA)-Like (high estrogen receptor/progesterone receptor expression) subtype (Ess 2018).
Important comorbidities	Significant comorbidities for patients with breast cancer include peripheral vascular disease, dementia, chronic pulmonary disease, liver diseases, and renal diseases (Ewertz 2018). These comorbid conditions exist in the population; however, those are not specific to breast cancer patients. In the cited reference, Charlson comorbidity score was calculated using these comorbidities for prognosis. The prevalence of comorbidities among women treated for breast cancer aged older than 66 is 32.2%, a statistic comparable to those without cancer at 31.8%.

Part II: Module SII. Nonclinical Part of the Safety Specification

Table 3: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
Toxicity		
• Acute or repeat-dose toxicity o Hepatotoxicity	In the 28- and 90-day nonclinical studies there were reversible hepatocellular and/or hepatobiliary effects, including generally minimal (≤2.5–fold) increases in serum markers of liver injury (including aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), liver weight increases, and centrilobular hepatocyte hypertrophy. These changes occurred at doses ≥3 mg/kg twice daily (BID) in rats (0.09-fold human exposures based on AUC_{12h}) and ≥10 mg/kg BID for cynomolgus monkeys (1.5 and 0.15-fold human exposure based on the 28- and 90-day studies, respectively). At non-tolerated doses in cynomolgus monkeys (30 and 45 mg/kg BID; 4- and 7–fold human exposures), liver was reported as friable, with hepatocyte cytoplasmic swelling and rarefaction, without any changes in serum liver parameters. There were no hepatic histologic changes indicating hepatocellular injury (eg, hepatic degeneration, inflammation, or necrosis) in any nonclinical study.	In clinical studies: elevated AST, ALT, and bilirubin (Grade 1 to 4) have been observed and were reversible with dose modification except in cases of progressive metastatic liver disease. Hepatotoxicity is considered an important identified risk. This risk will be monitored in the periodic safety update report (PSUR).
• Acute or repeat-dose toxicity o GI toxicity	In repeat-dose 28- and 90-day nonclinical studies, gastrointestinal clinical signs including vomiting and/or watery feces were observed in rats administered a nontolerated dose of 100 mg/kg BID (21–fold human exposure; dose reduction to 60 mg/kg BID after approximately 1 week) and in cynomolgus monkeys at ≥2.5 mg/kg BID (0.04-fold human exposure). There were no histologic changes associated with the gastrointestinal tract except in rats at non-survivable doses (gastrointestinal erosions and ulcers). * Human AUC_{12h} was 3.47 (µg·h/mL), determined in Clinical Study ONT-380-012, Part D.	In clinical studies, the most common adverse reactions have been mild to moderate (Grade 1 or 2) gastrointestinal reactions and included nausea, diarrhoea, and vomiting. Most events have been manageable with dose modifications and treatment with anti-diarrhoeals and anti-emetics as needed.

Table 3: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
Toxicity • Reproductive/ Developmental toxicity	A preliminary embryo-foetal development study (Study 20144956) in rabbits (6 dams/group) indicates that tucatinib caused embryo-foetal toxicity in the absence of significant maternal toxicity. Pregnant New Zealand White rabbits were administered either vehicle or suspensions of tucatinib orally twice daily on gestation days (GD) 7 through 19 at 0, 60, 90, 120, and 150 mg/kg/day. All surviving rabbits were euthanized on GD 29 and examined. The area under the plasma concentration-time curve (AUC) (0-12 hr) at 90 mg/kg/day in rabbits was approximately the same exposure as subjects dosed with the recommended dose of 300 mg BID (ARRAY-380-103, a phase 1 clinical pharmacology study). These data indicate that tucatinib is a selective embryo-foetal toxicant in rabbits. Foetal external and visceral malformations were observed at ≥90 mg/kg/day, including domed heads with severe dilation of the lateral and third ventricles. Other malformations included hyperflexed forepaw, herniated umbilicus, organ malposition, and vascular malformations and variations. Foetal skeletal variations corresponding to the domed heads were observed at 90, 120, and 150 mg/kg/day. Microscopic changes in female reproductive organs, and male mammary gland and prostate were observed in repeat-dose rat toxicity studies at 0.92-fold human exposure. The changes included uterine atrophy, vaginal mucification, changes in corpora lutea, lobular atrophy of the male mammary gland, and decreased organ weights (decreased uterus/cervix and prostate weights). During the recovery phase, these changes were partially or fully reversible. Reproductive changes were not observed in monkeys.	No pregnancies have been reported among subjects receiving tucatinib in clinical trials. Women of reproductive potential are advised of the potential risk of taking tucatinib while pregnant. Women of reproductive potential are also advised to use effective contraception during treatment and for at least 1 week after the last dose. Information is presented in sections 4.4 and 4.6 of the SmPC as well as section 2 of the package leaflet (PL) to minimise risk of pregnancy and provide guidance regarding breastfeeding while taking tucatinib.

Table 3: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
• Carcinogenicity	Carcinogenicity studies have not been conducted with tucatinib.	No impact on human usage is anticipated.
• Genotoxicity	Tucatinib has been evaluated *in vitro* and *in vivo* for genotoxicity. Tucatinib was negative in bacterial and mammalian mutagenesis assays, and in the mouse micronucleus test.	No impact on human usage is anticipated.
General Safety Pharmacology • Cardiovascular (including potential for QT interval prolongation)	In an *in vitro* human ether-a-go-go related gene (hERG)-channel assay, tucatinib showed inhibition only at very high doses. In telemeterized cynomolgus monkeys, there was no effect of tucatinib on cardiovascular function. In nonclinical studies conducted with tucatinib, left ventricular ejection fraction (LVEF) was not specifically measured; however, in repeat-dose studies up to 90 days with tucatinib in rats and cynomolgus monkeys, the evaluations of in-life clinical signs, blood pressure, heart rate, and morphologic evaluations of lung and heart did not show any evidence of decreased LVEF or its sequelae.	A dedicated TQT study (ONT-380-011) demonstrated no effect of tucatinib on QT prolongation, thus no impact on human usage is anticipated.
• Nervous system	In nonclinical repeat-dose studies up to 90 days in rats and cynomolgus monkeys, there were no changes in any endpoint, including neurological and histologic evaluations, indicating any effect of tucatinib on the brain. There were no effects of tucatinib on neurobehavioral function in rats.	No impact on human usage is anticipated.
• Respiratory	There were no effects of tucatinib on respiratory function in rats.	No impact on human usage is anticipated.
• Other	There were no effects of oral tucatinib on gastrointestinal propulsion in rats. Gastric secretion, acidity, and irritation were increased only at the highest dose tested. In nonclinical repeat-dose studies up to 90 days in rats and cynomolgus monkeys, there were no in-life or histologic observations indicating any effect of tucatinib on skin.	No impact on human usage is anticipated.

Table 3: Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Study Type/Type of Finding	Important Nonclinical Safety Finding	Relevance to Human Usage
Other toxicity related information or data	Tucatinib is a substrate of cytochrome P450 2C8 (CYP2C8) and cytochrome P450 3A (CYP3A). Tucatinib is an inhibitor of CYP2C8 and P-glycoprotein (P-gp) in vitro and a metabolism-dependent inactivator of CYP3A. Tucatinib inhibited organic cation transporter 2 (OCT2)/multidrug and toxin extrusion (MATE) 1/2-K-mediated transport of metformin and creatinine in vitro.	The potential of tucatinib to be a drug-drug interaction (DDI) perpetrator or victim was evaluated in the 2 clinical DDI studies (ONT380-012 and SGNTUC-020), a physiologically-based pharmacokinetic analysis, and in nonclinical *in vitro* and *in vivo* systems. Tucatinib is a strong inhibitor of CYP3A, the increase in midazolam-exposure in a DDI study was 5.7-fold. Tucatinib exposure was reduced ~50% when co-administered with strong CYP2C8/CYP3A inducers. Tucatinib exposure was increased ~3-fold when co-administered with strong CYP2C8 inhibitors. Gastric potential of hydrogen (pH) modulation with omeprazole did not impact tucatinib absorption. Tucatinib is a weak inhibitor of P-gp. Caution is recommended when co-administering with digoxin or other P-gp substrates with narrow therapeutic windows. Tucatinib is a weak inhibitor of CYP2C8, MATE1/2-K, and was not an inhibitor of cytochrome P450 2C9 (CYP2C9). Tucatinib inhibits MATE1/MATE2-K-mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine. The observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1. Information is presented in sections 4.4 and 4.5 of the SmPC regarding possible drug interactions with tucatinib.

Part II: Module SIII. Clinical Trial Exposure

Tucatinib is a potent, reversible HER2-targeted small molecule TKI being developed for the treatment of HER2+ solid tumors including breast, colorectal, and gastric cancers.

There are 10 completed studies (ARRAY-380-101, ARRAY-380-102, ARRAY-380-103, ONT-380-005, ONT-380-008, ONT-380-009, ONT-380-011, ONT-380-012, SGNTUC-015, SGNTUC-020) and 4 ongoing clinical studies (ONT-380-004, ONT-380-206 [HER2CLIMB], SGNTUC-016 [HER2CLIMB-02], SGNTUC-017 [MOUNTAINEER]) for tucatinib described below. Studies were conducted in the United States, Canada, Europe, Israel, and Australia.

Completed Clinical Studies:

- Study ARRAY-380-101 is a phase 1, open-label, multiple dose study that assessed the safety, tolerability and pharmacokinetics of tucatinib in adult subjects with advanced solid malignancies in the United States and Canada.
- Study ARRAY-380-102 is a phase 1, open-label, single dose, four-period study that assessed pharmacokinetics, relative bioavailability and safety of single 300 mg doses of tucatinib administered as 4 oral tucatinib formulations in fasted healthy adult subjects in the United States.
- Study ARRAY-380-103 is a phase 1, open-label, single dose, four-period study that compared the administration of the 300 mg tucatinib tablet with the 300 mg powder-in-capsule (PIC) formulation in the fasted state in healthy subjects as an assessment of relative bioavailability between the two formulations in the United States.
- Study ONT-380-005 is a phase 1b, open-label study to assess the safety and tolerability of tucatinib in adult subjects with HER2+ metastatic breast cancer following combination treatment of tucatinib + capecitabine; tucatinib + trastuzumab; or tucatinib + capecitabine + trastuzumab in the United States.
- Study ONT-380-008 is a phase 1, open-label study of the absorption, metabolism, and excretion of [^{14}C]-tucatinib following a single oral dose (PO) in healthy male and female subjects in the United States.
- Study ONT-380-009 is a phase 1, open-label, nonrandomized, single-dose parallel group study to assess the safety, tolerability, and pharmacokinetics in fasted, hepatically-impaired male and female subjects and fasted matched-control healthy subjects administered 300 mg of tucatinib in the United States.
- Study ONT-380-011 is a phase 1, randomized, partially double-blind, placebo- and positive-controlled study to evaluate the effect of tucatinib on cardiac repolarization in healthy subjects in the United States.
- Study ONT-380-012 is a phase 1, open-label, fixed-sequence, 5-part, drug-drug interaction study of tucatinib to evaluate the effects of CYP3A4 and CYP2C8 inhibition and induction on the pharmacokinetics of the substrates of CYP3A4, CYP2C8, CYP2C9, and P-gp in healthy subjects in the United States.

- SGNTUC-015 is a phase 1, open-label, safety, tolerability and pharmacokinetic study of tucatinib (ONT-380) in healthy Japanese and Caucasian subjects in the United States.
- SGNTUC-020 is a phase 1, open-label, fixed-sequence, drug-drug interaction study to evaluate the effects of tucatinib on the pharmacokinetics of a MATE substrate (metformin) in healthy subjects in the United States.

Ongoing Clinical Studies:

- Study ONT-380-004 is a phase 1b, open-label study to assess the safety and tolerability of tucatinib combined with ado-trastuzumab emtansine (trastuzumab emtansine; T-DM1) in adult subjects with HER2+ metastatic breast cancer in the United States and Canada. Enrollment has been completed; the data cut-off date for the primary analysis was 31-Jan-2018.
- Study ONT-380-206 (HER2CLIMB) is a global, pivotal, randomized, double-blind, controlled study of tucatinib versus placebo in combination with capecitabine and trastuzumab in subjects with previously-treated, unresectable locally advanced or metastatic HER2+ breast cancer in the United States, Canada, Europe, Israel, and Australia. Enrollment has been completed; the data cut-off date for the primary analysis was 04-Sep-2019. A follow-up safety analysis with a 29-May-2020 data cut-off was performed at the request of regulatory authorities.
- Study SGNTUC-016 (HER2CLIMB-02) is a global, randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic (LA/M) HER2+ breast cancer. Enrollment is ongoing.
- Study SGNTUC-017 (MOUNTAINEER) is a global, phase 2, open-label study of tucatinib combined with trastuzumab in subjects with HER2+ metastatic colorectal cancer (CRC). Seagen assumed sponsorship of this study on 16 September 2019. Enrollment is ongoing.

Excluding SGNTUC-016 (HER2CLIMB-02) and SGNTUC-017 (MOUNTAINEER), a total of 861 subjects across 12 clinical studies received at least 1 dose of tucatinib; 571 subjects with cancer and 290 subjects without cancer. Clinical trial exposure to tucatinib in these 12 clinical studies is presented herein by duration (Table 4), dose (Table 5), sex/age (Table 6) and race (Table 7).

Table 4: Exposure to Tucatinib in Clinical Trials by Duration

Duration of Exposure	Subjects (n)*	Person-Years*
Tucatinib Monotherapy		
<1 month	9	0.51
1 to <3 months	17	2.78
3 to <6 months	18	6.39
≥6 months	6	5.42
Total	50	15.10
Tucatinib+T-DM1		
<1 month	4	0.16
1 to <3 months	13	2.11
3 to <6 months	7	2.58
≥6 months	33	43.23
Total	57	48.08
Tucatinib+Trastuzumab		
<1 month	1	0.06
1 to <3 months	10	1.56
3 to <6 months	4	1.68
≥6 months	7	7.20
Total	22	10.49
Tucatinib+Capecitabine		
<1 month	0	
1 to <3 months	2	0.29
3 to <6 months	3	1.05
≥6 months	6	4.69
Total	11	6.03
Tucatinib+Trastuzumab+Capecitabine		
<1 month	23	0.94
1 to <3 months	80	13.00
3 to <6 months	96	37.44
≥6 months	232	290.44
Total	431	341.82

Table 4: Exposure to Tucatinib in Clinical Trials by Duration

Duration of Exposure	Subjects (n)*	Person-Years*
All Treatment Regimens Total		
<1 month	37	1.68
1 to <3 months	122	19.74
3 to <6 months	128	49.14
≥6 months	284	350.98
Total[a]	571	421.53
Studies in Subjects Without Cancer[b]		
Total for Tucatinib Exposure in Subjects Without Cancer	290	4.205

T-DM1 = trastuzumab emtansine
Person-time (years) is calculated for each subject (end of tucatinib treatment date – first dose date + 1)/365.25, and sum for all the subjects in the row.
[a]Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ONT-380-004: 31JAN2018, ARRAY 380-101: 26NOV2013
Source: [redacted] (02OCT20:12:07) Data: ADSL2
[b]Studies include ARRAY-380-102, ARRAY-380-103, ONT-380-008, ONT-380-009, ONT-380-011, ONT-380-012, SGNTUC-015, SGNTUC020. All were subjects without cancer. In Study ONT-380-009 subjects were hepatically-impaired (mild, moderate, and severe).
*Excludes tucatinib exposure from subjects who crossed over to tucatinib from placebo from ONT-380-206 (HER2CLIMB).

Table 5: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Dose ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

Dose of Tucatinib	Subjects (n)*	Person-Years*
Tucatinib Monotherapy		
25 mg BID	3	0.61
50 mg BID	3	0.54
100 mg BID	3	0.61
200 mg BID	3	0.93
300 mg BID	3	1.01
500 mg BID	4	1.35
600 mg BID	24	7.78
650 mg BID	3	1.17
800 mg BID	4	1.11
Total	50	15.10
Tucatinib+T-DM1		
300 mg BID	50	42.19
350 mg BID	7	5.89
Total	57	48.08
Tucatinib+Trastuzumab		
300 mg BID	18	7.41
350 mg BID	4	3.09
Total	22	10.49
Tucatinib+Capecitabine		
300 mg BID	7	4.65
350 mg BID	4	1.38
Total	11	6.03
Tucatinib+Trastuzumab+Capecitabine		
300 mg BID	431	341.82
Total	431	341.82

Table 5: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Dose ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

Dose of Tucatinib	Subjects (n)*	Person-Years*
All Treatment Regimens Total		
25 mg BID	3	0.61
50 mg BID	3	0.54
100 mg BID	3	0.61
200 mg BID	3	0.93
300 mg BID	509	397.08
350 mg BID	15	10.35
500 mg BID	4	1.35
600 mg BID	24	7.78
650 mg BID	3	1.17
800 mg BID	4	1.11
Total	571	421.53

T-DM1 = trastuzumab emtansine
Person-time (years) is calculated for each subject (end of tucatinib treatment date - first dose date + 1)/365.25, and sum for all the subjects in the row.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ONT-380-004: 31JAN2018, ARRAY-380-101: 26NOV2013.
Source: O:\Projects\Tucatinib\meta\ema_1780\v01\outputs\tlfs\pgms\t-expo-sum2.sas Output: t-expo-all-dose-safs-rmp rtf (02OCT20:12:07) Data: ADSL2
*Excludes tucatinib exposure from subjects who crossed over to tucatinib from placebo from ONT-380-206 (HER2CLIMB).

Table 6: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Age Group and Gender

ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

	Subjects*		Person-Years*	
Age Group	Male	Female	Male	Female
Tucatinib Monotherapy				
Adults (18-64 years)	2	36	0.78	10.62
Elderly (>=65 years)	3	9	0.69	3.01
65-74 years	3	8	0.69	2.70
75-84 years	0	1		0.31
Total	5	45	1.47	13.63
Tucatinib+T-DM1				
Adults (18-64 years)	0	46		44.12
Elderly (>=65 years)	0	11		3.96
65-74 years	0	11		3.96
75-84 years	0	0		
Total	0	57		48.08
Tucatinib+Trastuzumab				
Adults (18-64 years)	0	19		9.94
Elderly (>=65 years)	0	3		0.55
65-74 years	0	3		0.55
75-84 years	0	0		
Total	0	22		10.49
Tucatinib+Capecitabine				
Adults (18-64 years)	0	9		4.95
Elderly (>=65 years)	0	2		1.08
65-74 years	0	2		1.08
75-84 years	0	0		
Total	0	11		6.03
Tucatinib+Trastuzumab+Capecitabine				
Adults (18-64 years)	3	343	2.21	288.55
Elderly (>=65 years)	0	85		51.06
65-74 years	0	77		46.23
75-84 years	0	8		4.84
Total	3	428	2.21	339.61

Table 6: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Age Group and Gender

ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

	Subjects*		Person-Years*	
Age Group	Male	Female	Male	Female
All Treatment Regimens Total				
Adults (18-64 years)	5	453	2.99	358.18
Elderly (>=65 years)	3	110	0.69	59.67
65-74 years	3	101	0.69	54.53
75-84 years	0	9		5.14
Total	8	563	3.68	417.85

T-DM1 = trastuzumab emtansine
Person-time (years) is calculated for each subject (end of tucatinib treatment date - first dose date + 1)/365.25, and sum for all the subjects in the row.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ONT-380-004: 31JAN2018, ARRAY-380-101: 26NOV2013.
Source: O:\Projects\Tucatinib\meta\ema_1780\v01\outputs\tlfs\pgms\t-expo-sum2.sas Output: t-expo-all-age-safs-rmp.rtf (02OCT20:12:07) Data: ADSL2
*Excludes tucatinib exposure from subjects who crossed over to tucatinib from placebo from ONT-380-206 (HER2CLIMB).

Table 7: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Race ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

Race	Number of Subjects*	Person-Years*
Tucatinib Monotherapy		
Asian	4	0.88
Black or African American	4	1.83
Other	2	1.10
White	40	11.30
Unknown/Not Given/Missing	0	
Total	50	15.10
Tucatinib + T-DM1		
Asian	7	6.94
Black or African American	6	6.36
Other	0	
White	43	34.77
Unknown/Not Given/Missing	1	0.00
Total	57	48.08
Tucatinib + Trastuzumab		
Asian	0	
Black or African American	1	0.24
Other	0	
White	19	9.33
Unknown/Not Given/Missing	2	0.93
Total	22	10.49
Tucatinib+Capecitabine		
Asian	0	
Black or African American	0	
Other	0	
White	10	5.61
Unknown/Not Given/Missing	1	0.42
Total	11	6.03

Table 7: Summary of Tucatinib Treatment Exposure in Subjects with Cancer by Race ONT-380-206, ONT-380-005, ONT-380-004 and Array-380-101 Safety Population

Race	Number of Subjects*	Person-Years*
Tucatinib+Trastuzumab+Capecitabine		
Asian	19	20.10
Black or African American	42	27.92
Other	3	1.26
White	306	245.53
Unknown/Not Given/Missing	61	47.01
Total	431	341.82
All Treatment Regimens Total		
Asian	30	27.92
Black or African American	53	36.34
Other	5	2.36
White	418	306.54
Unknown/Not Given/Missing	65	48.36
Total	571	421.53

T-DM1 = trastuzumab emtansine
Person-time (years) is calculated for each subject (end of tucatinib treatment date - first dose date + 1)/365.25, and sum for all the subjects in the row.
Data cutoff: ONT-380-206: 29MAY2020, ONT-380-005: 06MAR2018, ONT-380-004: 31JAN2018, ARRAY-380-101: 26NOV2013.
Source: O:\Projects\Tucatinib\meta\ema_1780\v01\outputs\tlfs\pgms\t-expo-sum2.sas Output: t-expo-all-race-safs-rmp.rtf (02OCT20:12:07) Data: ADSL2
*Excludes tucatinib exposure from subjects who crossed over to tucatinib from placebo from ONT-380-206 (HER2CLIMB).

Part II: Module SIV. Populations Not Studied in Clinical Trials

II.C.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table 8: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Subjects who have received previous treatment with cumulative dose of doxorubicin >360 mg/m^2 or treatment with another anthracycline with cumulative dose approximately equivalent to >360 mg/m^2 doxorubicin	HER2-directed therapies have the potential to cause cardiotoxicity especially in the elderly when combined with anthracycline-based chemotherapy regimens. Previous exposure to high cumulative doses of anthracyclines may impair cardiac function and may increase risk of cardiotoxicity.	Yes	Not applicable.
Subjects who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Events of hepatotoxicity were observed in tucatinib studies, but these events and laboratory abnormalities were primarily Grades 1 and 2, transient, asymptomatic reversible, and manageable with dose modification. However, the hepatic safety profile in subjects with chronic liver conditions is unknown.	Yes	Not applicable.
Subjects with central nervous system (CNS) disease were excluded if they met any of the following criteria: • Untreated brain lesions >2.0 cm in size unless approved by the study medical monitor • Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total dose of >2 mg of dexamethasone (or equivalent)	At the time of study initiation, the effect of tucatinib on brain metastases was not definitively characterised, and these subjects were excluded in case systemic therapy was not adequate for subjects with rapidly progressing disease. In addition, cerebral edema was an adverse event of special interest at the time of study initiation, and it was unknown if there was a risk of developing cerebral edema in subjects	No	Analysis of data from ONT-380-206 do not indicate that cerebral edema is a risk associated with tucatinib. In addition, subjects with brain metastases on the study had a statistically significant and clinically meaningful improvement in progression free survival.

Table 8: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
• Any brain lesion requiring immediate local therapy • Poorly controlled generalised or complex partial seizures or signs of neurologic progression due to brain metastases notwithstanding CNS directed- therapy	with pre-existing brain metastases.		
Subjects with a history of other malignancy	Due to competing risks of death due to other active cancer, the treatment effect of tucatinib in breast cancer would be confounded. This population was excluded from clinical studies to enable clearer interpretation of data.	No	The safety profile is not anticipated to be different in this population.
Subjects with known impaired cardiac function or clinically significant cardiac disease	HER2-directed therapies have the potential to cause cardiotoxicity.	No	The risk of cardiac toxicity has been evaluated in the tucatinib clinical program. QT prolongation was studied in ONT-380-011 and the effect on LVEF function was studied in ONT-380-206. The safety profile is not anticipated to be different in this population.
Subjects known to be human immunodeficiency virus (HIV) positive	Due to competing risks of death due to intercurrent HIV-associated illness, the treatment effect of tucatinib in breast cancer would be confounded.	No	The safety profile is not expected to differ in this population.

Table 8: Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale for Not Including as Missing Information
Subject is pregnant, breastfeeding, or planning a pregnancy	In nonclinical studies, increased resorptions, decreased percentages of live foetuses, and skeletal, visceral, and external malformations were observed in foetuses at doses approximately equivalent to the human exposure at the recommended dose based on AUC. It is not known whether tucatinib is transferred into human milk.	No	Pregnant and lactating women are exclusion criteria in the tucatinib clinical program. Embryo-foetal toxicity has been adequately characterised in nonclinical studies.
Subjects that have used a strong cytochrome CYP2C8 or cytochrome CYP3A4 inducer or inhibitor within 3 to 5 elimination half-lives of the inhibitor or inducer prior to the start of tucatinib treatment	Non-clinical studies predict that tucatinib would be metabolized in the human liver primarily by CYP2C8 and CYP3A4. Subjects taking a concomitant medication that is a strong CYP2C8 or CYP3A4 inhibitor or inducer were excluded from clinical studies to enable clearer interpretation of data.	No	The safety profile has been adequately characterised in the tucatinib nonclinical and clinical program.

II.C.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II.C.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Table 9: Exposure of Special Populations Typically Under-represented in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Subjects with relevant comorbidities	
Subjects with hepatic impairment	A total of 37 subjects (0.10 person-years) were exposed to tucatinib in Study ONT-380-009. Subjects included those with normal hepatic function (15 subjects), mild hepatic dysfunction (8 subjects), moderate hepatic dysfunction (8 subjects), and severe hepatic dysfunction (6 subjects)
Subjects with renal impairment	Not included in the clinical development program because tucatinib is predominantly hepatobiliary eliminated.
Subjects with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised subjects	Not included in the clinical development program.
Subjects with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	In the clinical development program, the majority of subjects in the clinical development program were white.
Subpopulations carrying relevant genetic polymorphisms	Subjects enrolled were characterised by a biomarker, not based on genetic testing. Thus, this subpopulation is not applicable to the clinical development program.

Part II: Module SV. Post-authorisation Experience

Not applicable.

II.C.1 Post-authorisation Exposure

Tucatinib has not been authorised for marketing in any country.

SV.1.1 Methods Used to Calculate Exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Post-authorisation Use from Business Partners

Not applicable.

Part II: Module SVI. Additional EU Requirements for the Safety Specification

II.C.1 Potential for Misuse for Illegal Purposes

There is no evidence to suggest a potential for drug abuse or misuse in the tucatinib clinical development program. Tucatinib inhibits phosphorylation of HER2 and human epidermal growth factor receptor-3 (HER3), resulting in inhibition of downstream cell-signaling and cell-proliferation, and induces death in HER2 driven tumour cells. Thus, the mechanism of action is not consistent with pathways typically associated with addiction.

Part II: Module SVII. Identified and Potential Risks

II.C.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 10: Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reasons for Not Including an Identified or Potential Risk in the List of Safety Concerns	List of Risks
Risks with minimal clinical impact on subjects (in relation to the severity of the indication treated)	Nausea, vomiting, stomatitis, weight decrease, arthralgia, epistaxis, rash, drug-drug interactions
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	None
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the prescribing information (PI) are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised)	None
Known risks that do not impact the risk-benefit profile	None
Other reasons for considering the risks not important	None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 11: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Identified Risks	
Diarrhoea	Treatment-emergent adverse events (TEAEs) of diarrhoea observed across tucatinib studies were mainly low grade and manageable with dose modifications and treatment with anti-diarrhoeals on an "as needed" basis. In HER2CLIMB, 82% of subjects who received tucatinib experienced diarrhoea, including 13% with Grade 3 diarrhoea and 0.5% with Grade 4 diarrhoea. Both subjects who developed Grade 4 diarrhoea subsequently died, with diarrhoea as a contributor to death. Diarrhoea led to dose reduction in 6% of subjects and treatment discontinuation in 1% of subjects. The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures, including dose modifications, are in place in the SmPC.
Hepatotoxicity	TEAEs of transaminase and bilirubin elevations have been reported early in tucatinib treatment, and were primarily low grade, transient, and manageable with dose modifications. In HER2CLIMB, 6% of subjects who received tucatinib had a Grade 3 or higher adverse event (AE) of ALT increase, 5% had a Grade 3 or higher AE of AST increase, and 1.7% had a Grade 3 or higher AE of bilirubin increase. Hepatotoxicity led to dose reduction of tucatinib in 9% of subjects and discontinuation of tucatinib in 1.5% of subjects. The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures, including dose modifications, are in place in the SmPC.
Important Potential Risks	
Embryo-foetal toxicity	The risk-benefit impact is considered minimal as adequate risk communication and minimisation measures are in place in the SmPC. Prescribers are informed that tucatinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with tucatinib and that the pregnancy status of women of childbearing potential should be verified prior to initiating treatment with tucatinib. Female patients of childbearing potential are advised to avoid becoming pregnant and to use an effective method of contraception while receiving treatment with tucatinib and for up to 1 week after ending treatment. Male patients with female partners of reproductive potential are advised to use an effective method of contraception while receiving treatment with tucatinib and for at least 1 week after ending treatment.

Table 11: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Missing Information	
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Although cardiotoxicity was not seen specifically for tucatinib, HER2-directed therapies have the potential to cause cardiotoxicity, especially in the elderly when combined with anthracycline-based chemotherapy regimens. Cardiotoxicity with tucatinib is not considered a potential risk but there is a possibility that this could potentially be seen in patients with other significantly cardiotoxic chemotherapy agents and therefore the safety profile in this patient population may be different.
Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	In Study ARRAY-380-101, the dose limiting toxicity of tucatinib as monotherapy was found to be transient, reversible Grade 3 elevation of transaminases. Events of hepatotoxicity have also been observed in other tucatinib studies, but these events and laboratory abnormalities were primarily Grades 1 and 2, transient, asymptomatic, reversible, and manageable with dose modification. In a study examining tucatinib treatment in subjects with mild, moderate, or severe hepatic impairment, the safety profile showed that overall, a single oral dose of tucatinib 300 mg was considered to be safe and well tolerated in subjects with normal hepatic function or with mild, moderate, or severe hepatic impairment. The hepatic safety profile is not known in subjects with chronic conditions that impact the liver.
Long term safety	Ongoing clinical trials will provide additional information about the safety of tucatinib with long-term use. There is no evidence to suggest a different safety profile with long-term use.

II.C.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable, as this is an initial marketing authorisation application.

II.C.3 Details of Important Identified, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 12: Important Identified Risk: Diarrhoea	
Potential mechanisms	EGFR is highly expressed on colonic epithelial cells and regulates ion transport by EGF driven signaling in EGFR-EGFR homodimers. While HER2 expression is lower, it contributes to this regulation by forming competing EGFR-HER2 heterodimers. Inhibition of signaling by kinase inhibitors disrupts the regulation of ion transport and results in secretory diarrhoea. This type of diarrhoea has a different underlying mechanism than diarrhoea that results from insults such as mucosal damage or inflammation (Duan 2019) (Rugo 2019) (Van Sebille 2015). Tucatinib is a highly selective HER2 tyrosine kinase inhibitor. Its selectivity for HER2 over EGFR is >1000-fold in cellular assays of phosphorylation inhibition, therefore the ability of tucatinib to inhibit EGFR kinase activity that leads to GI toxicity is expected to be low. Any pharmacology driven GI toxicity after tucatinib treatment would be expected to be due to inhibition of HER2 kinase activity.
Evidence source(s) and strength of evidence	Tucatinib nonclinical and clinical studies In the clinical development program, subjects who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of diarrhoea events than subjects who received trastuzumab and capecitabine alone.
Characterisation of the Risk	
Frequency	In the HER2CLIMB tucatinib arm of safety population (n=404), 82% of subjects developed diarrhoea. The majority of diarrhoea events reported were Grade 1 to 2 in severity (69%). Grade 3 events were observed in 13% and Grade 4 events were observed in 0.5% of subjects across this population. A total of 17 subjects (4%) developed serious events (any grade). Both subjects who developed Grade 4 diarrhoea subsequently died, with diarrhoea as a contributor to death.
Severity	In the HER2CLIMB tucatinib arm of safety population, the majority of diarrhoea events reported were Grades 1 to 2 in severity. Grade 3 events were observed in 13% and Grade 4 events were observed in 0.5% of subjects.
Reversibility	In non-clinical trials, GI clinical observations, including watery feces were rapidly reversible. In the HER2CLIMB tucatinib arm of safety population, diarrhoea was manageable with dose modifications and treatment with anti-diarrhoeals on an “as needed” basis, and 81% of events resolved.
Long-term outcomes	The onset of diarrhoea was early (median onset was 12.0 days in the HER2CLIMB tucatinib arm), and the incidence of diarrhoea was similar throughout treatment cycles. The majority (81%) of events resolved. The occurrence of diarrhoea is not anticipated to impact long-term outcomes.
Impact on quality of life	Diarrhoea, mainly severe events, may diminish quality of life. On the tucatinib arm of the HER2CLIMB study, the majority of the diarrhoea events reported were mild in nature. Diarrhoea events were reported commonly and more frequently on the tucatinib arm compared to the control arm. Diarrhoea led to treatment discontinuation in 1% of subjects.

Table 12: Important Identified Risk: Diarrhoea	
Risk groups and risk factors	No specific risk groups at increased risk for diarrhoea have been identified with tucatinib treatment. Risk factors that could potentially be associated with an increased risk of diarrhoea include antibiotic use, side effects of other medications, intestinal abnormalities, food intolerance, and/or general wasting syndromes associated with cancer.
Preventability	Diarrhoea may be preventable with prophylactic use of anti-diarrhoeal medications. However, prophylactic anti-diarrhoeal medications were not mandated in tucatinib clinical studies, and no data is available to support its use.
Impact on the risk-benefit balance of the product	Based on available information, the risk of diarrhoea with tucatinib treatment does not impact the overall positive benefit-risk balance of the product in the context of oncology care. More data are being collected regarding this risk and any potential impact to the benefit-risk balance will continue to be evaluated.
Public health impact	Cases of diarrhoea have been reported in subjects treated with tucatinib; however, the public health impact is not considered to be high.

Table 13: Important Identified Risk: Hepatotoxicity	
Potential mechanisms	HER2 has been shown to be expressed on hepatocytes (Yan 2016). Nonclinical studies show no evidence of adverse effects on liver for rats or cynomolgus monkeys treated with tucatinib. Findings of minimal to mild increases in serum liver enzymes and bilirubin were observed in rats and cynomolgus monkeys administered tucatinib. However, there was no histologic evidence of tucatinib-related liver injury associated with these biochemical changes, which is consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib (Hall 2012). Non-adverse generally minimal (≤2.5-fold) increases in serum markers of liver injury (including AST, ALT, and bilirubin), liver weight increases, and centrilobular hepatocyte hypertrophy occurred at ≥6 mg/kg/day in rats and ≥20 mg/kg/day in cynomolgus monkeys treated with tucatinib. However, histologically, there was no evidence of liver injury, including no hepatic or biliary degeneration, inflammation, necrosis, fibrosis, or other sequelae of damage in any animal. Monkeys on the 28-day toxicity study euthanized moribund after approximately a week of dosing had histologic liver changes of hepatocyte swelling and rarefaction, but these animals had no evidence of hepatocellular injury and no changes in ALT, AST, and/or bilirubin. Therefore, the nonclinical studies do not show evidence of adverse effects on liver for rats or cynomolgus monkeys treated with tucatinib (m2.6.6, Section 3.1 and Section 3.2). Taken together, the generally minimally increased serum enzymes, liver weights, and centrilobular hypertrophy and the lack of histologic evidence of hepatocellular and hepatobiliary injury suggest that increased transaminases are consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib (Hall 2012).
Evidence source(s) and strength of evidence	Tucatinib nonclinical and clinical studies In the clinical development program, subjects who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of hepatotoxicity events than subjects who received trastuzumab and capecitabine alone.
Characterisation of the Risk	
Frequency	In the HER2CLIMB tucatinib arm of safety population (n=404), 44% developed hepatotoxicity, of which, 10% were Grade 3 or higher. A total of 2 subjects (0.5%) developed serious events (any grade), and there have been no fatal events reported in this population to date.
Severity	In the HER2CLIMB tucatinib arm of safety population, the majority of hepatotoxicity events reported were Grades 1 to 2 in severity; 6% of subjects who received tucatinib had a Grade 3 or higher AE of ALT increase, 5% had a Grade 3 or higher AE of AST increase, and 1.7% had a Grade 3 or higher AE of bilirubin increase.
Reversibility	In non-clinical trials, the observations are consistent with an adaptive response of the liver caused by induction of enzymes by tucatinib. The changes were generally minimal and reversible. In the HER2CLIMB tucatinib arm of safety population, hepatotoxicity was manageable with dose modifications and discontinuations with 82% of events resolved.
Long-term outcomes	The onset of hepatotoxicity events was early (median onset 36.0 days in the HER2CLIMB tucatinib arm), and the majority of events resolved. The occurrence of hepatotoxicity is not anticipated to impact long-term outcomes.
Impact on quality of life	Hepatotoxicity, mainly severe events, may diminish quality of life. On the tucatinib arm of the HER2CLIMB study, the majority of the hepatotoxicity events reported were primarily Grade 1 and 2. Hepatotoxicity events were reported commonly and more frequently on the tucatinib arm compared to the control arm.

Table 13: Important Identified Risk: Hepatotoxicity	
Risk groups and risk factors	Although no specific risk groups or risk factors have been identified with tucatinib treatment, patients with prior history of hepatic disease, hepatitis, chronic liver conditions, concomitant administration of agents and medications with known adverse hepatic effects, or impaired hepatic function at baseline may be at increased risk.
Preventability	Although patients likely to develop hepatotoxicity following exposure to tucatinib cannot be identified, the proposed labeling is sufficient and robust for early and adequate management. Per the SmPC, prescribers are advised to monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue tucatinib.
Impact on the risk-benefit balance of the product	Based on available information, the risk of hepatotoxicity with tucatinib treatment does not impact the overall positive benefit-risk balance of the product. More data are being collected regarding this risk and any potential impact to the benefit-risk balance will continue to be evaluated.
Public health impact	Cases of hepatotoxicity have been reported in subjects treated with tucatinib; however, the public health impact is not considered to be high.

Table 14: Important Potential Risk: Embryo-foetal toxicity	
Potential mechanisms	HER2 is essential in embryonic development. Mouse embryos homozygous for the deletion of the Erbb2 gene die on gestational day 10.5 with a lack of trabeculae in the developing heart and defects in the peripheral nervous system (Lee 1995). Mouse embryos with a kinase inactivated mutant of Erbb2 have similar findings, demonstrating that the catalytic activity of the HER2 kinase is essential in embryonic development (Chan 2002). Tucatinib administered to pregnant dams caused teratogenicity in rabbits and embryo-foetal toxicity in rats. In a preliminary embryo-foetal development study (Study 20144956) in rabbits (6 dams/group), tucatinib caused embryo-foetal toxicity in the absence of significant maternal toxicity. Foetal external and visceral malformations were observed at ≥90 mg/kg/day, including domed heads with severe dilation of the lateral and third ventricles. Other malformations included hyperflexed forepaw, herniated umbilicus, organ malposition, and vascular malformations and variations. The foetal skeletal evaluation showed skeletal malformations. The AUC12h at 90 mg/kg/day in rabbits was approximately the same exposure as subjects dosed with the recommended dose of 300 mg BID (m5.3.3.4, ONT-380-012 CSR Part D). These data indicate that tucatinib is a selective embryo-foetal toxicant in rabbits. In a preliminary embryo-foetal development study (m4.2.3.5.2, Study 20160869) in rats (6 dams/group), tucatinib caused embryo-foetal toxicity at a dose that was also toxic to dams. The embryo-foetal toxicity observed in nonclinical species is consistent with the role of HER2 in prenatal development and is similar to toxicity observed with other molecules directed against this target (m2.4, Section 4.5.2). Based on animal data, embryo-foetal toxicity is an important potential risk for tucatinib treatment. To date, there are no confirmed pregnancies in subjects treated with tucatinib (Module 2.7.4, Section 5.4).
Evidence source(s) and strength of evidence	Nonclinical trials
Characterisation of the Risk	
Frequency	The relationship between tucatinib use and embryo-foetal toxicity has not been established in humans. Subjects who are pregnant are excluded from all tucatinib clinical trials. Pregnancy testing is required for all women of childbearing potential. Contraception is also mandated for women of childbearing potential and males who have not undergone surgical sterilization and have female partners of childbearing potential.
Severity	Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to be severe. No clinical data are currently available.
Reversibility	Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to be irreversible. No clinical data are currently available.
Long-term outcomes	Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to have impact on long-term outcomes. No clinical data are currently available.
Impact on quality of life	Based on findings in animal studies, potential embryo-foetal toxicities are anticipated to have impact on quality of life. No clinical data are currently available.
Risk groups and risk factors	Risk factors and risk groups include women of childbearing potential, pregnant women, lactating women, and male patients with female partners of childbearing potential.
Preventability	This potential risk is considered preventable with effective contraception measures and avoiding breastfeeding.
Impact on the risk-benefit balance of the product	Impact on the risk-benefit balance is minimal considering the preventability of the risk.

Table 14: Important Potential Risk: Embryo-foetal toxicity	
Public health impact	Public health impact is minimal.

SVII.3.2 Presentation of the Missing Information

Table 15: Missing Information: Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	
Evidence source	HER2-directed therapies have the potential to cause cardiotoxicity especially in the elderly when combined with anthracycline-based chemotherapy regimens.
Anticipated risk/consequence	Although other HER2-directed therapies, including trastuzumab, have previously demonstrated the potential to cause LVEF decreased, in Study ONT-380-206 the incidence of LVEF decreased TEAEs was similar between the tucatinib and control arms. Overall, rates of ejection fraction changes were consistent across tucatinib studies, with lowest occurring in the tucatinib monotherapy study. In subjects previously treated with cumulative dose of doxorubicin >360 mg/m^2 or who have had a previous treatment with another anthracycline with cumulative dose approximately equivalent to >360 mg/m^2 doxorubicin there is a risk for cardiac adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated.

Table 16: Missing Information: Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	
Evidence source	Hepatotoxicity has been evaluated in the tucatinib clinical program with tucatinib monotherapy and in combination with other anti-cancer drugs (trastuzumab, capecitabine, T-DM1).
Anticipated risk/consequence	Adverse reactions have been transient, asymptomatic, reversible, and manageable with dose modification. In addition, a study to evaluate the magnitude of any alterations in tucatinib disposition or pharmacokinetics in subjects with mild, moderate, and severe hepatic impairment (Study ONT-380-009) was conducted. A total of 3 TEAEs were experienced by 3 of 37 subjects in this study; 2 TEAEs were considered Grade 1, and 1 TEAE was considered Grade 2 in severity, and 2 TEAEs were considered related to tucatinib. The Grade 2 TEAE (transaminases increased) was considered related to tucatinib. There was no obvious pattern of association between incidence of TEAEs and hepatic impairment status. Overall, a single oral dose of tucatinib 300 mg was considered to be safe and well tolerated in subjects with normal hepatic function or with mild, moderate, or severe hepatic impairment. Hepatotoxicity is an important identified risk of tucatinib and will be followed up via additional and routine pharmacovigilance activities.

Table 17: Missing Information: Long-term safety	
Evidence source	Ongoing clinical trials will provide additional information about the safety with long-term use of the product.
Anticipated risk/consequence	There is no evidence from long-term follow-up in ongoing trials to suggest a different safety profile with long-term use. Based on 29MAY2020 DCO, the median exposure to tucatinib in HER2CLIMB trial was 7.4 months (range, <0.1 to 43.6), 29.2% of subjects had received at least 12 months of tucatinib treatment, and all subjects have had the opportunity to be followed for at least 12 months. Current DCO demonstrates no clinically meaningful differences in the tolerability and safety of tucatinib in combination with trastuzumab and capecitabine. Additional pharmacovigilance activities are ongoing for further characterisation.

Part II: Module SVIII. Summary of the Safety Concerns

Table 18: Summary of Safety Concerns	
Important identified risks	Diarrhoea Hepatotoxicity
Important potential risks	Embryo-foetal toxicity
Missing information	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 19.

Table 19: Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hepatic Event Questionnaire	Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	To further characterise events of hepatic toxicity reported in patients treated with tucatinib in the postmarketing environment
Standard Adverse Experience Reporting Form	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	To monitor cardiotoxicity in patients administered tucatinib who have been previously treated with cumulative dose of doxorubicin >360 mg/m^2 or who have had a previous treatment with another anthracycline with cumulative dose approximately equivalent to >360 mg/m^2 doxorubicin in the postmarketing setting

III.2 Additional Pharmacovigilance Activities

Table 20: Additional Pharmacovigilance Activity: SGNTUC-016	
Study short name and title	**SGNTUC-016 (HER2CLIMB-02):** A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer.
Rationale and study objectives	Rationale: Further effort to assess and characterise important risks and missing information Safety concerns addressed: Diarrhoea, hepatotoxicity, embryo-foetal toxicity, missing information for patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin, and long-term safety Study objective: To evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. ***Primary*** • Compare progression-free survival by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms ***Key Secondary*** • Compare overall survival between treatment arms • Compare the objective response rate by investigator assessment per RECIST v1.1 between treatment arms ***Other Secondary*** • Evaluate the safety of tucatinib in combination with T-DM1
Study design	This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Subjects are randomized in a 1:1 manner to receive 21-day cycles of either tucatinib or placebo in combination with T-DM1.
Study population	Subjects ≥ 18 years of age and have unresectable LA/M HER2+ breast cancer with a life expectancy of at least 6 months. Subjects must have histologically confirmed HER2+ carcinoma by a sponsor-designated central lab, had prior treatment with a taxane and trastuzumab in any setting (separately or in combination), and must have progressed or have been intolerant of the last systemic therapy.
Milestones	Final clinical study report: projected [redacted]

Table 21: Additional Pharmacovigilance Activity: SGNTUC-017	
Study short name and title	**SGNTUC-017 (MOUNTAINEER):** Tucatinib plus Trastuzumab in Subjects with HER2+ Colorectal Cancer
Rationale and study objectives	Rationale: Further effort to assess and characterise important risks and missing information Safety concerns addressed: Diarrhoea, hepatotoxicity, embryo-foetal toxicity, and long-term safety Study objective: efficacy and safety study of tucatinib, administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC; further characterise long-term safety of tucatinib. ***Primary Objectives*** • To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by confirmed objective response rate per RECIST 1.1 criteria, according to blinded independent central review assessment ***Secondary Objectives*** • To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B • To assess the safety and tolerability of tucatinib monotherapy, in Cohort C
Study design	This is a multicenter, randomized, open-label, Phase 2 study of tucatinib, administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC. • Cohort A = ~40 subjects dosed with tucatinib and trastuzumab • Randomized cohorts: o Cohort B = ~40 subjects dosed with tucatinib and trastuzumab o Cohort C = 30 subjects dosed with tucatinib monotherapy
Study population	Subjects with HER2+, RAS wild-type, unresectable or metastatic CRC who, unless contraindicated, have previously received systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor monoclonal antibody; patients whose disease has deficient mismatch repair proteins or is microsatellite instability-High must also have received anti-PD-(L)1 monoclonal antibody, if indicated.
Milestones	Final clinical study report: projected [redacted]

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 22: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
SGNTUC-016: A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer (HER2CLIMB-02) Ongoing	To evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting; further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, missing information for patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin, long-term safety	Final CSR	[redacted]
SGNTUC-017: Tucatinib plus Trastuzumab in Subjects with HER2+ Colorectal Cancer (MOUNTAINEER) Ongoing	To evaluate efficacy and safety of tucatinib, administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC; further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, long-term safety	Final CSR	[redacted]

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 23: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities:
Diarrhoea	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for diagnostic tests to exclude infectious causes are included in SmPC Section 4.4. Other risk minimisation measures beyond the PI: • None
Hepatotoxicity	Routine risk communication: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Embryo-foetal toxicity	Routine risk communication: • SmPC Section 4,4, 4.6, and 5.3 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for verification of pregnancy status in females of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 Other risk minimisation measures beyond the PI: • None
Missing Information	
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None

Table 23: Description of Routine Risk Minimisation Measures by Safety Concern	
Safety Concern	**Routine Risk Minimisation Activities:**
	Other risk minimisation measures beyond the PI: • None
Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Routine risk communication for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures for hepatotoxicity to address the risk: • Recommendations for liver function monitoring are included in Section 4.4. Other risk minimisation measures beyond the PI: • None
Long term safety	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None

V.2 Additional Risk Minimisation Measures

Routine risk minimisation measures as described in PART V.1 are sufficient to manage the safety concerns of tucatinib.

V.3 Summary of Risk Minimisation Measures

Table 24: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Diarrhoea	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • Recommendation for diagnostic tests clinically indicated to exclude infections causes are included in SmPC Section4.4. • PL Section 2 and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Standard Adverse Experience Reporting Form (Annex 4) Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017
Hepatotoxicity	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • Recommendations for liver function monitoring are included in SmPC Section 4.4. • PL Section 2, 3, and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic Event Questionnaire (Annex 4) Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017
Embryo-foetal toxicity	Routine risk minimisation measures: • SmPC Section 4.4, 4.6, and 5.3 • Recommendation for verification of pregnancy status in women of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 • PL Section 2 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017

V.3 Summary of Risk Minimisation Measures

Table 24: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Standard Adverse Experience Reporting Form (Annex 4) Additional pharmacovigilance activities: • SGNTUC-016
Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	Routine risk minimisation measures for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • Recommendations for liver function monitoring are included in Section 4.4. • PL Section 2, 3, and 4 Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic Event Questionnaire (Annex 4) Additional pharmacovigilance activities: • None
Long-term safety	Routine risk minimisation measures: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for TUKYSA®

This is a summary of the risk management plan (RMP) for TUKYSA. The RMP details how more information will be obtained about TUKYSA's risks and uncertainties (missing information).

This summary of the RMP for TUKYSA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TUKYSA's RMP.

I. The medicine and what it is used for

TUKYSA is authorised in combination with trastuzumab and capecitabine for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least 2 prior anti-HER2 treatment regimens. It contains tucatinib as the active substance and it is given orally.

Further information about the evaluation of TUKYSA's benefits will be found in tucatinib's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage once approved.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TUKYSA, together with measures to minimise such risks and the proposed studies for learning more about TUKYSA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to subjects and healthcare professionals, such as warnings, precautions, and advice on correct use;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including period safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of tucatinib is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TUKYSA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Important identified risks are concerns for which there is sufficient proof of a link with the use of tucatinib. Important potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diarrhoea Hepatotoxicity
Important potential risks	Embryo-foetal toxicity
Missing information	Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease Long-term safety

II.B. Summary of Important Risks

Important identified risk: Diarrhoea	
Evidence for linking the risk to the medicine	Tucatinib nonclinical and clinical studies In the clinical development program, subjects who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of diarrhoea events than subjects who received trastuzumab and capecitabine alone.
Risk factors and risk groups	No specific risk groups at increased risk for diarrhoea have been identified with tucatinib treatment. Risk factors that could potentially be associated with an increased risk of diarrhoea include antibiotic use, side effects of other medications, intestinal abnormalities, food intolerance, and/or general wasting syndromes associated with cancer
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for diagnostic tests clinically indicated to exclude infectious causes are included in SmPC Section 4.4. Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Tucatinib nonclinical and clinical studies In the clinical development program, subjects who were treated with tucatinib in combination with trastuzumab and capecitabine showed a higher incidence of hepatotoxicity events than subjects who received trastuzumab and capecitabine alone.
Risk factors and risk groups	Although no specific risk groups or risk factors have been identified with tucatinib treatment, patients with prior history of hepatic disease, hepatitis, chronic liver conditions, concomitant administration of agents and medications with known adverse hepatic effects, or impaired hepatic function at baseline may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring are included in SmPC Section 4.4. Additional risk minimisation measures: • None

Important identified risk: Hepatotoxicity	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical trials
Risk factors and risk groups	Risk factors and risk groups include women of childbearing potential, pregnant women, lactating women, and male patients with female partners of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, 4.6, and 5.3 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for verification of pregnancy status in women of childbearing potential prior to initiating treatment with tucatinib is included in SmPC Section 4.6 • Recommendation for males and females of reproductive potential to use contraception during and up to at least 1 week after treatment is included in SmPC Section 4.6 Additional risk minimisation measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin	
Risk minimisation measures	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • SGNTUC-016 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients who are known carriers of hepatitis B and/or hepatitis C, or who have auto-immune hepatitis, sclerotizing cholangitis, or other known chronic liver disease	
Risk minimisation measures	Routine risk communication for hepatotoxicity: • SmPC Section 4.2, 4.4, and 4.8 • PL Section 2, 3, and 4 Routine risk minimisation activities recommending specific clinical measures for hepatotoxicity to address the risk: • Recommendations for liver function monitoring are included in Section 4.4 Other risk minimisation measures beyond the PI: • None

Missing information: Long term safety	
Risk minimisation measures	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the PI: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • SGNTUC-016 and SGNTUC-017 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TUKYSA.

II.C.2 Other Studies in Post-authorisation Development Plan

SGNTUC-016 (HER2CLIMB-02)

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting.

SGNTUC-017 (MOUNTAINEER)

This is a multicenter, randomized, open-label, Phase 2 study of tucatinib, administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC.

PART VII ANNEXES

Table of Contents

Annex 1. Eudravigilance Interface

Not applicable.

Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex II: Planned and Ongoing Studies from the Pharmacovigilance Plan			
Study	**Summary of Objectives**	**Safety Concerns Addressed**	**Protocol Link Milestone**
SGNTUC-016: A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer (HER2CLIMB-02) Category 3	Evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting Further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, missing information for patients with prior cumulative anthracycline doses equivalent to >360 mg/m^2 doxorubicin, long-term safety	Link to SGNTUC-016 protocol Projected final study report submission: [redacted]
SGNTUC-017: Tucatinib plus Trastuzumab in Subjects with HER2+ Colorectal Cancer (MOUNTAINEER) Category 3	Evaluate the efficacy and safety of tucatinib administered as monotherapy and in combination with trastuzumab, in subjects with HER2-positive, RAS wild-type, unresectable or metastatic CRC Further assess and characterise important risks and missing information	Diarrhoea, hepatotoxicity, embryo-foetal toxicity, long-term safety	Link to SGNTUC-017 protocol Projected final study report submission: [redacted]

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Table of Contents

Part A: Requested Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review with This Updated Version of the RMP

Not applicable.

Part B: Requested Amendments of Previously Approved Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review With This Updated Version of the RMP

Not applicable.

Part C: Previously Agreed Protocols for Ongoing Studies and Final Protocols Not Reviewed by the Competent Authority

Approved protocols:

Not applicable.

Final protocols not reviewed or not approved:

SGNTUC-016 Protocol AM1.1

SGNTUC-017 Protocol Amendment 9

Annex 4. Specific Adverse Drug Reaction Questionnaires

Follow-up Form Title	Version Number	Date of Follow-up Version
Hepatic Event Questionnaire	0.2	21-Jul-2020
Adverse Experience Reporting Form	0.2	21-Jul-2020

Hepatic Event Questionnaire

Patient Information		
Patient ID/Initials:	DOB (or age):	Gender: ☐ Male ☐ Female

Description of Event

1. What action was taken with SGN drug after event onset?

☐ No change
☐ SGN drug dose or dosing frequency decreased to _____on (date) _____
☐ SGN drug dose held on (date) _____
☐ SGN drug discontinued on (date) _____ due to event
☐ SGN drug discontinued on (date) _____ for reasons NOT due to event
☐ Other_____

2. If change in SGN drug dosing, did event abate or stop after the above action? ☐ Yes ☐ No

If Yes, please also complete question 5.

a. If yes, on what date? _____☐event abated ☐event fully resolved

3. Had there been intervening treatment? ☐ Yes ☐ No

a. If yes, please describe:

4. Had there been changes in patient's routine care, such as changes in concomitant meds prior to and after event onset? ☐ Yes ☐ No

a. If yes, please describe:

5. Was SGN drug administered again following event abatement/resolution? ☐ Yes ☐ No

a. If yes, on what date_____
b. Describe any changes to dose or frequency _____
c. Did event reoccur? ☐ Yes ☐ No
   - If yes, please describe (with date):

6. Were possible alternative explanation(s) identified: ☐ Yes ☐ No

If yes, please check all that apply:

☐ Progression of underlying disease (specify): _____
☐ Liver involvement ☐ Yes ☐ No
☐ Bone involvement ☐ Yes ☐ No
☐ Right sided heart failure/ cor pulmonale
☐ Connective tissue disorder/ auto-immune disease _____
☐ Change in glucocorticoid administration in month prior to C1D1 through present
☐ Concomitant medications (include herbs, OTCs, dietary supplements, illicit drugs, toxins): (specify, including start/stop dates)

_____

☐ Acute or Chronic Viral hepatitis:
(specify, including results of serologic studies and/or DNA/RNA load)

_____

☐ Biliary tract disorder

- ☐ Autoimmune hepatitis
- ☐ Alcoholic hepatitis/ cirrhosis
- ☐ Muscle disorder/injury
- ☐ Fatty liver or NASH
- ☐ Obesity
- ☐ Ischemic hepatitis
- ☐ Gilbert's Syndrome
- ☐ Sclerosing cholangitis
- ☐ Significant Infection (e.g. pneumonia, sepsis)
- ☐ Other known chronic liver disease
- ☐ Other Pre-existing and/or concurrent conditions (i.e., infection):

(specify)_____

7. List all dated oncology therapies, i.e., chemotherapy, immunotherapy, radiation (location):

8. Were any liver imaging studies performed such as abdominal sonogram or CT scan? If yes, specify, and include date of exam and copy of results, from C1D1 and time of event, as available.

9. If not already submitted, please provide all available liver function test results from C1D1 through event resolution (total bilirubin, AST, ALT, Alkaline Phosphatase, GGT) with dates and reference ranges.

	Date	T Bili	AST	ALT	ALP	GGT
C1D1						
Event onset						
Event resolution						

10. Alcohol use: type, amount and servings/day and times/week?

11. Results of hepatitis B and C and other viral testing done at screening:

SeattleGenetics

ADVERSE EVENT REPORT FORM

Reporter

Is the reporter a Health Care Professional (HCP)? ☐ Yes ☐ NO

Reporter Name: _____ Institution: _____ Address:_____

City: _____ State/Provice/Region: _____Country: _____ Zip/Postal Code: _____

Phone: _____ Email address: _____

Does the reporter agree to be contacted for further information about this report ☐ Yes ☐ No

Country where the event/events occurred: _____

Patient Information

First name: _____ Last name: _____ Birth Date: ___/___/___ Age: _____ (DD/MMM/YYYY)	Gender: ☐ Male ☐Female	Pregnant? ☐ Yes ☐ No ☐ Unknown	Height: _____ ☐ in ☐ cm	Weight _____ ☐ kg ☐ lbs	Ethnicity ☐ Hispanic/Latino ☐ Asian ☐ Black or Africa American ☐ American Indian or Alaskan Native ☐ White ☐ Native Hawaiian or other Pacific Islander

Seat le Genetics (Trade) Name	Trade name Indication	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Ongoing? Yes; No	Batch # / Lot #	Dosage/Unit	Route	Frequency	Action Taken 1. Dose not changed 2. Dose decreased 3. Dose increased 4. Discontinued due to AE 5. Discontinued not due toAE 6. Dose delayed (held)
		/ /	/ /		/				

Adverse event(s)	Serious Yes/No? If Yes, 1. Non-serious 2. Medically Significant 3. Death 4.Life threatening 5.Initial hospitaliza ion (date of admission / /) (DD/MMM/YYYY) 6.Prolonged hospitalization 7.Significant disability 8.Congenital anomaly 9.Medically Significant	Start Date (DD-MMM-YYYY)	Stop Date (DD-MMM-YYYY)	Outcome 1. Recovered/Resolved 2. Recovered/Resolved with sequelae, specify sequelae_____ 3. Stabilized 4. Recovering/Resolving 5. Improved 6. Not recovered/Not resolved 7. Fatal ★ If Fatal, please complete the section on Pg.2	Trade name drug /Event relationship 1. Related 2. Definitely related 3. Possibly related 4. Probably related 5. Unlikely related 6. Not related 7. Unassessable 8. Unknown	Did the event abate after cessation or dose reduction? 1. Yes 2. No 3. Unknown 4. Not applicable (N/A)	Did event reappear after drug was reintoduced? 1. Yes 2. No 3. Unknown 4. Not applicable (N/A)
		/ /	/ /				
		/ /	/ /				
		/ /	/ /				

Description of Adverse event:

ADVERSE EVENT REPORT FORM

Could underlying medical condi ions, other medications, or other factors account for the adverse event(s)?

☐Yes ☐No ☐Maybe

Please explain:

Death Details

★ Only complete if the outcome was Fatal: Date of death _____/ Primary Cause of Death: _____

Product Complaint

Was AE/AEs associated with Product Complaint ☐ Yes ☐ No

If Yes, please describe nature of the product complaint: _____ (make background white)

Concomitant Medications (Include prescribed medications, homeopathic treatments, herbal treatments, vitamins, supplements and other nonprescription over the counter (OTC) medications.)
Please provide concomitant medications below OR attach list: ☐ See attached list for Concomitant Medications

Drug name	Indication	Dosage/Unit	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Ongoing? Yes or No
			/ /	/ / ☐ N/A	
			/ /	/ / ☐ N/A	
			/ /	/ / ☐ N/A	
			/ /	/ / ☐ N/A	

Relevant Tests/Laboratory data (include dates with biopsy, tests with negative results and/or autopsy results)

Medical History/Current Conditions: Please provide medical history below **OR** attach list: ☐ See attached list for Medical History/Current Conditions

Condition	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Ongoing? Yes or No	Condition	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Ongoing? Yes or No
	/ /	/ / ☐ N/A			/ /	/ / ☐ N/A	
	/ /	/ / ☐ N/A			/ /	/ / ☐ N/A	
	/ /	/ / ☐ N/A			/ /	/ / ☐ N/A	
	/ /	/ / ☐ N/A			/ /	/ / ☐ N/A	
	/ /	/ / ☐ N/A			/ /	/ / ☐ N/A	

ADVERSE EVENT REPORT FORM

Prior Systemic Oncology therapy (list all prior therapies by cycle and date)
Did the subject receive cumulative dose of doxorubicin >360 mg/m2 or another anthracycline with cumulative dose approximately equivalent to >360 mg/m2 doxorubicin?
Prior Cancer Surgeries and Radiations (list all dated procedures, i.e., surgeries, radiation [location])
Drugs and or therapy used to treat AE/AE(s) : ☐ **Yes** ☐ **No** if Yes, specify drugs/therapy used for each AE: _____
Other safety information: Counterfeit
☐ Abuse ☐ Batch and lot tested and found within specifications ☐ Batch and lot tested and found not within specifications ☐ Counterfeit ☐ Drug taken by a someone other than the patient ☐ Drug taken beyond expiry date ☐ Medication error ☐ Misuse ☐ Occupational exposure ☐ Off label use ☐ Overdose ☐ Tampering

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

Not applicable.

Annex 6. Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

Not applicable.

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Annex 8. Summary of Changes to the Risk Management Plan Over Time

Not applicable.

SeattleGenetics

Protocol Number:	SGNTUC-016
Version:	Amendment 1.1; 20-Dec-2019
Protocol Title:	Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer **(HER2CLIMB-02)**
Investigational Product:	Tucatinib
Brief Title:	A study of tucatinib vs. placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with advanced or metastatic HER2+ breast cancer
Indication:	Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer
Phase:	3
IND Number:	119421
EudraCT Number	2019-005017-39
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	Evelyn L. Rustia, MD Seattle Genetics, Inc. Tel: [redacted] E-mail: [redacted]
SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number SGNTUC-016 **Version** Amendment 1.1; 20-Dec-2019 **Phase** 3	**Product Name** Tucatinib **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer **(HER2CLIMB-02)**

Study Objectives

Primary

- Compare progression-free survival (PFS) by investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms

Key Secondary

- Compare overall survival (OS) between treatment arms
- Compare the objective response rate (ORR) by investigator assessment per RECIST v1.1 between treatment arms

Other Secondary

- Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1 between treatment arms
- Evaluate PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms
- Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms
- Evaluate the ORR by BICR per RECIST v1.1 between treatment arms
- Evaluate the duration of response (DOR) by investigator assessment per RECIST v1.1 between treatment arms
- Evaluate the DOR by BICR per RECIST v1.1 between treatment arms
- Evaluate the clinical benefit rate (CBR; stable disease [SD] or non-complete response [CR]/non-progressive disease [PD] for ≥6 months or best response of complete response [CR] or partial response [PR]) by investigator assessment per RECIST v1.1 between treatment arms
- Evaluate the CBR by BICR per RECIST v1.1 between treatment arms
- Evaluate the safety of tucatinib in combination with T-DM1

Exploratory

[redacted]

Study Population

Eligible subjects are at least 18 years of age and have unresectable locally-advanced or metastatic (LA/M) human epidermal growth factor receptor 2 (HER2)-positive breast cancer with a life expectancy of at least 6 months. Subjects must have histologically confirmed HER2+ carcinoma, had prior treatment with a taxane and

trastuzumab in any setting (separately or in combination), and must have progressed or have been intolerant of the last systemic therapy. Hormone receptor (HR) status must also be known prior to randomization. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, adequate cardiac function, and adequate renal, hepatic, and hematologic function at baseline. Prior treatment with tucatinib, T-DM1, lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity) , neratinib, afatinib, trastuzumab deruxtecan (DS8201a), or any other investigational anti-HER2 or anti-epidermal growth factor receptor (EGFR) agent or HER2 tyrosine kinase inhibitor (TKI) agent is not permitted. Prior pertuzumab therapy is allowed, but not required. Subjects must be >3 weeks post-treatment from any prior systemic anti-cancer therapy (including hormonal therapy), non-central nervous system (CNS) radiotherapy or participation in another interventional clinical trial.

Subjects with untreated brain metastases on screening brain magnetic resonance imaging (MRI) are eligible if immediate local therapy is not required. Subjects with brain metastases previously treated with local therapy are eligible if the brain metastases are stable since treatment; or, if there has been progression since the prior local CNS therapy, immediate re-treatment with local therapy is not required. If treatment for newly identified lesions is initiated, subjects may still be eligible if other sites of evaluable disease are present and treatment is completed prior to the first dose of study treatment as follows: stereotactic radiosurgery (SRS) is completed ≥7 days prior, whole brain radiation therapy is completed ≥14 days prior, or time since surgical resection is ≥28 days. Ongoing use of systemic corticosteroids at a total daily dose of >2 mg of dexamethasone (or equivalent) for symptomatic control is not permitted. Subjects with poorly controlled generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy are not permitted.

Number of Planned Subjects

Approximately 460 subjects (approximately 230 subjects per treatment arm) will be randomized in this study.

Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Subjects will be randomized in a 1:1 manner to receive 21-day cycles of either tucatinib or placebo in combination with T-DM1. Randomization will be stratified by line of treatment for metastatic disease, HR status, presence or history of brain metastases, and ECOG performance status.

While on study treatment, subjects will be assessed for progression every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. After completion of study treatment and after occurrence of disease progression, subjects in both arms of the study will continue to be followed for survival until study closure or withdrawal of consent.

An Independent Data Monitoring Committee (IDMC) will periodically review relevant aggregate safety data (blinded and unblinded) and will make recommendations to the sponsor. Safety will also be monitored in an ongoing, blinded basis by the sponsor throughout the study.

Investigational Product, Dose, and Mode of Administration

Subjects will be randomized in a 1:1 manner to receive study treatment on a 21-day cycle, either:

- Control arm: Placebo given orally twice a day (PO BID); T-DM1 3.6 mg/kg given intravenously (IV) every 21 days
- Experimental arm: Tucatinib 300 mg PO BID; T-DM1 3.6 mg/kg IV every 21 days

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. In the absence of clear evidence of radiographic progression, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs. No crossover from placebo to

tucatinib will be allowed. Subjects assessed as having isolated progression in the brain per RECIST v1.1, may be eligible to continue on study treatment for clinical benefit after undergoing local therapy to CNS disease, with approval from the medical monitor.

Efficacy Assessments

Disease response per RECIST v1.1 (Eisenhauer 2009) will be assessed by both investigator assessment and BICR. Response assessments will include measurement of all known sites of unresectable LA/M disease (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose interruptions. Positron emission tomography (PET)/CT (if high quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other known sites of disease (e.g., skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions).

Contrast MRI of the brain will be required on this same schedule only in those subjects with prior history of brain metastases or brain metastases found at screening. Additional contrast MRIs of the brain may also be performed in subjects without known brain metastases if there is clinical suspicion of new brain lesions.

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each subject will continue until a PFS event per RECIST v1.1 by investigator assessment has been documented. Follow-up for survival will continue until study closure or withdrawal of consent.

[redacted]

Safety Assessments

Safety assessments will include surveillance and recording of AEs, physical examination findings, and laboratory tests. Assessment of cardiac ejection fraction will be performed by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO).

Statistical Methods

Stratification

Stratification factors will include line of treatment for metastatic disease (1st line vs. other), HR status (positive/negative), presence or history of treated or untreated brain metastases (yes/no), and ECOG performance status (0 vs. 1). Stratification for presence of brain metastases will be based upon medical history and investigator assessment of screening contrast brain MRI.

Sample Size Considerations

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of PFS events (hazard ratio [HR] of 0.70; median PFS from 6 months in the control arm to 8.57 months in the experimental arm).

A total of [redacted] PFS events will provide [redacted] power to detect a hazard ratio of 0.70 at a 2-sided significance level of 0.05 using a log-rank test. Approximately 460 subjects will be randomized in a 1:1 ratio to either the experimental arm or the control arm to observe [redacted] PFS events in approximately [redacted] after the first subject is randomized, assuming [redacted] of subject accrual, a 5% annual dropout rate, and [redacted] of follow-up after the last subject is randomized.

It is planned that follow-up for OS will continue after the primary analysis of PFS until approximately [redacted] OS events have been observed. With [redacted] events, it will provide [redacted] power to detect a hazard ratio of 0.70 in OS at a 2-sided significance level of 0.05 using a log-rank test. The final analysis of OS is estimated to take place approximately [redacted] after the primary analysis of PFS assuming that OS for the control arm is following an exponential distribution with a median of [redacted]

Analysis Methods

For the primary endpoint of PFS by investigator assessment, the 2 treatment groups will be compared using a 2-sided stratified log-rank test. Estimation of the hazard ratio will be based upon the stratified Cox regression model. PFS will also be summarized using the Kaplan-Meier method. All randomized subjects will be included in the primary analysis of PFS. Kaplan-Meier methodology will be used to estimate the PFS time curves, including the median. Similar methods will be used for the key and other secondary time-to-event endpoints and other exploratory time-to-event endpoints.

No interim analyses will be performed for the primary endpoint. If PFS per investigator is statistically significant, then there will be two possible analyses of the key secondary endpoint of OS. The first OS analysis is at the time of analysis of primary endpoint when approximately [redacted] PFS events per investigator assessment have occurred. The final OS analysis is planned when approximately [redacted] OS events have been observed. If the OS result is statistically significant at either the first or the final analysis, a formal statistical test of ORR will be performed.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BICR	blinded independent central review
BID	twice a day
CBC	complete blood count
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
[redacted]	[redacted] Questionnaire
EOT	end of treatment
[redacted]	[redacted]
ER	estrogen receptor
[redacted]	[redacted]
FACIT	The Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GFR	glomerular filtration rate
HCRU	healthcare resource utilization
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
HIV	human immunodeficiency virus
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio

IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
HR	hazard ratio
LA/M	locally-advanced or metastatic
LFT	liver function test
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NCI-PRO-CTCAE	National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDX	patient-derived
PET	positron emission tomography
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PR	progesterone receptor
PRO	patient-reported outcome
PTT	partial thromboplastin time
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic oxoloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRS	stereotactic radiosurgery
T-DM1	ado-trastuzumab emtansine
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBRT	whole-brain radiation therapy

1 INTRODUCTION

1.1 HER2+ Breast Cancer

Breast cancer is the most common form of cancer in women worldwide, and the second leading cause of cancer-related death in the United States (Ferlay 2013; Siegel 2018). In 2018, the estimated number of men and women that were newly diagnosed with breast cancer in the United States was 268,670 and there were 40,920 deaths overall due to the disease (Siegel 2018). Approximately 15%–20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) (American Cancer Society 2018; Giordano 2014; Howlader 2014; Owens 2004). HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and historically have been associated with poorer overall survival (OS) compared to HER2 negative cancers (Slamon 1987).

The introduction of HER2-targeted therapy using either antibody-based therapies or small molecule tyrosine kinase inhibitors (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the neoadjuvant/adjuvant and metastatic settings (Baselga 2012b; Geyer 2006; Slamon 2001; Verma 2012). Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, was the first anti-HER2 agent approved by the Food and Drug Administration (FDA) for use in the treatment of HER2+ breast cancer, and remains the backbone of treatment in the neoadjuvant, adjuvant, and metastatic settings, usually in combination with a taxane (Slamon 2001; Vogel 2002).

The development of trastuzumab has been followed by the approval of multiple anti-HER2 agents for the management of HER2+ breast cancer including:

- Pertuzumab, a monoclonal antibody that binds to the HER2 receptor at a site different from trastuzumab, was approved in combination with trastuzumab and docetaxel as first-line therapy for patients with metastatic disease (Swain 2015), and for the neoadjuvant treatment of patients with early stage breast cancer (either greater than 2 cm in diameter or node positive) (Gianni 2016) (PERJETA® Prescribing Information, Genentech, Inc., December 2018). More recently, it was approved for the adjuvant treatment of patients with HER2+ early breast cancer at high risk of recurrence (von Minckwitz 2017).
- Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate composed of trastuzumab, a thioether linker, and a derivative of the antimitotic agent maytansine, was approved for the treatment of patients with HER2+ metastatic breast cancer (mBC) who previously received trastuzumab and a taxane (prior therapy for metastatic disease, or development of recurrence during or within 6 months of completing adjuvant therapy) (Verma 2012) (KADCYLA® Prescribing Information, Genentech, Inc., December 2018). More recently, T-DM1 showed superior efficacy relative to trastuzumab in the adjuvant therapy management of subjects who had less

than a pathological complete remission to neoadjuvant trastuzumab-based therapy in the KATHERINE trial (von Minckwitz 2019).

- Two TKIs, lapatinib and neratinib have been approved. Lapatinib targets both the HER2 receptor and the epidermal growth factor receptor (EGFR) and was approved in combination with capecitabine in patients with metastatic disease who have progressed following prior trastuzumab, anthracycline, and taxane therapy (Geyer 2006) (TYKERB® Prescribing Information, Novartis Pharmaceuticals Corp., December 2018). Lapatinib has also been approved in combination with letrozole in postmenopausal patients with hormone receptor (HR) positive metastatic disease (Schwartzberg 2010). Neratinib, a pan-Erb inhibitor, was approved for the extended adjuvant treatment of patients with high-risk early stage HER2+ breast cancer, to follow adjuvant trastuzumab-based therapy (Chan 2016). Lapatinib and neratinib have been associated with toxicities including diarrhea and rash that are likely associated with EGFR inhibition. As an example, over 40% of subjects in the neratinib adjuvant ExteNET study experienced Grade ≥3 diarrhea, and antidiarrheal prophylaxis is now recommended with neratinib use (NERLYNX® Prescribing Information, Puma Biotechnology, Inc., June 2018). Therefore, more selective small molecule inhibitors of HER2 that could be combined with other anti-HER2 therapies to improve clinical outcomes are needed.

HER2-targeted therapies for the management of metastatic HER2+ breast cancer have led to meaningful prolongation in the median survival of these subjects; however, essentially all subjects in the metastatic setting ultimately progress (Swain 2015; Verma 2012). There have also been significant improvements in the outcomes for early stage HER2+ breast cancer, but despite these improvements, up to a quarter of all subjects treated with anti-HER2 therapy in the adjuvant setting relapse (Chan 2016; Gianni 2012; von Minckwitz 2017). In addition, treatment and prevention of brain metastases continue to be a significant unmet need for subjects with HER2+ breast cancer, with up to 50% of subjects with metastatic disease eventually developing brain metastases (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013).

1.2 Use and Sequencing of T-DM1 in the Metastatic Setting

As noted above, T-DM1 is approved for the treatment of HER2+ mBC. The sequencing of therapy may differ, however, depending on whether a subject has de novo versus relapsed metastatic HER2+ mBC.

The current standard of care for patients with de novo HER2+ metastatic disease consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line treatment, followed by T-DM1 in second line (Giordano 2014). This standard is based upon data demonstrating a significant improvement in OS in the CLEOPATRA trial as initial therapy in the metastatic setting, where median OS was 56.5 months (95% confidence interval [CI]: 49.3, not reached) in the pertuzumab + trastuzumab + docetaxel combination group versus 40.8 months (95% CI: 35.8, 48.3) in the trastuzumab + docetaxel group (hazard ratio [HR]=0.68) (Swain 2015). T-DM1 was approved as a second-line therapy based upon prolongation of PFS and OS in

metastatic subjects previously treated with trastuzumab and taxane in the metastatic setting, or who relapsed within 6 months of completion of adjuvant therapy, based on the results of the EMILIA trial. Among 991 randomly assigned subjects, median PFS was 9.6 months with T-DM1 versus 6.4 months with lapatinib + capecitabine (HR=0.65; 95% CI: 0.55, 0.77; P<0.001), and median OS of 30.9 months versus 25.1 months (HR=0.68) (Verma 2012).

The sequencing of therapies may differ for patients who relapse after treatment for early-stage disease with the approval of pertuzumab in both the neoadjuvant and adjuvant settings. Patients now diagnosed with metastatic disease after relapsing from early stage disease often have already been treated with pertuzumab, a clinical scenario which did not exist at the time of the EMILIA trial. The best treatment approach for these patients is not clear, as there are not sufficient data to support re-treatment with pertuzumab in this setting versus treatment with T-DM1. In the CLEOPATRA trial of first-line pertuzumab therapy (pertuzumab + trastuzumab + docetaxel versus trastuzumab + docetaxel), only 11% of subjects had previously been exposed to trastuzumab in neoadjuvant or adjuvant disease, and the trial also excluded subjects who relapsed from early disease <12 months after adjuvant therapy. Moreover, the PHEREXA study of pertuzumab in subjects with metastatic disease previously treated with trastuzumab failed to demonstrate any benefit by adding pertuzumab therapy (Urruticoechea 2018). Although the original T-DM1 pivotal trial (EMILIA) limited first-line metastatic therapy to those subjects who relapsed within 6 months of adjuvant therapy, given that there are little data to support retreatment of subjects with pertuzumab after metastatic relapse, T-DM1 may be considered as a first-line therapy for metastatic disease in a post-pertuzumab setting to avoid the likelihood of acquired resistance to pertuzumab plus trastuzumab and taxane, as well as cumulative toxicities such as taxane-associated-neuropathy.

Another uncertainty, introduced by contemporaneous development of pertuzumab and T-DM1, is that efficacy of T-DM1 in the metastatic setting after treatment with pertuzumab-based regimens is not well known. Because pertuzumab was not yet available, the EMILIA pivotal trial did not include subjects previously treated with pertuzumab, so it may not reflect the current patient population in this setting. The TH3RESA trial of T-DM1 in the third-line+ setting demonstrated a median PFS of 6.2 months (95% CI: 5.59, 6.87) with T-DM1 treatment (Krop 2014), while the earlier line EMILIA trial had demonstrated PFS of 9.6 months (HR=0.65; 95% CI: 0.55, 0.77; P<0.001) (Verma 2012). However, more recent data from the post-pertuzumab era in subjects treated with T-DM1 after pertuzumab have reported time on treatment and PFS in the range of 4–5.3 months (Dzimitrowicz 2016; Fabi 2017; Tiwari 2018), suggesting that T-DM1 efficacy after pertuzumab may be less than the original efficacy reported in the EMILIA trial. Notwithstanding some of the above uncertainties regarding current T-DM1 efficacy, it is a standard of care and can be further improved upon.

1.3 Brain Metastases

Over the last 2 decades, advances in the development of cancer therapies for HER2+ mBC have resulted in better control of systemic disease. Because of this significant improvement,

subjects live longer (as demonstrated by increases in PFS and OS) and more subjects develop brain metastases. Clinical trials suggest that there is an increased risk of first relapse occurring in the central nervous system (CNS) in subjects who have received trastuzumab-based adjuvant therapy (Clayton 2004; Olson 2013a; Olson 2013b), and up to 50% of HER2+ subjects with metastatic disease will develop CNS metastases at some point during the course of the disease (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013). The increasing prevalence of CNS metastases in subjects with HER2+ breast cancer may be due to several factors (Lin 2004). First, HER2+ breast cancer appears to display a special tropism for the CNS tissue. Second, with better control of non-CNS disease, subjects may be living longer allowing CNS metastases to become more of a critical clinical issue. Finally, the CNS may represent a sanctuary site for HER2+ disease, as large molecules such as trastuzumab and pertuzumab do not penetrate the blood-brain barrier to any meaningful extent at approved doses. The evidence suggests that drug blood-brain barrier permeability is most likely a function of not only P-glycoprotein expression but also the interplay of molecule size, charge, lipophilicity, tumor neovasculature anatomy, and plasma protein binding (Gerstner 2007). Therefore, HER2-targeted therapies that distribute into the brain are needed.

Treatment for brain metastases usually includes either surgical resection, radiosurgery, and/or whole brain radiotherapy in addition to continuation of systemic anti-HER2 therapy. Unfortunately, these treatments often result in significant neurologic toxicities, which may impair quality of life (QoL). Stereotactic radiosurgery (SRS) has been increasingly used to avoid the neurologic toxicities of whole-brain radiotherapy, but the trade-off for this decrease in toxicity has been inferior control of distant brain relapse outside of the radiation fields (Brown 2016; Chang 2009; Kaidar-Person 2016). No systemic agents are approved for treatment of HER2+ mBC, and generally these subjects are treated outside of clinical trials with therapies not labeled for this indication (Lin 2015). In addition, subjects with brain metastases have historically been excluded from clinical trials.

Breast cancer subjects with HER2+ brain metastases have a worse prognosis relative to those without CNS disease. In population-based registries of HER2+ mBC subjects enrolled at diagnosis, evidence of brain metastases leads to a shortened survival relative to subjects without brain metastases (Brufsky 2011). Among the 377 subjects with brain metastases, median OS from the date of initial mBC diagnosis was 26.3 months (range: 1.0 to 60.9 months) compared to 44.6 months (range: 0.5 to 59.7 months) in the 635 subjects who did not have CNS metastases (Brufsky 2011).

As with many systemic therapies, T-DM1 may also be less efficacious in patients with brain metastases than in patients without. While subjects with active brain metastases were excluded from the EMILIA and TH3RESA T-DM1 trials, subjects with stable treated brain metastases were included. In the EMILIA trial, subjects with brain metastases treated with T-DM1 had no significant improvement in PFS compared to the control arm (5.9 months versus 5.7 months; HR=1.00; 95% CI: 0.54, 1.84; P=1.000) and the PFS of 5.9 months in subjects with brain metastases compared unfavorably to the median PFS of 9.6 months in the trial overall, although there was an improvement in OS (Krop 2015). In the third-line+

TH3RESA trial, subjects with stable treated brain metastases had similar median PFS but shorter median OS compared to subjects without [PFS: 5.8 months versus 6.2 months (Krop 2015); OS: 17.3 months versus 23.7 months (Krop 2017)]. Most recently, data from the KATHERINE trial demonstrated that adjuvant treatment with T-DM1 for high-risk subjects yielded a significant improvement in DFS, but failed to have any significant impact on the development of brain metastases (von Minckwitz 2019).

Overall, systemic therapies for HER2+ mBC have not yet demonstrated a clinically meaningful impact on the treatment of brain metastases. Development of treatments for this patient population remains an important unmet medical need, and addressing this need will require including these subjects in clinical trials.

1.4 Tucatinib

Tucatinib (ONT-380) is an orally-available, reversible HER2 small molecule TKI. Two key features of tucatinib are its potency and selectivity for HER2 compared to the closely-related kinase EGFR. Tucatinib is approximately 6-fold more potent in its inhibition of HER2 compared to lapatinib, the only currently approved HER2 TKI for patients with metastatic disease. In addition, tucatinib is highly selective for HER2 compared to EGFR. With a 500-fold increase in potency for HER2 inhibition compared to EGFR, it has the potential to inhibit HER2 signaling while avoiding known EGFR-related side effects (e.g., severe skin rash and gastrointestinal toxicity). This unique feature also differentiates tucatinib from other HER2 inhibitors, including both neratinib and lapatinib, which inhibit HER2 and EGFR with similar potency and are associated with side effects related to EGFR inhibition.

Tucatinib is being developed as a novel treatment for patients with metastatic HER2+ breast cancer, including patients with brain metastases. Clinical trials are ongoing to examine the safety and efficacy of tucatinib when combined with other anti-HER2 therapies.

A complete summary of the nonclinical and clinical data for tucatinib is provided in the Investigator's Brochure.

1.4.1 Rationale for Tucatinib in Combination with T-DM1

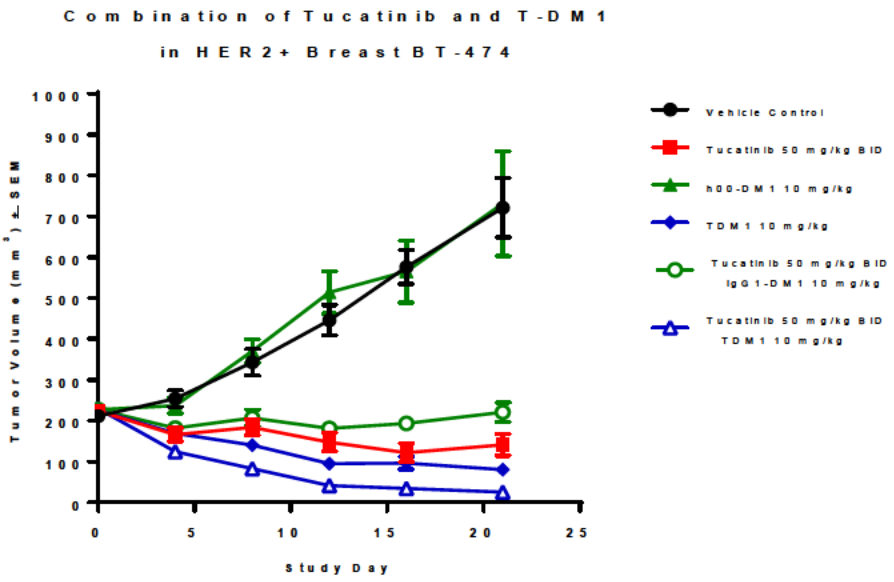
Treatment failures in HER2+ breast cancer may result from primary or acquired resistance to HER2 blockade (Lu 2001; Nahta 2006; Pohlmann 2009; Scaltriti 2007). There is evidence that dual targeting of HER2, either through combination of 2 different HER2-targeted antibodies or through use of an antibody-based therapy and a TKI, can lead to further improvements in efficacy in metastatic disease (Baselga 2012a; Baselga 2012b). In particular, combination of a small molecule TKI with an antibody-based therapy may be effective, as it may help overcome resistance to antibody-mediated inhibition via an alternative mechanism of receptor inhibition. For example, lapatinib has been shown to have increased activity in combination with trastuzumab compared to lapatinib alone, even when given to subjects who have previously progressed on prior trastuzumab-based therapy (Blackwell 2010; Blackwell 2012).

T-DM1 treatment results in the targeted delivery of the potent anti-mitotic DM1 to HER2+ tumor cells, which binds to tubulin and causes mitotic arrest and cell death (Lewis Phillips 2008). Combining tucatinib with T-DM1 may potentially improve upon the efficacy of T-DM1 through increased inhibition of HER2 signal transduction, including blockade of both the -Erk-/MEK and phosphatidylinositol 3-kinase (PI3K)/AKT pathways. Inhibition of pro-survival signaling mediated by the PI3K/AKT pathway, together with DM1 toxin delivery, may result in increased cell death, potentially overcoming or delaying the development of resistance.

1.4.2 Tucatinib + T-DM1 Preclinical Experience

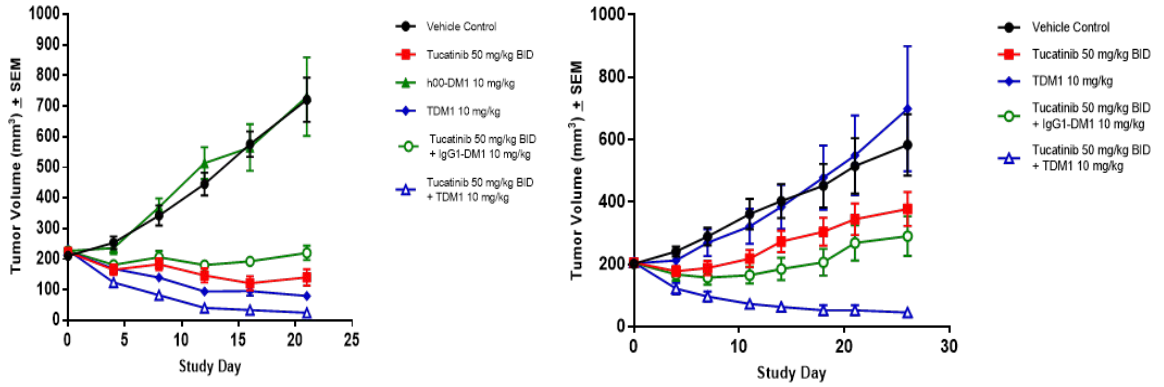
Pre-clinical data show the combination of tucatinib with T-DM1 results in improved anti-tumor activity in HER2+ breast cancer models. In HER2+ tumor-derived cell lines, tucatinib in combination with T-DM1 can result in additive or synergistic activity (data not shown). In addition, the combination of tucatinib and T-DM1 was more effective than either drug individually in the BT-474 cell line-derived xenograft model (Figure 1) and in 2 HER2+ patient-derived (PDX) breast cancer models (Figure 2). Each of the HER2+ PDX models are estrogen receptor /progesterone receptor -negative, immunohistochemistry 3+ for HER2, and contain genomic amplification of the HER2 gene.

Figure 1: Combination of tucatinib and T-DM1 in HER2+ breast cell line-derived xenograft model



Mice bearing BT474 subcutaneous xenografts were treated by oral gavage with tucatinib, intravenous T-DM1 or control IgG1DM1, or a combination of tucatinib with both drugs, at the dose levels and schedules as indicated.

Figure 2: Combination of tucatinib and T-DM1 in HER2+ patient-derived breast cancer model



Mice bearing HER2+ subcutaneous xenografts were treated by oral gavage with tucatinib, intravenous T-DM1 or control IgG1DM1, or a combination of tucatinib with both drugs, at the dose levels and schedules as indicated.

In the T-DM1 resistant PDX models, tucatinib inhibited tumor growth and the combination of tucatinib with T-DM1 produced increased tumor control when compared with either drug alone in the cell line derived BT-474 model, and in both PDX models.

1.4.3 Tucatinib + T-DM1 Clinical Experience

One clinical trial has been conducted to evaluate the safety, tolerability, and preliminary clinical activity of tucatinib in combination with T-DM1. Study ONT-380-004 is a phase 1b, open-label, multicenter, 3+3 dose-escalation study in subjects with HER2+ mBC, designed to identify the maximum-tolerated dose (MTD) or recommended phase 2 dose (RP2D) of tucatinib in combination with T-DM1. Subjects had a history of prior therapy with trastuzumab and a taxane, separately or in combination; for subjects in the dose-escalation and MTD-expansion cohorts, prior therapy with trastuzumab and a taxane must have been for metastatic disease. For subjects in the CNS disease-expansion cohorts, trastuzumab and taxane (together or separately) might have been given at any time prior to study enrollment as part of neoadjuvant therapy, adjuvant therapy, or therapy for metastatic disease.

Fifty-seven T-DM1-naive subjects were treated (Borges 2018). The tucatinib MTD was determined to be 300 mg administered orally twice per day (PO BID) in combination with the approved dose of T-DM1 (3.6 mg/kg every 21 days). Among the 50 subjects treated at the MTD, the most common adverse events (AEs) occurring in ≥40% of subjects were nausea, diarrhea, fatigue, epistaxis, headache, vomiting, constipation, and decreased appetite; the majority of AEs were Grade 1 or 2. In these 50 subjects, the median PFS was 8.2 months (95% CI: 4.8, 10.3); the clinical benefit rate (CBR; subjects with best response of complete response (CR) or partial response [PR], or stable disease [SD] for >6 months) among 48 evaluable subjects was 58% (28 subjects). Thirty-four of 50 subjects (68%) treated with the MTD had measurable disease and were evaluable for response with an objective response rate (ORR) of 47% (1 subject with CR, 15 subjects with PR 14 subjects with SD, and 4 subjects with disease progression). Among the subjects whose disease responded to treatment, the median duration of response (DOR) was 6.9 months (95% CI: 2.8, 19.8).

Thirty of 50 subjects (60%) treated at the MTD had brain metastases at study entry. Of these, 21 of 30 subjects (70%) had either untreated or previously treated and progressive brain metastases. Median PFS among subjects with brain metastases was 6.7 months (95% CI: 4.1, 10.2). Twenty-one of these 30 subjects had measurable disease and were evaluable for response with an ORR of 48% (1 subjects with CR, 9 subjects with PR, 10 subjects with SD, and 1 subject with progressive disease). Among these subjects, the median duration of overall response was 7 months (95% CI: 1.5, NE), according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Seattle Genetics internal data). The combination of tucatinib with T-DM1 was found to have a tolerable safety profile, with evidence of clinical activity, including in subjects with brain metastases.

1.4.4 Rationale for Study

The development and approval of multiple targeted agents for HER2+ breast cancer over the last 20 years has led to improvements in response rates, PFS, and OS. However, in most cases, subjects with mBC progress on currently available therapy and cannot be cured. The intent of this phase 3, randomized trial is to assess whether the addition of tucatinib to T-DM1 can not only improve the efficacy observed with T-DM1 as second-line therapy in subjects with metastatic HER2+ breast cancer that failed trastuzumab and taxane, but also whether the combination can be effective against CNS metastases in HER2+ breast cancer (an area of continued medical need).

Given tucatinib's selectivity for HER2 over EGFR, it has the potential to provide dual HER2 inhibition by combining with other oral anti-HER2 agents with fewer significant EGFR-related toxicities such as severe diarrhea. The combination of tucatinib and T-DM1 was found to be well-tolerated and showed clinical activity in the ONT-380-004 study. ONT-380-004 included a meaningful number of subjects with brain metastases, and preliminary data suggests activity, including intracranial responses and a similar median PFS in subjects with brain metastases compared to those without (Borges 2018; Murthy 2018). A systemic therapy such as tucatinib that effectively treats existing brain metastases could control neurologic symptoms of brain metastases and potentially delay the need for radiotherapy or surgical resection, thus avoiding the sequelae associated with progressive brain metastases and their local treatment. Furthermore, a systemic treatment effective against micrometastases could potentially prevent or delay the eventual development of clinically evident brain metastases. Based on preclinical data demonstrating improved anti-tumor activity of tucatinib in combination with T-DM1, as well as the experience on the phase 1b ONT-380-004 trial, the addition of tucatinib to T-DM1 could potentially further improve the efficacy of T-DM1 and the standard-of-care management, including in subjects with brain metastases.

2 OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of tucatinib versus placebo in combination with T-DM1 in subjects with unresectable locally-advanced or metastatic (LA/M) HER2+ breast cancer. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints

Objective	Corresponding Endpoint
Primary	
• Compare PFS by investigator assessment per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1, as determined by investigator assessment
Key Secondary	
• Compare OS between treatment arms	• OS
• Compare the ORR by investigator assessment per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by investigator assessment
Other Secondary	
• Evaluate PFS by BICR per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1, as determined by BICR
• Evaluate PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms	• PFS per RECIST v1.1, by investigator assessment in subjects with brain metastases at baseline
• Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms	• PFS per RECIST v1.1, by BICR in subjects with brain metastases at baseline
• Evaluate the ORR by BICR per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by BICR
• Evaluate the duration of response (DOR) by investigator assessment per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by investigator assessment
• Evaluate the DOR by BICR per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by BICR
• Evaluate the CBR (SD or non-CR or non-progressive disease [PD] for ≥6 months or best response of CR or PR) by investigator assessment per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by investigator assessment
• Evaluate the CBR by BICR per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by BICR
• Evaluate the safety of tucatinib in combination with T-DM1	• Incidence of AEs
Exploratory	
[redacted]	[redacted]

Objective	Corresponding Endpoint
[redacted]	[redacted]

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with T-DM1 in subjects with unresectable LA/M HER2+ breast cancer who have had prior treatment with a taxane and trastuzumab in any setting. Subjects will be randomized in a 1:1 manner to receive 21-day cycles of treatment in 1 of the following 2 treatment groups:

- Control arm: Placebo given PO BID; T-DM1 3.6 mg/kg given intravenously (IV) every 21 days
- Experimental arm: Tucatinib 300 mg PO BID; T-DM1 3.6 mg/kg IV every 21 days

Tucatinib or placebo will be dispensed to subjects in a double-blinded manner. Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing date, allowing for dose holds or delays with T-DM1. Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

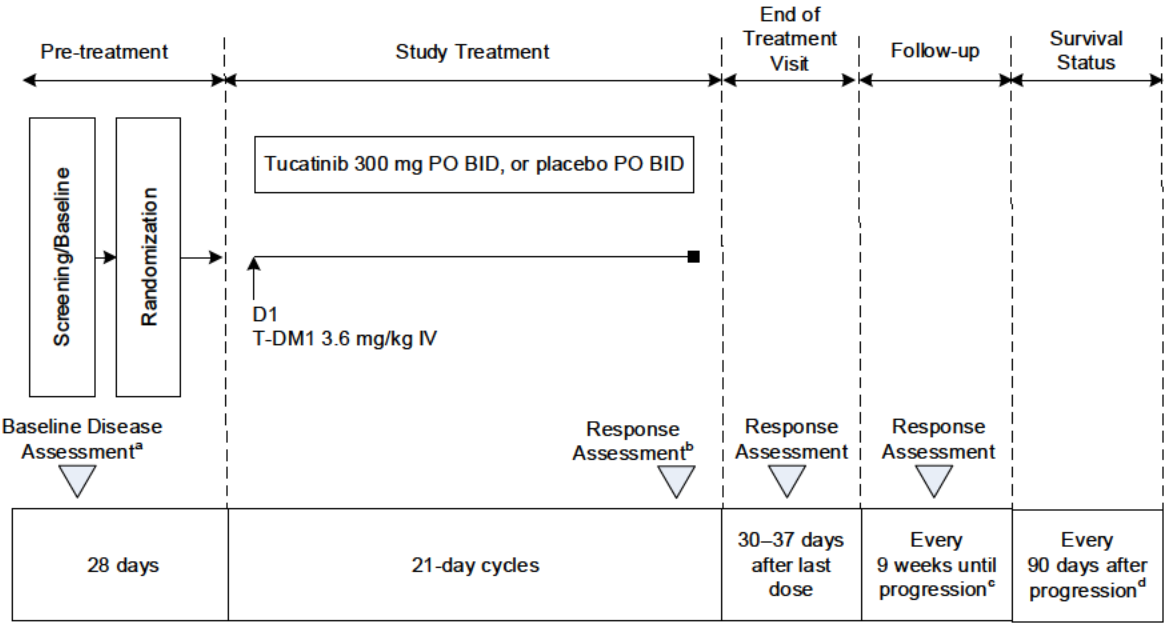
Disease response and progression will be assessed using RECIST v1.1. While on study treatment, radiographic disease evaluations will be performed every 6 weeks for the first 24 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions. In the absence of clear evidence of radiographic progression, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs. Subjects assessed as having isolated progression in the brain per RECIST v1.1, may be eligible to continue on study treatment for clinical benefit after undergoing local therapy for CNS disease, with approval from the medical monitor (see Section 4.4.1.1).

After completion of study treatment and after occurrence of disease progression, subjects in both arms of the study will continue to be followed for survival until study closure or withdrawal of consent.

Safety will be monitored on a blinded basis by the sponsor throughout the study. An independent data monitoring committee (IDMC) will regularly review all relevant aggregate safety data (blinded and unblinded).

Approximately 460 subjects (approximately 230 subjects per treatment arm) will be randomized in this study. A study schema is provided in Figure 3. See APPENDIX A for a schedule of evaluations.

Figure 3: Study schema



a Includes measurement of all known sites of unresectable LA/M disease via radiographic imaging. Assessment for brain metastases is performed with contrast magnetic resonance imaging (MRI) of the brain for all subjects, regardless of prior history of brain metastases.

b Response assessments are performed every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter, irrespective of dose holds or interruptions. Contrast brain MRI is required on this same schedule only in those subjects with known brain metastases.

c For subjects who discontinue study treatment prior to disease progression by investigator assessment (per RECIST v1.1), response assessments are performed every 9 weeks until disease progression, death, withdrawal of consent, or study closure. Contrast brain MRI is required on this same schedule only in those subjects with known brain metastases.

d After documented progression (per RECIST v1.1) or clinical progression by investigator assessment, continued follow-up for survival is performed every 90 days until death, withdrawal of consent, or study closure, whichever comes first.

[redacted]

3.1.1 Independent Data Monitoring Committee

The IDMC will be responsible for monitoring the safety of subjects in the study at regular intervals. The IDMC will look at blinded and unblinded data including deaths, discontinuations, dose reductions, AEs, and serious adverse events (SAEs) on a regular basis. The IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study for excessive toxicity. A separate IDMC Charter will outline the committee's composition, members' roles and responsibilities, and describe IDMC procedures. The sponsor will provide a copy of each IDMC recommendation to the investigators.

3.1.2 Stopping Criteria

Reasons for prematurely terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects, either through a safety review by the sponsor or an independent safety assessment by the IDMC.
- Subject enrollment is unsatisfactory.

3.1.3 End of Study

The study ends once the number of events required for analysis of endpoints (see Section 9.1) has been reached (estimated 5 years after first subject enrolled) or when the last subject completes the last visit, or last contact, discontinues from the study, or is lost to follow-up,

whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.3.2).

3.2 Discussion and Rationale for Study Design

Despite advances in treatment, unresectable LA/M HER2+ breast cancer is incurable. The primary goals of treatment remain to extend life and palliate symptoms while preserving QoL. As demonstrated by the phase 1 clinical experience, tucatinib has shown activity and a manageable safety profile in heavily pretreated subjects with unresectable LA/M HER2+ breast cancer, including those with brain metastases (Borges 2018; Hamilton 2018; Moulder 2017; Murthy 2018). All subjects enrolled in this study will receive either tucatinib or placebo in combination with T-DM1, a recommended standard of care regimen for treatment of patients with metastatic HER2+ who have progressed after prior treatment with trastuzumab and a taxane. Treatment with T-DM1 has been shown to prolong both PFS and OS in this population when compared to capecitabine and lapatinib (Verma 2012).

Patients with brain metastases from HER2+ breast cancer represent an important unmet medical need, and these patients are frequently excluded from clinical trials. This trial screens all subjects at baseline to determine if occult brain metastases are present, and subjects with brain metastases are included in the trial provided they do not require immediate local therapy and with medical monitor approval. The inclusion of this subject population is supported by data from ONT-380-004, the phase 1b study of tucatinib + T-DM1, in which a majority of subjects had brain metastases (Murthy 2018). Subjects with brain metastases in this trial had similar safety and efficacy outcomes compared to subjects without, and the activity of this combination will be further evaluated in this trial. Subjects randomized to placebo will be treated with T-DM1, which has been described in multiple smaller series to also show early evidence of activity in subjects with brain metastases (Jacot 2016; Krop 2017; Krop 2015).

The randomized, blinded trial design and the selection of PFS as the primary endpoint are based on the considerations outlined in the FDA Guidance for Industry “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics”) and the European Medicines Agency (EMA; “Guideline on the Evaluation of Anticancer Medicinal Products in Man”, EMA/CPMP/ 205/95 Rev.5) for approval of anticancer drugs. Defined as the time from randomization until objective tumor progression or death, PFS is a direct reflection of tumor growth and can be assessed before determination of a survival benefit. Furthermore, because PFS includes death from any cause, it may be a correlate to OS, a secondary endpoint of this study. An additional advantage of PFS is that its determination is not confounded by subsequent therapy. Standardized criteria (RECIST v1.1) will be employed to evaluate progression. To ensure consistent unbiased application of these criteria, all imaging studies performed to confirm disease status and to assess progression during the study will be submitted to an independent third-party imaging core laboratory for blinded review, and all subjects will have evaluations for progression performed on the same schedule.

3.2.1 Method of Assigning Subjects to Treatment Groups

Following informed consent and screening assessments, subjects will be randomly assigned to study treatment in a 1:1 ratio. Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

Randomization will be stratified by:

- Line of treatment for metastatic disease: 1st line vs. other
- HR status: negative vs. positive
- Presence or history of treated or untreated brain metastases: yes vs. no
- Eastern Cooperative Oncology Group (ECOG) performance status: 0 vs. 1

3.2.2 Rationale for Selection of Doses

In Study ONT-380-004, the phase 1b study of tucatinib administered in combination with T-DM1, the RP2D was defined as 300 mg PO BID. T-DM1 will be given at the full dose of 3.6 mg/kg IV every 21 days as approved for single-agent use.

3.2.3 Blinding and Unblinding

Maintaining the blind of the study is crucial for achieving the study objectives. Unblinding an individual subject treatment assignment may only occur when one of the following circumstances is applicable:

1. At the time of study closure, the study treatment assignment will be provided to the investigator.
2. Unblinding a subject's treatment assignment prior to study closure must be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the clinical management of the subject. In the event of such an emergency circumstance, a formal unblinding procedure, carried out by a third party organization will be followed to allow the investigator to immediately access a subject's treatment assignment (see Study Manual). Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence.

Details regarding unblinding procedures are described in the Study Manual.

3.2.3.1 Unblinding for Safety Monitoring

Safety data is monitored by an IDMC. Unblinding of aggregate safety data for ongoing safety monitoring and risk/benefit assessment by the IDMC will be performed through an independent Data Coordinating Center to ensure the integrity of the study.

Suspected unexpected serious adverse reactions will be unblinded in accordance with local regulatory reporting requirements. Pre-specified personnel from the sponsor Drug Safety Department will unblind the identity of study medication for any unexpected (as per the

Investigator's Brochure) SAEs that are considered to be related to the blinded study drug (tucatinib or placebo).

4 STUDY POPULATION

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Histologically confirmed HER2+ metastatic breast carcinoma, as determined by sponsor-designated central laboratory testing on tumor tissue submitted prior to randomization (see Section 7.1.1), from either:
   a. Archival tissue (most recent tumor tissue sample preferred)
   b. If archival tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated is required
2. History of prior treatment with a taxane and trastuzumab in any setting, separately or in combination. Prior pertuzumab therapy is allowed, but not required.
3. Have progression of unresectable LA/M breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Measureable or non-measurable disease assessable by RECIST v1.1
5. HR (estrogen receptor [ER]/ progesterone receptor [PR]) status must be known prior to randomization
6. Age ≥18 years at time of consent
7. ECOG performance status score of 0 or 1 (see APPENDIX B for conversion of performance status using Karnofsky scale, if applicable)
8. Life expectancy ≥6 months, in the opinion of the investigator
9. Adequate hepatic function as defined by the following:
   a. Total bilirubin ≤ 1.5 X upper limit of normal (ULN), except for subjects with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 X ULN
   b. Transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase [AST/SGOT] and alanine aminotransferase/serum glutamic pyruvic transaminase [ALT/SGPT]) ≤ 2.5 X ULN (≤ 5 X ULN if liver metastases are present)
10. Adequate baseline hematologic parameters as defined by:
    a. Absolute neutrophil count ≥1.5 X 10^3/μL
    b. Platelet count ≥100 X 10^3/μL
    c. Hemoglobin ≥9 g/dL

d. In subjects transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support

11. Estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation as applicable (see Section 7.8.4).
12. International normalized ratio (INR) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤ 1.5 X ULN, unless on medication known to alter INR and PTT/aPTT.
13. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment (see Section 6.2.2 for exceptions)
14. For subjects of childbearing potential, as defined in Section 4.3, the following stipulations apply:

    a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of study treatment. A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.

    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study drug administration

    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study drug administration

    d. If sexually active in a way that could lead to pregnancy, must consistently use highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration.

       Highly effective methods of birth control include:

       - Intrauterine device
       - Bilateral tubal occlusion/ligation
       - Vasectomized partner
       - Sexual abstinence when it is the preferred and usual lifestyle choice of the subject

15. For subjects who can father children, the following stipulations apply:

    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final study drug administration

    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

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

17. Subject must be willing and able to comply with study procedures

18. ***CNS Inclusion*** – Based on screening contrast brain magnetic resonance imaging (MRI), subjects must have at least **one** of the following:

    a. No evidence of brain metastases

    b. Untreated brain metastases not needing immediate local therapy. For subjects with untreated CNS lesions >2.0 cm in diameter on screening contrast brain MRI, approval from the medical monitor is required prior to enrollment.

    c. Previously treated brain metastases

        i. Brain metastases previously treated with local therapy may either be stable since treatment or may have progressed since prior local CNS therapy, provided that there is no clinical indication for immediate re-treatment with local therapy in the opinion of the investigator

        ii. Subjects treated with CNS local therapy for newly identified lesions found on contrast brain MRI performed during screening for this study may be eligible to enroll if all of the following criteria are met:

            - Time since SRS is ≥7 days prior to first dose of study treatment, time since whole-brain radiation therapy (WBRT) is ≥14 days prior to first dose of study treatment, or time since surgical resection is ≥28 days

            - Other sites of evaluable disease are present

        iii. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

4.2 Exclusion Criteria

1. Prior treatment with tucatinib, neratinib, afatinib, trastuzumab deruxtecan (DS-8201a), or any other investigational anti-HER2, anti-EGFR, or HER2 TKI agent. Prior treatment with lapatinib within 12 months of starting study treatment (except in cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity)
2. Prior treatment with T-DM1
3. History of allergic reactions to trastuzumab or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 infusion related reactions to trastuzumab that were successfully managed, or known allergy to any of the excipients in the study drugs
4. Treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, experimental agent or participation in another interventional clinical trial ≤3 weeks prior to first dose of study treatment. An exception for the washout of hormonal therapies is gonadotropin releasing hormone agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications.
5. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Alopecia;
    - Neuropathy, which must have resolved to ≤ Grade 2;
    - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
6. Clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension as determined by the investigator
    - Any history of symptomatic CHF, left ventricular systolic dysfunction or decrease in ejection fraction
    - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy
    - ≥ Grade 2 QTc prolongation on screening electrocardiogram (ECG)
7. Known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
8. Known carrier of Hepatitis B or Hepatitis C or has other known chronic liver disease
9. Known to be positive for human immunodeficiency virus.

10. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study drug
11. Unable to swallow pills or has significant gastrointestinal disease which would preclude the adequate oral absorption of medications
12. Use of a strong CYP3A4 or CYP2C8 inhibitor within 2 weeks, or use of a strong CYP3A4 or CYP2C8 inducer within 5 days prior to the first dose of study treatment (see Appendix C and Appendix D). CYP3A4 or CYP2C8 inducers and inhibitors are also prohibited as concomitant medications within two weeks of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates (Appendix E:) should be avoided two weeks before enrollment and during study treatment.
13. Unable to undergo contrast MRI of the brain
14. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
15. Evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment
16. ***CNS Exclusion*** – Based on screening brain MRI, subjects must not have any of the following:
    a. Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
    b. Ongoing use of systemic corticosteroids for control of symptoms of brain metastases at a total daily dose of >2 mg of dexamethasone (or equivalent). However, subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible with approval of the medical monitor.
    c. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to the subject (e.g., brain stem lesions). Subjects who undergo local treatment for such lesions identified by screening contrast brain MRI may still be eligible for the study based on criteria described under CNS Inclusion 17c (ii).
    d. Known or concurrent leptomeningeal disease as documented by the investigator
    e. Poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

4.3 Childbearing Potential

A person of childbearing potential is anyone born female, who has experienced menarche, and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as

12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male, who has testes, and who has not undergone surgical sterilization (e.g., vasectomy followed by a clinical test proving that the procedure was effective).

4.4 Removal of Subjects From Therapy or Assessment

Seattle Genetics 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 case report form (CRF).

4.4.1 Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- AE
- Progressive disease (PD; per RECIST v1.1), as assessed by the investigator
- Second disease progression after isolated progression in brain (see Section 4.4.1.1 regarding initial CNS-only progression)
- Investigator decision due to clinical progression
- Pregnancy or begins breastfeeding while on trial
- Investigator decision (other)
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

In the absence of clear evidence of disease progression (per RECIST v1.1), or development of CNS symptoms or radiographic changes thought to pose potential immediate risk to subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs (Section 7.2), as defined in RECIST v1.1. If study treatment is discontinued for reasons other than unequivocal disease progression (per RECIST v1.1) or death, subjects will continue in long-term follow-up until criteria for subject withdrawal from the study are met (Section 4.4.2). Every effort should be made to collect scans and clinical data until disease progression, in order to document a PFS event date. Following disease progression, subjects will continue in long-term follow up for survival.

Subjects who withdraw consent from the interventional portion of the study should specify whether to allow continued follow-up and further data collection subsequent to their withdrawal of consent, including but not limited to follow-up through medical records, public records, or other public platform. Every attempt should be made to follow the subject until progression, death, or administrative study closure.

In the absence of progression, subjects who discontinue T-DM1 due to a T-DM1-related toxicity, may continue receiving tucatinib/placebo alone. Subjects who discontinue tucatinib/placebo may continue to receive T-DM1 alone.

4.4.1.1 Continuation on Study Treatment After CNS-Only Progression

If a subject is found to have isolated progression in the CNS per RECIST v1.1 (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and does not have progression of disease outside the CNS, the subject may be eligible to continue on study treatment after completion of local treatment (radiotherapy or surgery) of any progressive brain/dural metastases to allow for clinical benefit. Local treatment must be completed prior to the subject's next response assessment timepoint. Subjects may continue on study treatment for clinical benefit after this PFS event in the brain, however, requires discussion with and documented approval from the study medical monitor and subjects may continue until either systemic progression or a second isolated CNS progression. The subject will remain on the same treatment arm assigned initially, and may continue on study provided the following criteria are met and the subject continues to receive clinical benefit:

- The subject is not experiencing any worsening of cancer-related symptoms or signs indicating clinically significant progression of disease. Subjects who are clinically deteriorating (e.g., have a decline in ECOG or Karnofsky performance status, symptomatic rapid disease progression requiring urgent medical intervention) and unlikely to receive further benefit from continued treatment should discontinue study treatment
- The subject is tolerating study drug
- Review and concurrence by the medical monitor
- Subject has no evidence of unequivocal systemic progression
- Subject has not had a previous isolated CNS progression while on study
- Subject will be re-consented prior to continuing treatment on study

Study treatment may be held up to 6 weeks to allow local CNS therapy. Longer holds must be discussed and approved by the medical monitor. Interruption and re-initiation of study treatment is described in Section 5.2.

4.4.2 Subject Withdrawal From Study

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

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death

5 TREATMENTS

5.1 Treatments Administered

Subjects will be randomized in a 1:1 manner to receive 1 of the following study treatments, either:

- Control arm: Placebo tablets PO BID, and T-DM1 3.6 mg/kg IV every 21 days, or
- Experimental arm: Tucatinib 300 mg PO BID, and T-DM1 3.6 mg/kg IV every 21 days

5.1.1 Investigational Study Drug (Tucatinib or Placebo)

Tucatinib, the investigational agent under study in this protocol, is a kinase inhibitor that selectively inhibits HER2, and displays limited activity against the related kinase EGFR.

Tucatinib and placebo are supplied as yellow oval (150 mg) or round (50 mg) capsule-shaped tablets for oral administration. Investigational study drug (tucatinib or placebo) will be supplied in a blinded manner. No treatment crossover from placebo to tucatinib will be allowed.

Detailed information describing the preparation, administration, and storage of the investigational study drug (tucatinib or placebo) is located in the Pharmacy Instructions.

5.1.1.1 Description

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

Tucatinib matching placebo tablets are formulated with common pharmaceutical excipients, but they do not contain the active ingredient. They are coated to be identical in appearance to active tablets and are supplied in the same format to maintain blinding.

5.1.1.2 Method of Procurement

The investigational study drug (tucatinib or placebo) will be provided by the sponsor.

5.1.1.3 Dose and Administration

The investigational study drug (tucatinib or placebo) will be administered PO BID and may be taken with or without food. Dose modifications of tucatinib or placebo are described in Section 5.2. Subjects will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, subjects will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

Subjects will be instructed to take tucatinib/placebo tablets twice each day (once in the morning, and once in the evening) approximately 8-12 hours between doses in the same calendar day. It is recommended that if a subject misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study subjects and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Subject compliance with investigational study drug dosing instructions will be assessed with the use of subject diaries and study drug accountability.

5.1.1.4 Overdose

In the event of an overdose of investigational study drug (tucatinib or placebo), defined as any dose greater than the prescribed dose, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of tucatinib or placebo administered, subject weight) and AEs, if any.

5.1.1.5 Storage and Handling

Tablets of tucatinib and placebo are packaged in round, high-density polyethylene bottles containing a desiccant, with an induction sealed liner and child-resistant plastic closure cap. Bottles of tucatinib or placebo tablets are to be stored under refrigeration at 2–8°C in a secure, access-limited location.

The tablets are coated with a non-hazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the Pharmacy Instructions for more information.

5.1.1.6 Packaging and Labeling

Each bottle of investigational study drug will be labeled in compliance with applicable regulatory requirements.

5.1.1.7 Study Drug Accountability

Tucatinib or placebo used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib and placebo are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty bottles, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study. All used and unused bottles of tucatinib or placebo should be handled according to the sponsor's instructions.

5.1.2 T-DM1

5.1.2.1 Description

T-DM1 (KADCYLA®) is a HER2-targeted antibody and microtubule inhibitor conjugate, which is indicated, as a single agent, for the treatment of patients with HER2+ mBC who have previously received trastuzumab and a taxane, either separately or in combination.

5.1.2.2 Method of Procurement

T-DM1 is commercially available and details regarding sourcing of T-DM1 may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

5.1.2.3 Dose, Preparation, and Administration

T-DM1 3.6 mg/kg IV will be administered on Day 1 of each 21-day cycle. T-DM1 should be prepared and administered per instructions in the KADCYLA package insert. T-DM1 will be administered IV per institutional guidelines, under the direction of the investigator.

Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing date, allowing for dose holds or delays with T-DM1. Dose modifications of T-DM1 are described in Section 5.2.

5.1.2.4 Overdose

For this trial, an overdose will be defined as any dose greater than the prescribed dose of T-DM1. In the event of an overdose, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of T-DM1.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of T-DM1 administered, subject weight) and AEs, if any.

5.1.2.5 Storage and Handling

T-DM1 should be stored according to the package insert.

5.2 Dose Modifications

Investigational study drug (tucatinib or placebo) and T-DM1 dose-reduction recommendations are described in Table 2 and Table 3, respectively. Guidelines for dose modification recommendations (including dose holds, dose reduction, or discontinuation of drug) in response to potential AEs are described in the tables in Section 5.2.3. Dose reductions or treatment interruption/discontinuation for reasons other than those described in Section 5.2.3 may be made by the investigator if it is deemed in the best interest of subject safety. Whenever possible, these decisions should first be discussed with the study medical monitor.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib/placebo and T-DM1. An AE may be considered related to tucatinib/placebo alone, T-DM1 alone, to both drugs, or to neither. In the event that the relationship is unclear, discussion should be held with the study medical monitor, to discuss which study drug(s) should be held and/or modified.

Doses held for toxicity will not be replaced. Investigational study drug (tucatinib or placebo) or T-DM1 should be discontinued if a delay greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the study medical monitor.

In the event of isolated progression in the CNS, study treatment may be held up to 6 weeks to allow local CNS therapy. Tucatinib/placebo and T-DM1 are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib and T-DM1 is unknown. Study treatment may be reinitiated ≥7 days after completion of SRS, ≥14 days after WBRT, and ≥28 days after surgical resection. Plans for holding and reinitiating study drugs before and after local therapy will require discussion with, and documented approval from, the medical monitor.

Protocol-defined visits and cycle numbering will be determined by T-DM1 dosing, allowing for dose holds or delays with T-DM1. In the event T-DM1 is discontinued but study treatment with tucatinib/placebo continues, protocol-defined visits and cycle numbering will proceed using a 21-day cycle regardless of dose holds or delays for tucatinib/placebo.

5.2.1 Tucatinib or Placebo Dose Reductions

Up to 3 dose reductions of tucatinib/placebo are allowed. In the case of recurrent toxicity after 3 dose reductions, treatment with tucatinib/placebo should be discontinued. Dose reductions of larger intervals than those described in Table 2 may be made at the discretion of the investigator, but dose reductions to below 150 mg BID are not allowed. Subjects who would require a dose reduction to below 150 mg BID should discontinue treatment with tucatinib/placebo.

Tucatinib/placebo dose should not be re-escalated after a dose reduction is made.

Table 2: Tucatinib/placebo: Recommended dose reduction schedule for adverse events*

Dose Reduction Schedule	Tucatinib/Placebo Dose Level
Starting dose	300 mg PO BID
1st dose reduction	250 mg PO BID
2nd dose reduction	200 mg PO BID
3rd dose reduction	150 mg PO BID
Requirement for further dose reduction	Discontinue treatment

* Dose reductions of greater intervals than those recommended in this table (i.e., more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator and approved by the medical monitor. However, tucatinib/placebo may not be dose reduced below 150 mg BID.

5.2.2 T-DM1 Dose Reductions

Up to 2 dose reductions of T-DM1 will be allowed (Table 3). In the case of recurrent toxicity after 2 dose reductions, treatment with T-DM1 should be discontinued.

T-DM1 dose should not be re-escalated after a dose reduction is made.

Table 3: T-DM1: Recommended dose reduction schedule for adverse events

Dose Reduction Schedule	T-DM1 Dose Level
Starting dose	3.6 mg/kg
1st dose reduction	3 mg/kg
2nd dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

5.2.3 Dose Modifications for Adverse Events

5.2.3.1 General Guidelines

General dose modification guidelines for investigational study drug (tucatinib or placebo) and T-DM1 are provided in Table 4 for clinical AEs.

Separate dose modification guidelines are provided for AEs of hepatotoxicity (Table 5), nodular regenerative hyperplasia (Section 5.2.3.3), thrombocytopenia (Table 6), left ventricular dysfunction (Table 7), and pulmonary toxicity (Section 5.2.3.6).

Table 4: Dose modifications for clinical adverse events related to either tucatinib/placebo or T-DM1

	Tucatinib/Placebo	T-DM1
Clinical Adverse Event	Related to tucatinib/placebo	Related to T-DM1
≥ Grade 3 AEs other than Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Reduce to next lowest dose level.
Grade 3 nausea, vomiting or diarrhea WITHOUT maximal use of antiemetics or antidiarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level.
Grade 3 nausea, vomiting or diarrhea WITH maximal use of antiemetics or antidiarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 4 nausea, vomiting or diarrhea regardless of use of anti-emetics or anti-diarrheals	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.
Grade 1 or 2 diarrhea with complicating features[b]	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 3 rash WITHOUT maximal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Optional dose reduction to next lowest dose level.
Grade 3 rash WITH maximal use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Optional dose reduction to next lowest dose level.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.

a No dose modifications are required for alopecia

b Moderate to severe abdominal cramping, nausea or vomiting ≥ National Cancer Institute's (NCI) CTCAE Grade 2, decreased performance status, fever, sepsis, neutropenia, frank bleeding, or dehydration.

5.2.3.2 Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities, regardless of relationship to study drug (Table 5).

For subjects with documented Gilbert's disease, contact the medical monitor for guidance regarding dose modifications.

Table 5: Dose modification guidelines for liver function abnormalities (regardless of relationship to tucatinib/placebo or T-DM1)

	Tucatinib/Placebo	T-DM1
Grade 2 elevation of ALT and/or AST of >3.0 to ≤5 X ULN	Dose modification not required	Dose modification not required
Grade 3 elevation of ALT and/or AST (> 5–20 X ULN)	Hold until severity ≤ Grade 1. Restart at next lowest dose level.	Hold until severity ≤ Grade 1. Restart at next lowest dose level.
Grade 4 elevation of ALT and/or AST (>20 X ULN)	Discontinue drug	Discontinue drug
Elevation of ALT and/or AST >3 X ULN AND Bilirubin >2 X ULN	Discontinue drug	Discontinue drug
Grade 2 elevation of bilirubin (> 1.5–3 X ULN)	Hold until severity ≤ Grade 1. Restart at same dose level.	Hold until severity ≤ Grade 1. Restart at same dose level.
Grade 3 elevation of bilirubin (>3 to ≤10 X ULN)	Hold until severity ≤ Grade 1. Restart at next lowest dose level.	Hold until severity ≤ Grade 1. Restart at next lowest dose level.
Grade 4 elevation of bilirubin (>10 X ULN)	Discontinue drug	Discontinue drug

5.2.3.3 Nodular Regenerative Hyperplasia

Investigational study drug (tucatinib or placebo) and T-DM1 should be discontinued permanently in subjects diagnosed with nodular regenerative hyperplasia, regardless of relationship to study drug.

5.2.3.4 Thrombocytopenia

T-DM1 dose modification are required for thrombocytopenia, regardless of relationship to T-DM1 (Table 6). Dose modification of investigational study drug (tucatinib or placebo) is not required for thrombocytopenia.

Table 6: Dose modification guidelines for thrombocytopenia

	Tucatinib/Placebo	T-DM1
Grade 3 thrombocytopenia Platelet count 25,000/mm^3 to < 50,000/mm^3	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥75,000/mm^3), and then restart at same dose level
Grade 4 thrombocytopenia Platelet count < 25,000/mm^3	Dose modification not required	Hold until platelet count recovers to ≤ Grade 1 (≥75,000/mm^3), and then reduce one dose level

5.2.3.5 Left Ventricular Dysfunction

Investigational study drug (tucatinib or placebo) and T-DM1 dose modification guidelines for left ventricular dysfunction, regardless of relationship to study drug, are provided in Table 7.

Table 7: Dose modification guidelines for left ventricular dysfunction

Symptomatic CHF	LVEF <40%	LVEF 40% to ≤45% and decrease is ≥10% points from baseline	LVEF 40% to ≤45% and decrease is <10% points from baseline	LVEF >45%
Discontinue T-DM1 and tucatinib/placebo	Do not administer T-DM1 or tucatinib/placebo.	Do not administer T-DM1 or tucatinib/placebo.	Continue treatment with T-DM1 and tucatinib/placebo.	Continue treatment with T-DM1 and tucatinib/placebo.
	Repeat LVEF assessment within 3 weeks.	Repeat LVEF assessment within 3 weeks.	Repeat LVEF assessment within 3 weeks.	
	If LVEF <40% is confirmed, discontinue T-DM1 and tucatinib/placebo.	If the LVEF has not recovered to within 10% points from baseline, discontinue T-DM1 and tucatinib/placebo.		

5.2.3.6 Pulmonary Toxicity

T-DM1 should be permanently discontinued in subjects diagnosed with interstitial lung disease (ILD) or pneumonitis, regardless of relationship to T-DM1.

5.3 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent through the safety reporting period.

5.3.1 Required Concomitant Therapy

There are no required concomitant therapies. For subjects with CNS metastases, prophylactic pre-treatment systemic corticosteroids may be administered at the discretion of the investigator.

5.3.2 Permitted Concomitant Therapy

Subjects may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. However, efforts should be made to maintain stable doses of concomitant medications during the course of study treatment.

Supportive treatments will be given according to label instructions as medically indicated. Concomitant medications can be administered at the investigator's discretion to conform to standard practice during the treatment period.

- Influenza vaccinations (without live virus) are permitted during the study

- If surgery or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor), these concomitant procedures are permitted for non-target non CNS lesions only in situations where other disease remains assessable by RECIST v1.1 (Appendix F). These interventions should be avoided if clinically feasible until after the second response assessment. The medical monitor should be consulted prior to the intervention occurring.
- Corticosteroids
    - Subjects requiring systemic corticosteroids for control of brain metastases at a dose of >2 mg of dexamethasone (or equivalent) on the first day of study treatment are not eligible to begin study treatment, and should not be randomized until doses ≤2 mg can be achieved
    - After initiation of study treatment, corticosteroids may be initiated for control of CNS symptoms only after consultation and approval of the medical monitor
    - For subjects with CNS metastases, prophylactic pre-treatment systemic corticosteroids may be administered at the discretion of the investigator
    - Premedication with corticosteroids solely for contrast used in scans or MRI can be used without prior medical approval
    - Subjects requiring systemic steroids for control of other comorbidities (e.g., asthma or auto-immune diseases) may be eligible after consultation and approval of the medical monitor
- Transfusion support with blood products is permitted. (However, note that no transfusions are permitted from <14 days prior to starting study treatment until the initiation of study treatment in order to establish adequate hematologic parameters for study eligibility independent of transfusion support.)

5.3.3 Prohibited Concomitant Therapy

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices
- Anti-cancer therapy, including but not limited to chemotherapy or hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal sites, which may be given after consultation with the medical monitor, provided that there remain other sites of measurable disease accessible by RECIST v1.1 (see Section 5.3.2)
- Strong inhibitors or inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within two weeks of discontinuation of study treatment (see Appendix C)

- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within two weeks of discontinuation of tucatinib / placebo treatment (see Appendix D)

The following therapies should be used with caution during the study

- Subjects on anti-coagulant treatment should be closely monitored during study treatment
- Sensitive substrates of CYP3A (Appendix E:); tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information
- Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

5.4 Treatment Compliance

Study drug administration will be documented in source documents and the CRF.

Study-drug compliance will be assessed on a subject-by-subject basis using subject diaries. The pharmacist or designee will record the number of investigational study drug (tucatinib or placebo) tablets dispensed to each individual subject, and the number of tablets returned to the clinic at the end of each cycle.

Data regarding the administration and dose of T-DM1 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 CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related AE, as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Study assessments will continue regardless of any dose holds or delays.

A schedule of events is provided in APPENDIX A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2 Screening Period

6.2.1 HER2 Testing (Up to 1 Year Before the Screening Visit)

Subjects may consent to submit an archival tumor specimen for central assessment to complete HER2 expression testing up to one year before the screening visit. Subjects must be informed that HER2 testing consent is not informed consent for the study and participation in HER2 testing does not guarantee study eligibility.

- HER2 expression testing consent
- Submission of archival tumor specimen for central assessment to confirm HER2 expression meets eligibility requirements (see Section 7.1.1)
- Confirmatory central HER2 testing, with archival tissue showing HER2-positivity by fluorescence in situ hybridization (FISH)

6.2.2 Screening Visit (Day –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history (see Section 7.1)
- Collection of concomitant medication information
- Confirm HER2+ status
    - Confirmation from an archival tumor specimen for central assessment to confirm HER2 expression (see Section 7.1.1 for eligibility requirements).
    - If archival tissue that meets requirements is not available, a fresh tumor biopsy must be obtained and submitted for central assessment for HER2 testing
- HR status must be known prior to randomization (HR+[positive]: ER+ and/or PR+; HR-[negative]: Both ER- and PR-negative)
- ECG (see Section 7.8.6.2)
- ECHO, or MUGA to include at a minimum LVEF (see Section 7.8.6.1); the testing modality chosen in screening should be used for subsequent cardiac assessments in order to allow comparison

- High-quality spiral contrast computed tomography (CT; preferred); positron emission tomography (PET)/CT (if high quality CT scan is included), and/or non-brain MRI scan may be done as appropriate (see Section 7.2). At a minimum, scans must include chest, abdomen, and pelvis. Additional appropriate imaging of any other known sites of disease (e.g., skin lesion photography for skin lesions, bone imaging for bone lesions) should also be performed at the investigator's discretion.
- Contrast MRI scan of the brain for all subjects for assessment of brain tumor burden (see Section 7.2.1)
    - For subjects with brain metastases discovered during screening or a history of brain metastases, confirm that relevant MRI brain reports and CNS treatment records can be obtained

* For subjects with unsuspected brain metastases discovered at screening and who go on to receive immediate local therapy to the CNS or who require a fresh tumor biopsy for HER2 confirmation, the screening process may be delayed beyond the 28-day screening window. Certain screening evaluations may not need to be repeated outside the 28-day screening window with medical monitor approval. This includes the following: informed consent and ECHO/MUGA. All other safety labs and assessments will need to be repeated if outside the 28 day window for these subjects. If local CNS therapy involves radiation treatment, do not repeat the contrast MRI of the brain prior to starting study treatment. If local CNS therapy involves surgical resection, a post-operative contrast MRI of the brain is required prior to starting study treatment.

6.2.3 Baseline Visit (Day –7 to Day 1)

- Physical examination (see Section 7.8.2), including height and weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECOG performance status (APPENDIX B)
- Blood samples for laboratory testing (as listed in Section 7.8.4)
    - Serum chemistry
    - Liver function tests (LFTs)
    - Complete blood count (CBC) with differential
    - Coagulation panel
- For persons of childbearing potential, serum or urine pregnancy test (see Section 7.8.5) within 7 days of first study treatment
- Review HER2+ status and laboratory results, and confirm eligibility prior to randomization.

6.3 Randomization (Day –5 to Day 1)

- Occurs after eligibility per inclusion/exclusion criteria is confirmed. Randomization MUST occur on or before Cycle 1 Day 1, such that dosing commences within 5 days after randomization.

6.4 Treatment Period (21-day cycles)

6.4.1 Cycle 1 Day 1

- Physical examination, including weight*
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECG (predose*)
- ECOG performance status*
- Predose blood samples for laboratory testing. Review results to confirm eligibility prior to first dose of study treatment:
  - Serum chemistry *
  - LFTs*
  - CBC with differential*

- Dispense tucatinib or placebo and administer the first dose of tucatinib/placebo and provide dosing diary to subject. (Subject will self-administer the remainder of doses during the treatment cycle and document in the diary.) ‡
- Administer T-DM1 at 3.6 mg/kg IV ‡

* Predose assessments do not need to be repeated if performed within 1 day prior to Cycle 1, Day 1.

‡ Study drugs may be administered in any order and can be given simultaneously.

6.4.2 Cycle 1 Day 12 (±3 days)

- Physical examination, including weight
- Vital signs
- ECOG performance status
-
- Review subject diary for tucatinib/placebo drug compliance
- Blood samples for laboratory testing

- Serum chemistry
- LFTs
- CBC with differential

- Provide tucatinib/placebo day-of dosing instructions for the Cycle 2 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib/placebo)

6.4.3 Cycle 2 Day 1, and Day 1 of All Subsequent Cycles (–1 to +3 days)

- [redacted]
- Physical examination, including weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECOG performance status

Blood sample collections:

- All cycles: Predose blood samples for laboratory testing. Must be performed within 1 day prior to Day 1 of the treatment cycle. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments:
  - Serum chemistry
  - LFTs
  - CBC with differential
  - For persons of child-bearing potential only: predose serum or urine pregnancy test (see Section 7.8.5) within 7 days prior to Day 1 of the treatment cycle.

[redacted]

Study treatment administration:

- Review subject diary for tucatinib/placebo drug compliance from previous cycle and dispense tucatinib/placebo for next cycle
- Administer the morning dose of tucatinib/placebo. (Subject will self-administer the evening dose.) ‡
- Administer T-DM1 given IV ‡
- Cycles 3–5 only: Provide tucatinib/placebo day-of dosing instructions for the next cycle's Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib/placebo) and ensure subject withholds AM tucatinib dose on Day 1 of next cycle

‡ Study drugs may be administered in any order and can be given simultaneously.

[redacted]

6.4.5 Cycle 2 Day 12 (±3 days)

- Blood sample for LFTs (total bilirubin, AST, and ALT)
- Review subject diary for tucatinib/placebo drug compliance
- Provide tucatinib/placebo day-of dosing instructions for the Cycle 3 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib/placebo)

[redacted]

6.4.6 Every 6 Weeks (-7 days) as Determined by Cycle 1 Day 1, through Week 24, then Every 9 Weeks (-7 days) through End of Treatment

- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or non-brain MRI scan may be done as appropriate (see Section 7.2). The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated
- Contrast MRI of the brain (only in subjects with brain metastases at baseline, as defined in Section 7.2.1) and assessment of CNS lesions (brain and/or dura).
- If cycles are delayed for any reason continue with initial scan schedule as determined by the date of Cycle 1 Day 1 visit
- If an interim unscheduled assessment is performed, scans should continue to be done on schedule, with scheduling determined by the date of Cycle 1 Day 1. In cases of

medical contraindication for repeat scans, contact the medical monitor to discuss as, in some instances, assessments done at an unscheduled timepoint may not need to be repeated if medically contraindicated as approved by the medical monitor

6.4.7 Every 12 Weeks as Determined by Screening Exam (–7 days)

- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline
- If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment

6.5 End of Treatment Visit (30 to 37 days after last dose of study treatment)

If End of Treatment (EOT) Visit evaluations are completed before 30 days after the last dose of study treatment, the subject will be contacted 30 to 37 days following the last dose of study treatment to assess for AEs.

- [redacted]
- [redacted]
- Physical examination, including weight
- Vital signs (blood pressure, heart rate, temperature, and respiration rate)
- ECG
- ECOG performance status
- Blood samples for laboratory testing
  - Serum chemistry
  - LFTs
  - CBC with differential
  - Coagulation panel
  - For females of child-bearing potential only (if not done within the last 30 days): serum or urine pregnancy test (see Section 7.8.5)
- [redacted]
- Only in subjects who discontinue study treatment for reasons other than radiographic disease progression: high-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan included), and/or non-brain MRI scan may be done as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated. Not required if imaging was performed within 30 days of discontinuing study treatment.

- Contrast MRI of the brain for all subjects and assessment of CNS lesions. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.
- ECHO or MUGA, using the same cardiac testing modality performed in Screening/Baseline. Not required if ECHO/MUGA was done within the previous 12 weeks (excluding the Screening/Baseline assessment).
- Review subject diary for tucatinib/placebo drug compliance from last cycle of study treatment
- For persons of childbearing potential: Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Testing may be performed at home. If performed at home, site staff will contact the subject monthly to confirm testing was performed and obtain pregnancy test results.

6.6 Long-Term Follow-up

Subjects who discontinue study treatment will remain on study for follow-up until withdrawal from the study. A subject may discontinue study treatment without withdrawing from the study (Section 4.4.1). If a subject discontinues study treatment, every attempt should be made to follow the subject until progression, death, or administrative study closure.

For subjects who discontinue study treatment prior to disease progression (per RECIST v1.1), the following assessments must be obtained every 9 weeks (±1 week) starting from the date of the last imaging scan, until investigator-assessed disease progression (per RECIST v1.1), death, withdrawal of consent, or study closure, in order to document a PFS event date:

- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or non-brain MRI scan as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.
- Contrast MRI of the brain (only in subjects with brain metastases at baseline, as defined in Section 7.2.1) and assessment of CNS lesions (brain and/or dura)
- [redacted]
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.8.5):
  - Confirm with the subject that monthly pregnancy tests have been performed and review results
  - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment

Once a subject experiences PD (per RECIST v1.1) or clinical progression as assessed by the investigator, subjects will continue in long-term survival follow-up. The following information must be collected starting 90 days (±7 days) from the date of the last imaging

scan and continuing every 90 days (±7 days) until death, withdrawal of consent, or study closure.

- Subject contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anti-cancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to contact the subject are unsuccessful.
- [redacted]
- For persons of childbearing potential (for 7 months after the last dose of study treatment; see Section 7.8.5):
  - Confirm with the subject that monthly pregnancy tests have been performed and have been negative
  - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment
- More frequent long-term follow-up may be conducted as needed for OS event tracking

6.7 Subject 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.

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only subjects who meet all inclusion and exclusion criteria specified in Sections 4.1 and 4.2 will be enrolled in this study.

Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing to determine subject eligibility; confirmatory HER2 testing may be performed on archival tissue or a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated (see Section 7.1.1).

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

All measurable and evaluable lesions will be assessed and documented at Screening/Baseline (see Section 7.2). A contrast MRI of the brain is performed to evaluate for the presence of brain metastases (see Section 7.2.1). Subjects with brain metastases at study entry may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 7.1.2.

A physical examination including height and weight (Section 7.8.2), vital signs (Section 7.8.3), ECOG performance status (APPENDIX B), clinical laboratory testing (Section 7.8.4), and pregnancy testing (Section 7.8.5) will be done at Screening/Baseline.

7.1.1 Confirmation of HER2 Expression for Study Eligibility

Archival or freshly-obtained tumor tissue (most recent tumor tissue sample preferred) must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing prior to randomization. The central laboratory will require sufficient tumor tissue to generate 5 unstained charged slides for HER2 expression testing. Archived tumor samples must be formalin-fixed and paraffin-embedded. If archival tissue that meets sample requirements is not available, fresh tissue from a tumor site (metastatic site preferred as applicable) suitable for biopsy must be obtained and submitted for confirmatory HER2 testing.

HER2 expression will be analyzed using FISH (DAKO pharmDx), and positivity will be assessed according to the package insert for HER2 interpretation.

A tumor suitable for biopsy should be accessible, not previously irradiated, and without contraindication to biopsy, in the opinion of the investigator. Tissue samples obtained via resection, excision, punch (skin lesions only), or core needle from a tumor site are suitable for testing. Fine needle aspiration, brushing, cell pellets from pleural effusion, forceps, and lavage samples are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content; e.g., samples should contain a minimum of 100 tumor cells that preserve cellular context and tissue architecture, regardless of the needle gauge used to collect the sample or the retrieval method.

See the Central Laboratory Manual for more details.

7.1.2 Treatment for Brain Metastases Prior to Study Entry

Subjects with brain metastases at study entry may be eligible for study participation if they meet the eligibility criteria described in Sections 4.1 and 4.2. In order to minimize the risk of symptomatic cerebral edema in subjects with brain metastases in this study, subjects with high-risk metastases, including those requiring immediate local therapy, those with rapidly progressing lesions, those requiring corticosteroids at the start of the study (>2 mg of dexamethasone or equivalent per day) for control of CNS symptoms, and those with larger untreated lesions, are excluded from the trial. However, if these subjects are amenable to immediate CNS-directed therapy with either surgery or radiation, they may undergo local therapy and then be eligible for the trial. Under select circumstances subjects may receive corticosteroid therapy for acute management of symptomatic local edema, as long as contrast brain MRI does not show clear evidence of CNS progression. All such instances require approval from the study medical monitor.

Immediate local therapy to the CNS may delay the screening process beyond the 28-day screening window, in which case the requirement for a repeat contrast MRI after completion of local therapy and prior to starting study treatment is as follows:

- For subjects who receive brain radiotherapy during the screening period, the original baseline contrast brain MRI will serve as the baseline for comparison for further response assessments.
- For subjects who undergo surgical resection of brain metastases during the screening period, a post-operative contrast brain MRI will be performed and will serve as the baseline for comparison for further response assessments.

For subjects with brain metastases discovered during screening or a history of brain metastases, relevant MRI brain reports and CNS treatment records should be obtained and available for CRF source verification.

7.2 Response/Efficacy Assessments

Radiographic scans and additional imaging assessments (if applicable) will be performed at protocol-specified time points outlined in Section 6 and APPENDIX A, or if disease progression is suspected. Clinical response of PD, SD, PR, or CR will be determined at each assessment according to RECIST v1.1 (Eisenhauer 2009), by the investigator and by BICR. Clinical management decisions will be based on local investigator assessment to ensure that treatment decisions are made in a timely manner; results of centralized review will not be available to investigators for clinical decision making.

All known sites of metastatic or locally advanced unresectable disease should be assessed by radiographic imaging at Screening/Baseline to document sites of extracranial disease and tumor burden. Imaging, preferably by high quality spiral contrast CT scan (with oral and/or IV contrast), should include the chest, abdomen, and pelvis, at a minimum; PET/CT (if high quality CT scan is included) and/or MRI scan may also be done as appropriate. If a CT scan

with contrast is contraindicated (i.e., in subjects with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed instead, with MRI scans of the abdomen and pelvis. At the investigator's discretion, other appropriate imaging (e.g., skin lesion photography for skin lesions, nuclear bone scan imaging for bone lesions) should be used to assess additional known sites of measurable disease. The same imaging modalities employed in Screening/Baseline should be used for all subsequent response assessments during study treatment and in the follow-up period, unless otherwise clinically indicated. If any other radiographic or assessment exam, including pathology from any on-study biopsies or procedures, is conducted per standard of care, the assessment information will be collected in the CRF. All imaging will be collected for retrospective BICR.

In the event of equivocal progression, for example a new lesion which is small in size (defined as a equivocal new lesion) and no imminent threat to subject safety, all efforts should be made to continue the subject until unequivocal radiologic progression or clinical progression is documented. Demonstration of an unequivocal new lesion constitutes disease progression (Appendix F).

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee) upon request. All imaging will be submitted or uploaded for retrospective BICR as soon as reasonably possible (e.g., within approximately 2 weeks) following the date of assessment. Refer to the Study Manual for instructions on collecting and submitting tumor imaging studies to the third-party imaging core laboratory for BICR.

7.2.1 Evaluation of Brain Metastases

Brain MRI imaging will be performed locally and collected prospectively for centralized independent review. However, treatment decisions will be made on the basis of local review of radiologic imaging.

Contrast MRI scan of the brain will be performed for all subjects at Screening/Baseline to assess tumor burden in the brain and/or dura and identify subjects with brain metastases at baseline. CT of the brain will not be allowed, and subjects with known contraindications to undergoing contrast MRI imaging will be excluded from the study. Subjects are considered to have brain metastases at baseline with any of the following:

- Any history of brain metastases
- Any brain metastases at baseline
- Brain lesions of equivocal significance at baseline

Only subjects with documented brain metastases at baseline, as defined above, will continue to have follow-up contrast MRIs of the brain on the same schedule as non-CNS response assessments (Section 6 and APPENDIX A). Contrast MRIs of the brain may also be performed in subjects without known brain metastases if there is clinical suspicion of new brain lesions. All subjects will have an additional contrast MRI of the brain at the EOT visit,

unless one has been performed within 30 days of discontinuing study treatment or the reason for going off treatment was progression in the brain.

In subjects with baseline brain lesions, at least one brain lesion should be included in the baseline RECIST lesion selection as either a target or non-target lesion. As an exception, however, when unsuspected brain metastases are discovered at screening and immediate CNS-directed therapy is administered, treated lesions should not be selected as target lesions but as non-target lesions for the purpose of disease assessment by RECIST v1.1.

Copies of brain imaging must be made available for review by the sponsor (or its designee), upon request. Copies of all brain imaging will be submitted or uploaded for retrospective BICR as soon as reasonably possible (e.g., within approximately 2 weeks) following the date of assessment. Refer to the Study Manual for instructions on collecting and submitting brain imaging studies to the third-party imaging core laboratory for BICR.

7.2.2 Isolated Progression in the Brain

In subjects with isolated progression in the brain per RECIST v1.1 (including either parenchymal brain or dural metastases but not skull-based or leptomeningeal metastases) and does not have progression of disease outside the CNS, the subject may be eligible to continue on study treatment after completion of local treatment (radiotherapy or surgery) to the brain/dural metastases to allow for clinical benefit with medical monitor approval. This approach approximates standard clinical practice in this clinical scenario.

Because the primary endpoint of the study is PFS, every effort should be made to avoid radiation or surgery to target lesions in the brain in the absence of PD by RECIST v1.1 unless clinically necessary in the opinion of the investigator. Target lesions, once treated with local CNS therapy, cannot be adequately assessed for subsequent response to systemic therapy. Because of this, if a subject continues on assigned study therapy after local CNS treatment to a target lesion, special consideration must be given for evaluation of the treated target lesion and the impact on the overall RECIST v1.1 assessment.

Following CNS-directed therapy for isolated CNS disease progression, RECIST v1.1 criteria would continue to measure CNS target lesions(s) if previously identified and used in the overall estimation of the sum of diameters measuring total disease burden. However, following treatment, measurement of the treated CNS target lesion(s) would use the immediate pre-CNS treatment measurement. If a subsequent decrease in the size of a treated CNS lesion post-treatment is seen, the immediate pre-CNS treatment longest diameter would be used for RECIST measurement. Should a treated CNS lesion enlarge following CNS-directed therapy that was identified as a target lesion, the new and larger longest diameter is to be used for RECIST measurement.

Additionally, treatment changes which may mimic progression will be taken into account, and subjects with possible “pseudo-progression” should continue on study until unequivocal evidence of radiographic or clinical progression is present. In the absence of clear evidence of PD (per RECIST v1.1), development of CNS symptoms or radiographic changes thought

to pose potential immediate risk to subject, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST v1.1.

After discontinuing study treatment, subjects may receive further care as determined by their physician.

7.8 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety will be monitored over the course of the study by an IDMC as described in Section 3.1.1.

7.8.1 Adverse Events

7.8.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical

investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study treatment) should be recorded from study Day 1 (predose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in an SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.

Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.8.1.6 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's (NCI) CTCAE, Version 4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for Serious Adverse Events, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib or placebo, T-DM1) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.8.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity

- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

If applicable: Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and the SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. Symptomatic clinical deterioration due to disease progression as determined by the investigator will not be reported as an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 7 months after the last dose of study drug(s), including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s), will also be recorded on the Adverse Events and Pre-existing Conditions CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.8.1.1) should be reported as SAEs.

7.8.1.3 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 the EOT Visit or 30 days after the last study treatment (tucatinib or placebo, T-DM1), whichever is later. However, all study protocol-related AEs are to be recorded from the time of study 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.

7.8.1.4 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

The completed SAE form and SAE Fax Cover Sheet are to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email address or fax number specified on the SAE report form).

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

7.8.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.8.1.4).

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity, as well as other SAEs that are not study endpoints but are known consequences of the underlying disease or condition that are anticipated to occur in the study population, should not be reported to the FDA as individual IND safety reports per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Assessment for IND Safety Reporting Guidance for Industry (draft guidance December 2015).

In this study, the SAEs that do not require individual IND safety reports to the FDA are progression of the underlying cancer. These anticipated SAEs will be reviewed periodically by an IDMC and Seattle Genetics Drug Safety Department. If upon review, an SAE is occurring at a higher rate than that which would be expected for the study drug treatment arm, then an IND safety report for the SAE will be submitted to the FDA.

7.8.1.6 Adverse Events of Special Interest

An AE of special interest (AESI) can be any serious or nonserious AE that is of scientific or medical concern as defined by the sponsor and specific to the program, for which ongoing monitoring and rapid communication to the sponsor may be appropriate.

The AESIs will need to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 7.8.1.4).

Potential drug-induced liver injury

Any potential case of drug-induced liver injury (DILI) as assessed by laboratory criteria for Hy's Law will be considered as a protocol-defined event of special interest. The following laboratory abnormalities define potential Hy's Law cases:

AST or ALT elevations that are > 3 X ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 X the ULN, except in subjects with documented Gilbert's syndrome. Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology.

Asymptomatic left ventricular systolic dysfunction

In general, asymptomatic declines in LVEF should not be reported as AEs since LVEF data are collected separately in the electronic CRF (eCRF). However, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and an SAE, and must be reported to the sponsor.

Cerebral Edema

Any event of cerebral edema not clearly attributable to progression of disease should be reported as an AESI.

7.8.2 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.8.3 Vital Signs

Vital sign measurements are to include heart rate, systolic and diastolic blood pressure, temperature, and respiration rate. Vital signs should be measured after the subject has been sitting/resting.

7.8.4 Clinical Laboratory Tests

The following laboratory assessments will be performed by the local laboratory to evaluate safety at scheduled timepoints (see APPENDIX A) and make clinical decisions during the course of the study:

- The serum chemistry panel is to include the following tests: albumin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, inorganic phosphorus, lactate dehydrogenase, magnesium, potassium, sodium, total protein, and uric acid
- LFTs include ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin (and direct bilirubin when total bilirubin is >ULN)
- The CBC with differential is to include the following tests: CBC with differential that includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with 5-part differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- The coagulation panel is to include the following tests: INR, prothrombin time, and PTT
- The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL.

  GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

- A serum or urine β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) for subjects of childbearing potential (see Section 7.8.5)

7.8.5 Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) will be performed at baseline, within 7 days prior to Day 1 of each treatment cycle, and at the EOT Visit. A negative pregnancy result is required before the subject may receive study treatment.

Subjects with false positive results and documented verification that the subject is not pregnant are eligible for study participation. Similarly, subjects with false positive results that develop during study treatment are allowed to continue treatment with documented verification that the subject is not pregnant.

After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months. Subjects may do monthly home pregnancy tests and report interim results at long-term follow-up visits. Pregnancy tests may also be repeated as requested per institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations.

7.8.6 Cardiac Function

7.8.6.1 MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

7.8.6.2 Electrocardiogram

ECGs will be performed at baseline predose on Cycle 1 Day 1. To correct for heart rate, QT intervals should be calculated using the Fridericia formula (QTcF).

7.9 Appropriateness of Measurements

Response will be assessed according to RECIST v1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and subject inconvenience associated with CT and PET scanning

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and clinical laboratory data will be graded using standardized criteria for oncology (NCI CTCAE v4.03).

[redacted]

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's Brochure/ package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding and randomization
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is

suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

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

8.5 Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor i the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

9 DATA ANALYSIS METHODS

An overview of study outcome measurements is provided in Table 10.

Table 10: Overview of study outcome measurements

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
Primary Objective			
• Compare PFS by investigator assessment per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1 as determined by investigator assessment	• PFS per RECIST v1.1 by investigator assessment	• Up to approximately 5 years
Key Secondary Objectives			
• Compare OS between treatment arms	• OS	• OS	• Up to approximately 5 years
• Compare the objective response rate (ORR) by investigator assessment per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by investigator assessment	• ORR per RECIST v1.1 by investigator assessment	• Up to approximately 3 years
Other Secondary Objectives			
• Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1 between treatment arms	• PFS per RECIST v1.1, as determined by BICR	• PFS per RECIST v1.1 by BICR	• Up to approximately 5 years
• Evaluate PFS by investigator assessment per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms	• PFS per RECIST v1.1, by investigator assessment in subjects with brain metastases at baseline	• PFS per RECIST v1.1 by investigator assessment	• Up to approximately 5 years
• Evaluate PFS by BICR per RECIST v1.1 in subjects with brain metastases at baseline between treatment arms	• PFS per RECIST v1.1, by BICR in subjects with brain metastases at baseline	• PFS per RECIST v1.1 by BICR	• Up to approximately 5 years
• Evaluate the ORR by BICR per RECIST v1.1 between treatment arms	• ORR per RECIST v1.1, by BICR	• ORR per RECIST v1.1 by BICR	• Up to approximately 3 years
• Evaluate the duration of response (DOR) by investigator assessment per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by investigator assessment	• DOR per RECIST v1.1 by investigator assessment	• Up to approximately 5 years
• Evaluate the DOR by BICR per RECIST v1.1 between treatment arms	• DOR per RECIST v1.1, by BICR	• DOR per RECIST v1.1 by BICR	• Up to approximately 5 years

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• Evaluate the CBR (SD or non-CR or nonprogressive disease [PD] for ≥6 months or best response of CR or PR) by investigator assessment per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by investigator assessment	• CBR per RECIST v1.1 by investigator assessment	• Up to approximately 3 years
• Evaluate the CBR by BICR per RECIST v1.1 between treatment arms	• CBR per RECIST v1.1, by BICR	• CBR per RECIST v1.1 by BICR	• Up to approximately 3 years
• Evaluate the safety of tucatinib in combination with T-DM1	• Incidence of AEs	• Incidence of AEs	• Through 1 month following last dose; up to approximately 9 months overall per subject
Exploratory Objectives			
[redacted]	[redacted]	[redacted]	[redacted]

9.1 Determination of Sample Size

This study is designed to detect a tucatinib treatment effect of at least a 30% reduction in risk of PFS events (hazard ratio of 0.70; median PFS from 6 months in the control arm to 8.57 months in the experimental arm).

A total of [redacted] PFS events will provide [redacted] power to detect a hazard ratio of 0.70 at a 2sided significance level of 0.05 using a log-rank test. Approximately 460 subjects will be randomized in a 1:1 ratio to either the experimental arm or the control arm to observe [redacted] PFS events in approximately [redacted] after the first subject is randomized, assuming [redacted] of subject accrual, a 5% annual dropout rate, and [redacted] of follow-up after the last subject is randomized.

If the final analysis of the primary endpoint is statistically significant, a formal statistical test of OS is planned at the same time. It is also planned that follow-up for OS will continue after the primary analysis of PFS until approximately [redacted] OS events have been observed. With [redacted] events, it will provide [redacted] power to detect a hazard ratio of 0.70 in OS at a 2-sided significance level of 0.05 using a log-rank test. The final analysis of OS is estimated to take place approximately [redacted] after the primary analysis of PFS, assuming that the OS for the control is following an exponential distributions with a median of [redacted].

9.2 Study Endpoint Definitions

9.2.1 Primary Endpoint: PFS per Investigator Assessment

PFS per investigator is defined as the time from the date of randomization to the investigator assessment of disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. For subjects who continue on study treatment after isolated CNS progression per RECIST v1.1, PFS per investigator will be calculated from the date of randomization to the first (or earliest) investigator assessment of disease progression. Subjects without documentation of PD, or death at the time of analysis, will be censored at the date of the last tumor assessment with an overall response of CR, PR, SD or non-CR/non-PD.

If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of randomization.

Detailed methodology, including handling rules for missing assessments and censoring approaches for the analysis of PFS, is provided in the Statistical Analysis Plan (SAP).

9.2.2 Key Secondary Endpoints

9.2.2.1 Overall Survival

OS is defined as the time from randomization to death due to any cause.

For a subject who is not known to have died by the end of study follow-up, observation of OS is censored on the date the subject was last known to be alive (i.e., the date of last

contact). Subjects lacking data beyond the day of randomization will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

9.2.2.2 Objective Response Rate by Investigator Assessment

ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST v1.1. Subjects whose disease response cannot be assessed will be considered as non-responders for calculating the ORR. ORR by investigator assessment is based on investigator response assessments.

9.2.3 Other Secondary Endpoints

9.2.3.1 PFS per BICR

PFS per BICR is defined as the time from the date of randomization to the centrally-reviewed documented disease progression according to RECIST v1.1 or death from any cause, whichever occurs first. Subjects without documentation of PD or death at the time of analysis, will be censored at the date of last radiographic disease assessment with an overall response of CR, PR, SD or non-CR/non-PD.

9.2.3.2 PFS per Investigator Assessment and BICR in Subjects with Brain Metastases at Baseline

PFS per investigator assessment and BICR in subjects with brain metastases at baseline is defined in the same manner as the primary endpoint of PFS per investigator assessment. For this endpoint, PFS per investigator assessment and BICR will be analyzed in the subset of subjects with brain metastases at baseline per the CRF.

9.2.3.3 Objective Response Rate by BICR

ORR is defined as the proportion of subjects with CR or partial response (PR) according to RECIST v1.1. Subjects whose disease response cannot be assessed will be considered as non-responders for calculating the ORR. ORR per BICR is based on BICR response assessments..

9.2.3.4 Duration of Response

DOR is defined as the time from first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of disease progression per RECIST v1.1 or death from any cause, whichever occurs earlier. Only subjects with an objective response will be included in the analysis of duration of response. DOR per investigator is based on investigator response assessments and DOR per BICR is based on BICR response assessments.

9.2.3.5 Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of subjects with stable disease (SD) or non-CR or non-PD for ≥6 months or best response of CR or PR according to RECIST v1.1. CBR per investigator is based on investigator response assessments and CBR per BICR is based on BICR response assessments.

9.2.4 Exploratory Endpoints

[redacted]

9.3 Statistical and Analytical Plans

The statistical methods are outlined below; additional analysis details will be provided in the SAP. The SAP will be finalized prior to study unblinding. Exploratory analyses of the data not described in the following subsections may be conducted as deemed appropriate. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

9.3.1 General Considerations

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% CIs for time-to-event data.

9.3.1.1 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study that will enroll approximately 460 subjects. Subjects will be randomized in a 1:1 manner to receive either tucatinib or placebo in combination with T-DM1. Randomization

will be stratified by line of treatment for metastatic disease, HR status, presence or history of brain metastases, and ECOG performance status.

Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

The blinding plan for the safety and efficacy data will be specified in the SAP.

9.3.1.2 Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 9.3.1.1). Please note, if the sample size of one strata by a stratification factor is too small, the statistical analysis will not include this randomization stratification factor in the statistical analysis, such as stratified log-rank test and stratified Cox regression model. This minimum sample size requirement will be specified in the SAP. Covariates may be considered for adjustment in exploratory analyses.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of time-to-event endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP.

9.3.1.4 Multicenter Studies

This study will be conducted at multiple study centers, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

9.3.1.5 Multiple Comparisons and Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05, a fixed sequential testing procedure will be used to test the primary endpoint of PFS per investigator assessment and the key secondary endpoints of OS and ORR per investigator. If the PFS per investigator assessment is positive at the two-sided 0.05 level, OS will be tested twice with an overall two-sided alpha of 0.05. The first test of OS will be performed at the same time as the primary PFS analysis when approximately [redacted] PFS events per investigator assessment are observed. The final test of OS will occur when approximately [redacted] OS events are observed from the study. The Lan-DeMets O'Brien-Fleming approximation spending function (Chen 2014) will be used for the calculation of the alpha level at the first and final tests of OS based on the actual number of OS events observed at the interim. If OS result is statistically significant at either the first or the final analysis, a formal statistical test of ORR per investigator assessment will be performed. Detailed rejection boundaries of P-values will be specified in the SAP.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study treatment unless otherwise specified in the analysis plan.

9.3.1.6 Analysis Sets

The intent-to-treat (ITT) analysis set will include all randomized subjects. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received. The primary analysis of the efficacy endpoints will be based on the ITT analysis set.

The safety analysis set will include all randomized subjects who receive at least one dose of tucatinib or placebo, or T-DM1. Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment.

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

9.3.1.7 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.8 Timing of Analyses

There is only one formal analysis of the primary endpoint PFS per investigator assessment which will occur after approximately [redacted] PFS events in the ITT analysis set have occurred. The analysis cutoff date for this analysis will be determined once approximately [redacted] PFS events per investigator assessment have been observed. This is estimated to be approximately [redacted] after randomization of the first subject.

The key secondary endpoint of OS will be analyzed twice. The first analysis will be performed at the same time as the primary analysis of PFS per investigator assessment, and the final analysis of OS will occur when approximately [redacted] OS events have occurred. The final OS analysis is estimated to occur [redacted] after completion of the primary analysis of PFS. ORR by investigator assessment will be formally tested if OS is statistically significant at either the first or the final analysis.

9.3.2 Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3 Subject Characteristics

The following baseline characteristics will be summarized by treatment group

- Subject demographics
- Disease history
- Prior disease-related therapies; and
- Baseline disease characteristics

Concomitant medications, separately for medications taken prior to enrollment and while on study, will be listed and summarized by treatment group.

Details will be provided in the SAP.

9.3.4 Treatment Compliance

Treatment compliance (percent of actual to planned dosing) for tucatinib/placebo will be summarized by treatment group.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

The stratified log-rank test will be used in the primary evaluation of PFS differences between the treatment arms in the ITT analysis set using a two-sided significance level of 0.05. A stratified Cox proportional-hazards (PH) model, will be used to estimate the hazard ratio and its 95% CI. Both stratified log-rank and Cox PH models will take into account the stratification factors for randomization. Please note, if the sample size of one stratum from a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a stratum to be included in the statistical model will be specified in the SAP.

All events entered in the database at the time of analysis will be included in the analysis of PFS, even if there are more than the prespecified number of events.

Kaplan-Meier curves depicting PFS in the 2 treatment arms will be generated. Additionally, median PFS and the 2-sided 95% CIs for the median will be reported using the complementary log-log transformation method (Collett 1994). Detailed methodology is provided in the SAP.

9.3.5.2 Secondary Efficacy Analyses

OS will be analyzed using similar methods used for the primary endpoint. The stratified log-rank test will be used to evaluate the OS differences between the treatment arms. A stratified Cox proportional-hazards model will be used to estimate the hazard ratio and its 95% CI. Both stratified log-rank and Cox PH models will take into account the stratification factors for randomization. Please note, if the sample size of one strata by a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a strata to be included in the statistical model will be specified in the SAP.

Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment group using the ITT analysis set. The median OS and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment group.

Secondary endpoints of PFS in subjects with brain metastases and PFS by BICR will be analyzed using same method used for the primary endpoint.

Response Rates – Objective Response Rate and Clinical Benefit Rate

Data summaries for ORR will be provided for the Response Evaluable Set (subjects in ITT with measurable disease at baseline). The 95% CI of ORR will be estimated for each treatment group. Additionally, comparison of ORR between treatment groups will be conducted using two-sided Cochran-Mantel-Haenszel test controlling for the study stratification factors.

A similar approach will be used for the CBR analysis, but the analysis for CBR will be applied to the ITT analysis set.

Duration of Response

Only subjects with a confirmed response will be included in the analysis of duration of response (DOR). DOR is defined as the time from first documented objective response (CR or PR that is subsequently confirmed) to documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first. DOR will be graphically described using Kaplan-Meier methodology. The median DOR and its 95% CI will be provided for the 2 treatment arms.

9.3.9 Safety Analyses

Safety is assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG performance status, and changes in cardiac ejection fraction results. AEs will be classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE criteria.

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by treatment arm using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.9.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and treatment group. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

All collected AE data will be listed by treatment group, study site, subject number, and cycle. Separately, all serious AEs and AEs of special interest (e.g., any DILI, asymptomatic left ventricular systolic dysfunction, and/or cerebral edema) will be analogously listed.

A separate listing of all on-study deaths will be presented.

9.3.9.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4 Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

Changes from baseline in laboratory values (hematology, coagulation, chemistry, and liver function) will be summarized by treatment group and scheduled visit. Laboratory shift tables

will also be provided by treatment group and scheduled visit. Abnormal values (relative to respective normal ranges) will be flagged in listings.

Additional analytical methods for a more thorough investigation of LFTs (including temporal/simultaneous summaries and figures) will be specified in the SAP.

9.3.9.5 Vital Signs, Physical Examination Findings, and ECOG Performance Status

The frequency and percentage of subjects with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs. ECOG performance status shift tables will likewise be provided by treatment group and scheduled visit.

9.3.9.6 Cardiac Ejection Fraction

Cardiac ejection fraction data will be summarized by treatment group by baseline and post-baseline assessment. Corresponding shift tables will also be provided by treatment group and baseline and post-baseline assessment.

9.3.10 Interim Analyses

No formal interim analyses are planned for the primary endpoint. The key secondary endpoint of OS will be analyzed twice. The first OS analysis is at the time of analysis of primary endpoint when approximately [redacted] PFS events per investigator assessment have occurred. The final analysis of OS will be performed when approximately [redacted] OS events have occurred. The Lan-DeMets O'Brien-Fleming approximation spending function (Chen 2014) will be used for calculation of the alpha level at the first and final tests of OS based on the actual number of OS events observed at the interim. If the OS result is statistically significant at either the first or the final analysis, a formal statistical test of ORR by investigator assessment will be performed. Detailed rejection boundaries of P-values will be specified in the SAP.

10 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); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

It is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 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.

10.3.1 Investigator Information

Sample text: The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2 Protocol Amendments and Study Termination

Protocol amendments will be submitted to the IRB/IEC prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

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

10.4 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

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.

10.5 Clinical Trial Agreement

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 trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

		Pre-Screening	Screening/ Baseline		Random-ization	Cycle 1		Subsequent 21-Day Cycles		Response Assessments		ECHO/ MUGA	EOT	Follow-up	Survival Status
	Day	Up to 1 year before Screening Visit	D -28 to 1	D -7 to 1	Within 5D of 1st dose	D1	D12	D1	D12[A]	Every 6 weeks, through Week 24[B]	Every 9 weeks, beginning Week 24[B]	Every 12 weeks[C]	Within 30-37D after last dose[D]	Every 9 weeks until progression[E]	After progression, every 90 days[F]
	Visit Window						±3d	−1 to +3d	±3d	−7d	−7d	−7d		±1 week	±7d
HER2 Expression Testing	HER2 testing consent	X			Eligibility documentation submitted to sponsor prior to randomization										
	Submit tumor sample for HER2 testing (Section 7.1 1)	X[G]	X[G,H]												
Screening/ Baseline Assessments	Study informed consent		X[H]												
	Inclusion/exclusion		X												
	Medical history		X												
	Physical examination			X		X[I]	X	X					X		
	Height			X											
	Weight			X		X[I]	X	X					X		
	Vital signs			X		X	X	X					X		
Safety Assessments	ECOG performance status			X		X[I]	X	X					X		
	ECHO or MUGA[J]		X									X	X[K]		
	ECG[L]		X			X[I]							X		
	CBC with differential			X		X[I]	X	X[M]					X		
	Serum chemistry			X		X[I]	X	X[M]					X		
	Liver function tests			X		X[I]	X	X[M]	X				X		
	Coagulation panel			X									X		
	Pregnancy test (FOCBP)[N]			X				X					X[O]	X[O]	X[O]
	Con meds and AEs		Collect any related to study protocol procedures[P]			Collect from Day 1 (predose) through 30 days post last dose or through EOT visit, whichever is later									
Treatment	Dispense tucatinib/placebo					X		X							
	Administer T-DM1					X		X							
	Review subject diary						X	X	X				X		
	Provide dosing instructions for next visit's day-of dose						X	X[Q]	X						
[redacted]	[redacted]					X		X					X	X	X
	[redacted]					X	X	X	X				X	X	X
	[redacted]					X	X	X	X				X		
	[redacted]					X	X	X	X				X		
	[redacted]							X					X		
[redacted]	[redacted]					See Section 7 3									
	[redacted]					X		X[T]					X		
Response Assessments	CT (chest, abdomen, pelvis)[J]		X							X	X		X[U]	X[U]	
	Additional imaging of other known sites of disease, as appropriate[J]		X							X	X		X[U]	X[U]	
	Brain MRI		X[V]							X[W]	X[W]		X[X]	X[U,W]	

A	Cycle 2 only.
B	Scheduling determined by date of Cycle 1, Day 1 visit.
C	Scheduling determined by date of Screening ECHO/MUGA. However, if there is an interim assessment, subsequent ECHO/MUGAs should be performed every 12 weeks as determined by the date of the most recent interim assessment. See Section 7.8.6.1.
D	If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.
E	Scheduling determined by date of the last imaging scan. See Section 6.6.
F	Scheduled 90 days (±7 days) from the date of the last imaging scan. May be either an in-person assessment, contact by telephone, or review of publicly available information (if reasonable efforts to contact the subject are unsuccessful). See Section 6.6
G	Archival tissue specimen may be submitted up to 1 year prior to screening visit. If archival tissue is unavailable, a fresh tumor biopsy must be obtained (Section 6 2.2).
H	All subjects must sign informed consent for the study before Screening/Baseline procedures are conducted, including obtaining a fresh tumor biopsy for those subjects who require one to be performed for HER2 confirmation. The HER2 testing pre-screening consent is not informed consent for the study.
I	Assessment does not need to be repeated, if already done within 1 day of study visit (i.e , as part of Screening/Baseline visit). Confirm lab results prior to initiating study treatment dosing.
J	Use the same assessment modality throughout the study. See Section 7.2.
K	Perform ECHO/MUGA if not done within the previous 12 weeks (excluding the Screening/Baseline assessment).
L	Cycles 1 only. On Cycle 1 Day 1, ECGs will be done pre-tucatinib/placebo dose.
M	Predose labs can be done within 1 day prior to study visit. Confirm lab results prior to continuing study treatment dosing.
N	Females of childbearing potential only: can be performed within 7 days prior to study treatment dosing on Day 1 of cycle. Confirm negative pregnancy test prior to continuing study treatment dosing.
O	Females of childbearing potential only: monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Subject will be asked to confirm that monthly pregnancy tests have been performed and have been negative.
P	From time of study informed consent
Q	Cycles 3–5 only.
[redacted]	[redacted]
T	Cycle 3 Day 1 only
U	Only in subjects who discontinue study treatment for reasons other than radiographic disease progression. Response assessments at the EOT visit are not required if performed within 30 days of discontinuing study treatment.
V	For subjects with brain metastases discovered during screening or a history of brain metastases, confirm that relevant MRI brain reports and CNS treatment records can be obtained.
W	Required only for subjects with brain metastases at baseline, as defined in Section 7.2.1.
X	Contrast MRI of the brain required for all subjects. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		ECOG	
Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.		
80	Normal activity with effort; some signs or symptoms of disease.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.		
20	Very sick, hospitalization indicated. Death not imminent.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.		
0	Dead	5	Dead

APPENDIX C: CYP3A4 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP3A4 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b, c]	Elimination Half-life[d] (hours)
Strong Inhibitors	
Macrolide Antibiotics	
Clarithromycin	3–7 hours
Troleandomycin	2 hours
Azole Antifungals	
Itraconazole	16-28 hours (single dose), 34-42 hours (repeat dose)
Ketoconazole (systemic)	2–8 hours
Voriconazole	Dose dependent
Posoconazole	27–35 hours
Other	
Nefazodone	2–4 hours
Diltiazem	3–4 hours
White grapefruit juice	~ 4–5 hours[e]
Strong Inducers	
Barbiturates	Variable
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours[f]

Note: Any additional CYP3A4 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#potency)

b EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Strong CYP3A inhibitors are defined as those drugs that increase the area under the concentration-time curve (AUC) of oral midazolam or other CYP3A substrates ≥ 5-fold. Ritonavir, indinavir, nelfinavir, atazanavir, and saquinavir are also strong CYP3A3 inhibitors, but would not be used in this study as subjects with known human immunodeficiency virus are excluded.

d drug package insert

e (Bailey 1998)

f (Kerb 1996)

APPENDIX D: CYP2C8 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP2C8 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b]	Elimination Half-life[c] (hours)
Strong Inhibitors	
Clopidogrel	6 hours
Gemfibrozil	1–2 hours
Strong Inducer	
Rifampin	3–5 hours

Note: Any additional CYP2C8 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#potency)

b EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug package insert

APPENDIX E: CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

The following table provides examples of clinical substrates for CYP3A-mediated metabolism and is not intended to be an exhaustive list.

Sensitive (AUC increase ≥5-fold with strong index inhibitor)	**Moderate Sensitive** (AUC increase 2 to 5-fold with strong index inhibitor)
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[a], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[b], midazolam, naloxegol, nisoldipine, saquinavir[a], simvastatin[b], sirolimus, tacrolimus, tipranavir[a], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[c], colchicine, eliglustat[d], pimozide, rilpivirine, rivaroxaban, tadalafil
budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[a], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in area under the concentration-time curve (AUC) of ≥5fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction (DDI) studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to < 5fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥ 10fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

a Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.
b Acid form is an organic anion transporting polypeptide 1B1 (OATP1B1) substrate.
c Listed based on pharmacogenetic studies.
d Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010).

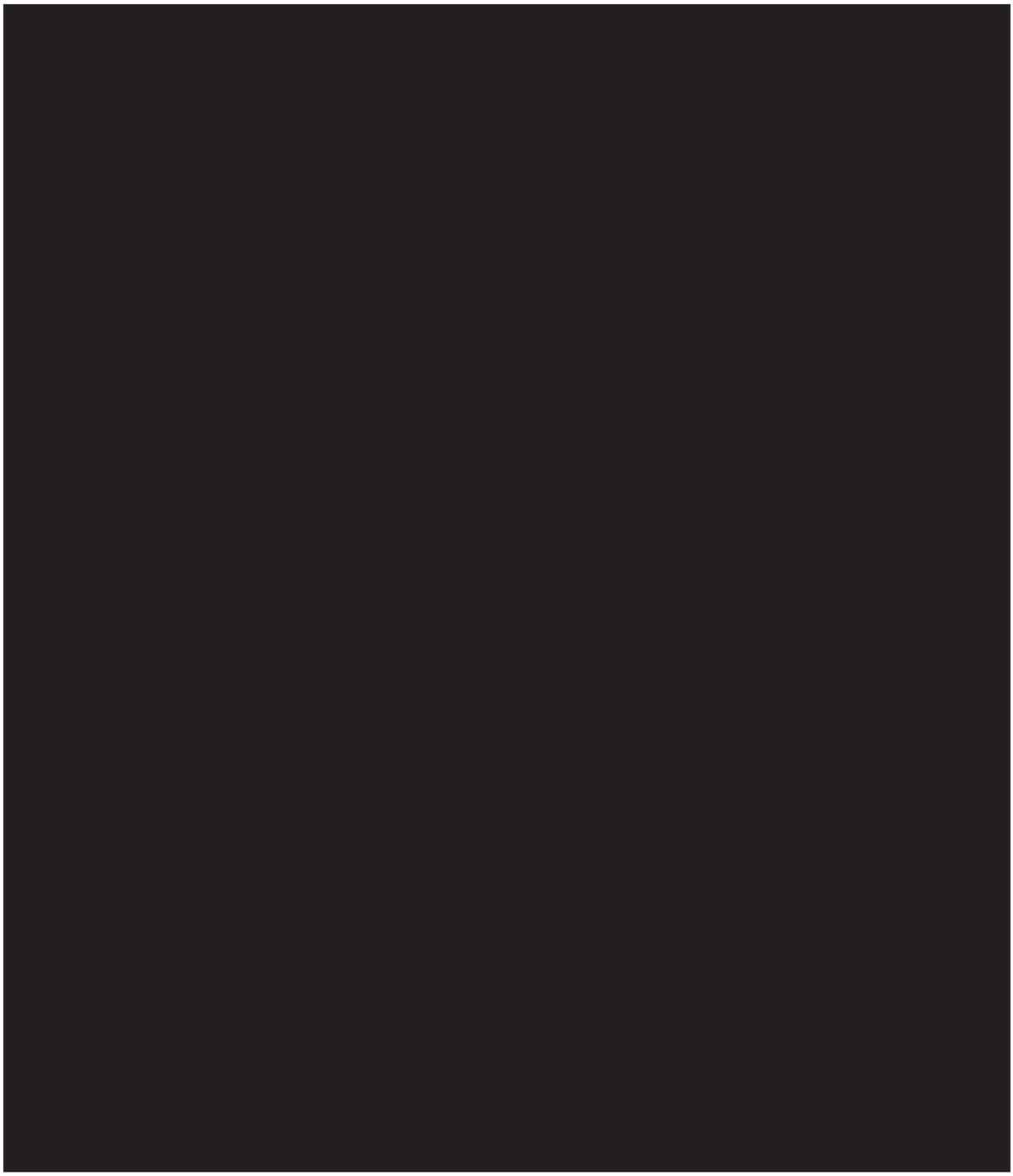
Source: (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-1)

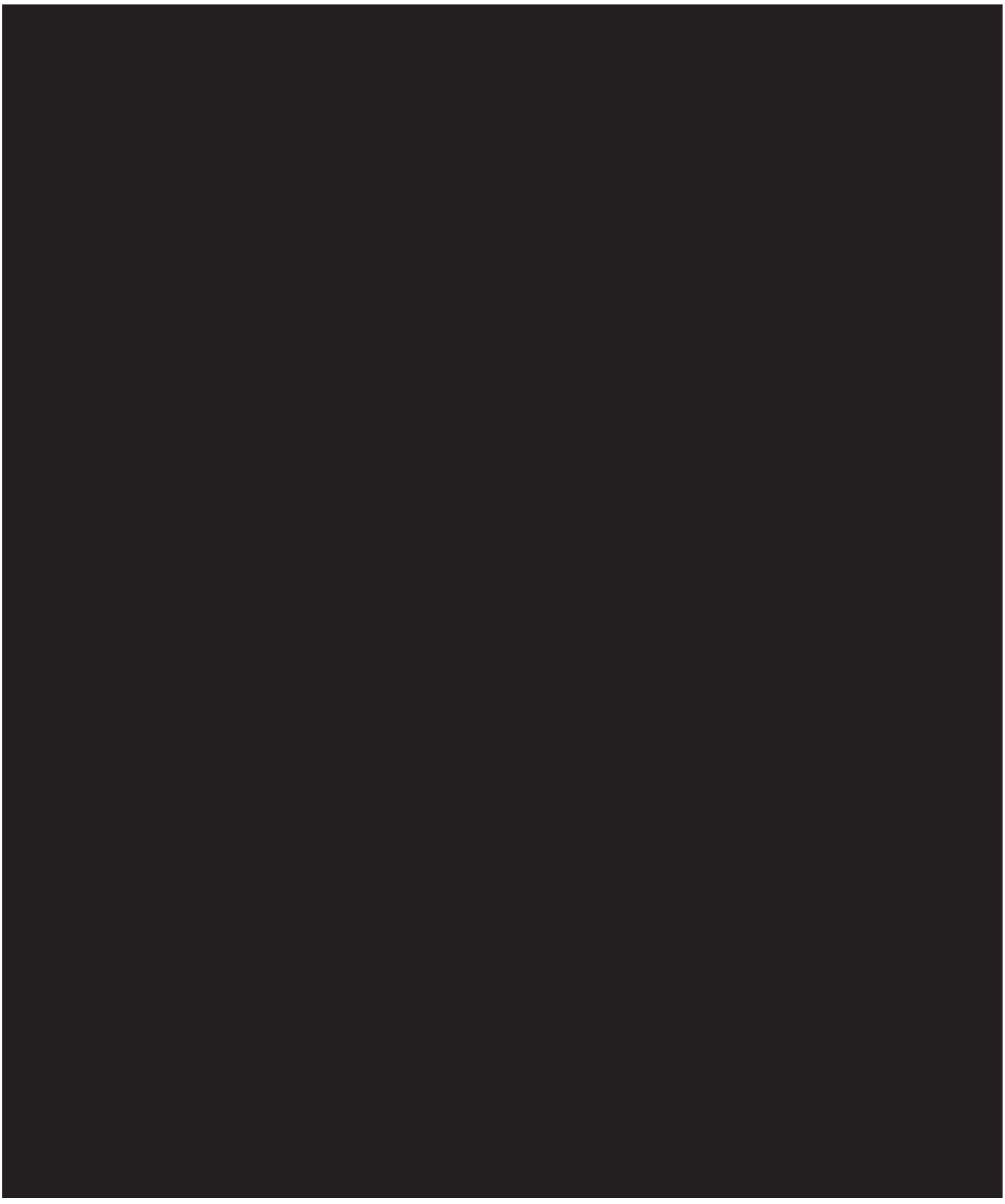
APPENDIX F: RECIST VERSION 1.1

Response Evaluation Criteria in Solid Tumors

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of 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 increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Measurable lesion	Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

From RECIST v1.1 (Eisenhauer 2009)





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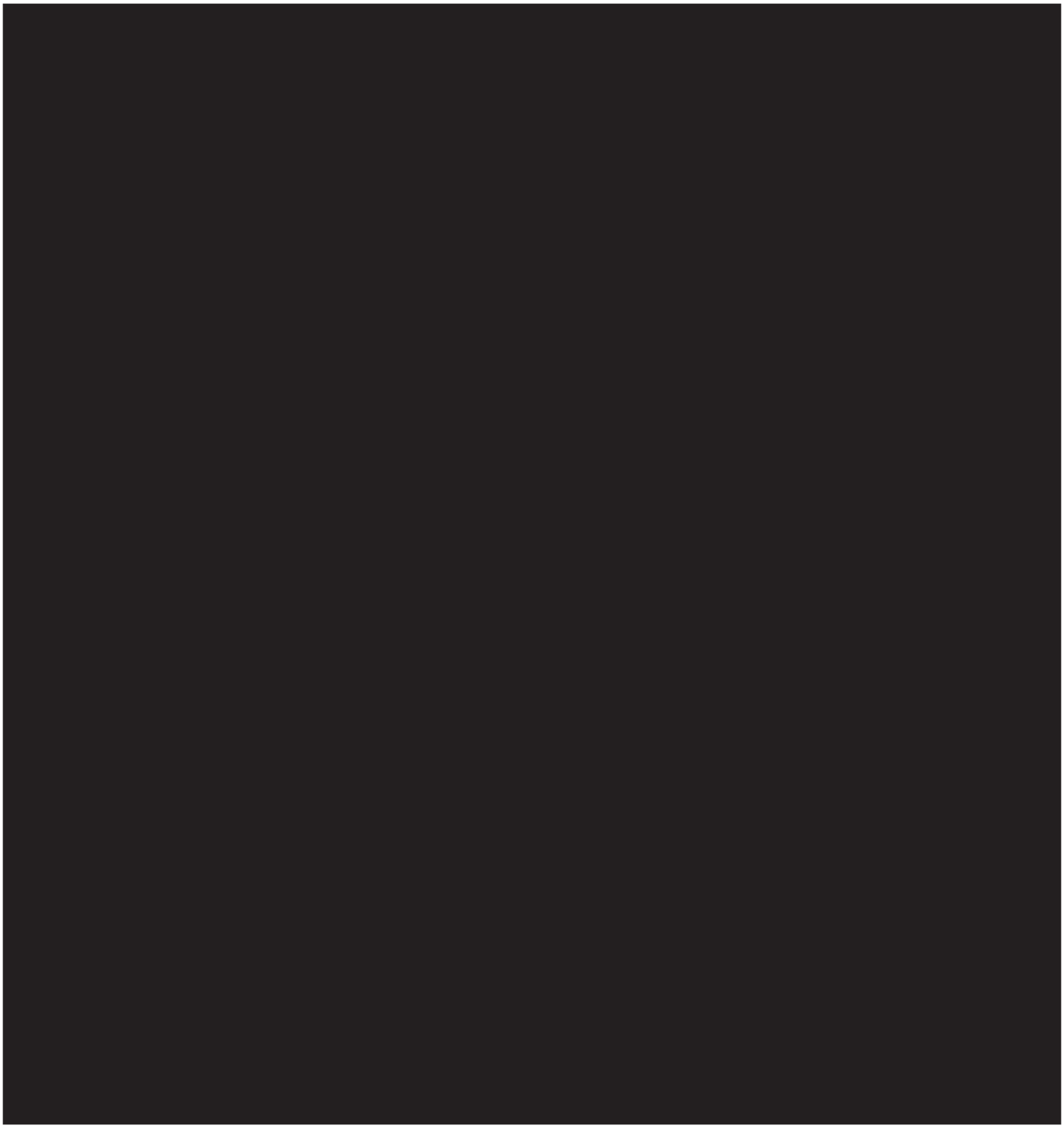
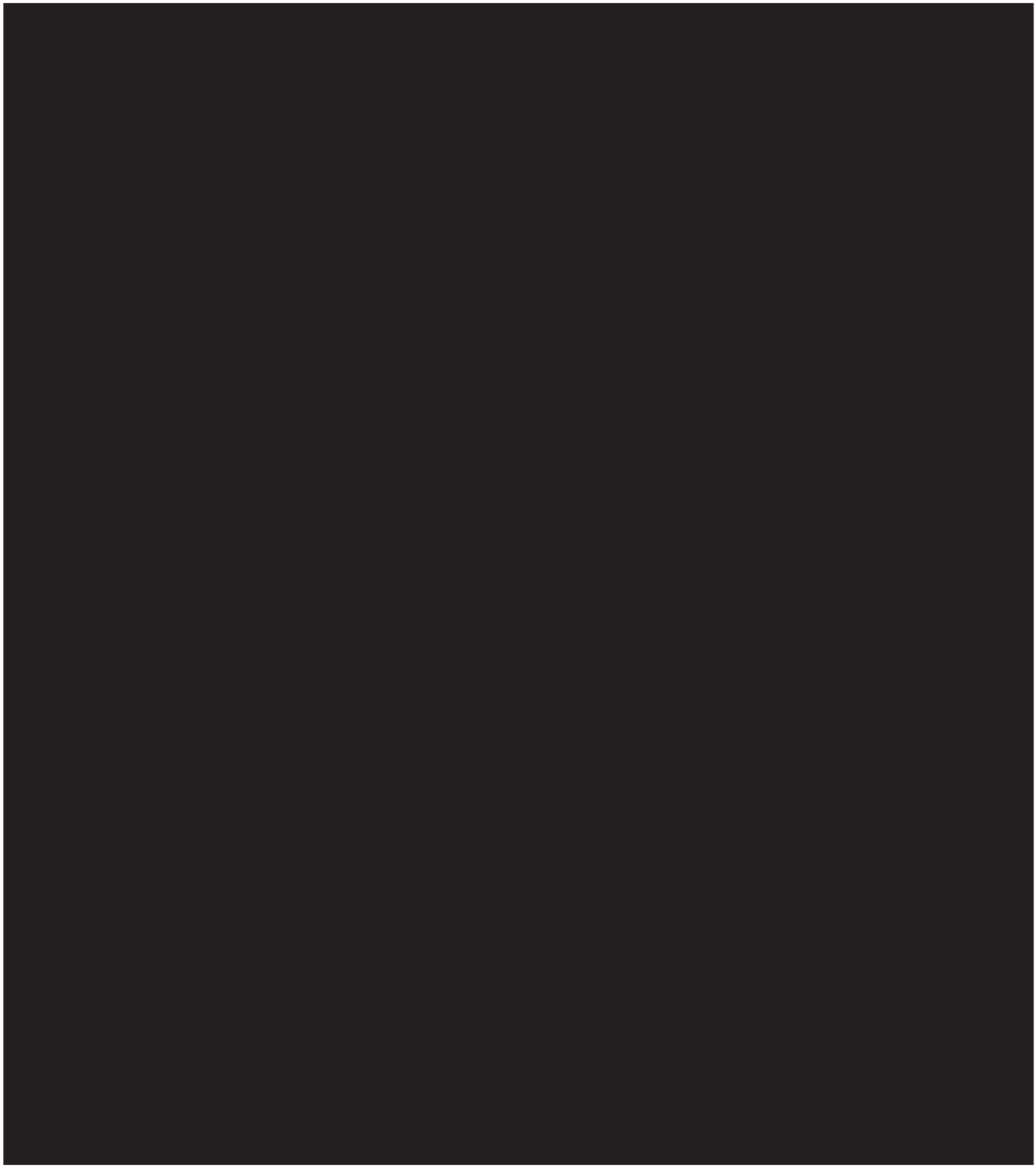
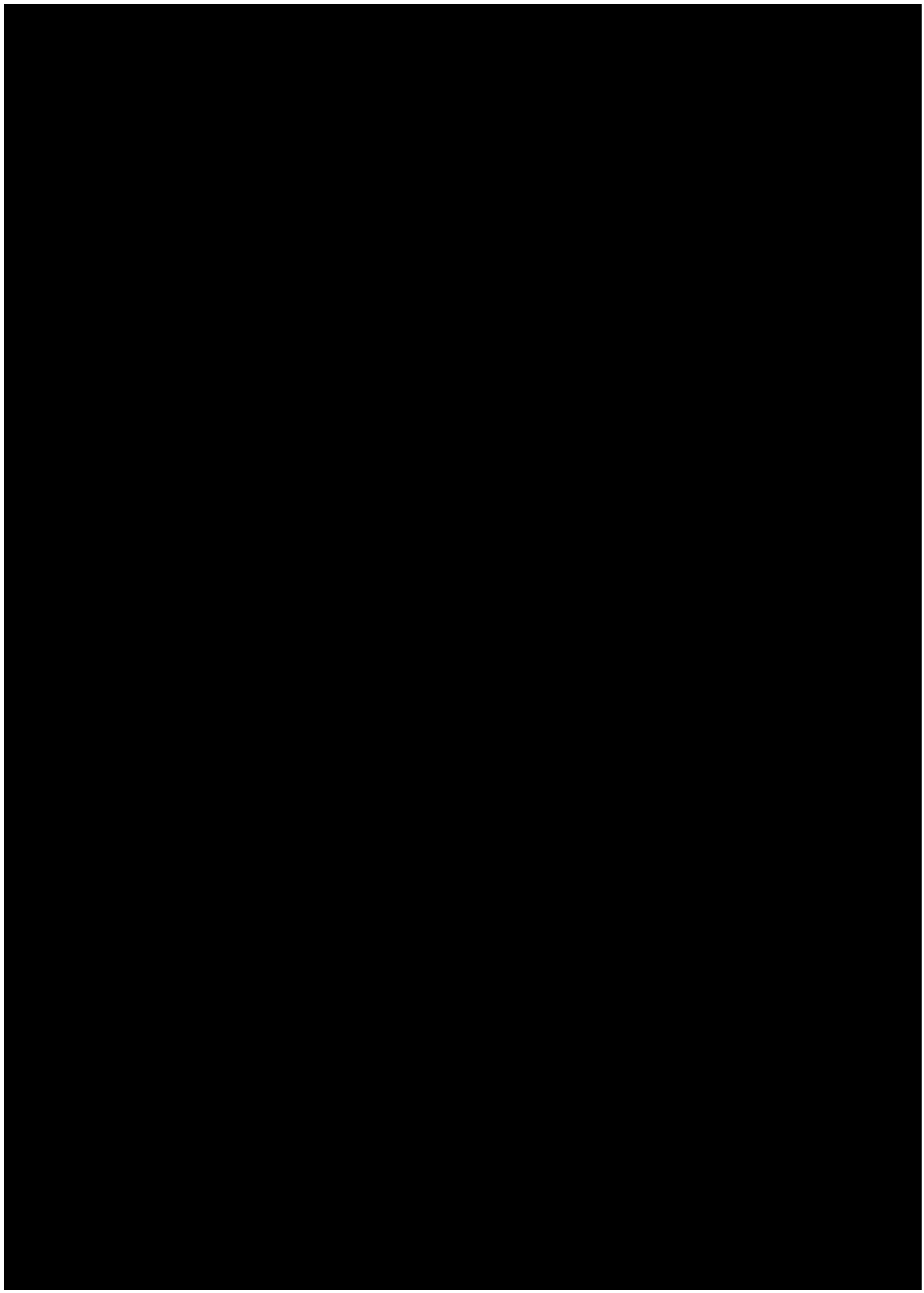
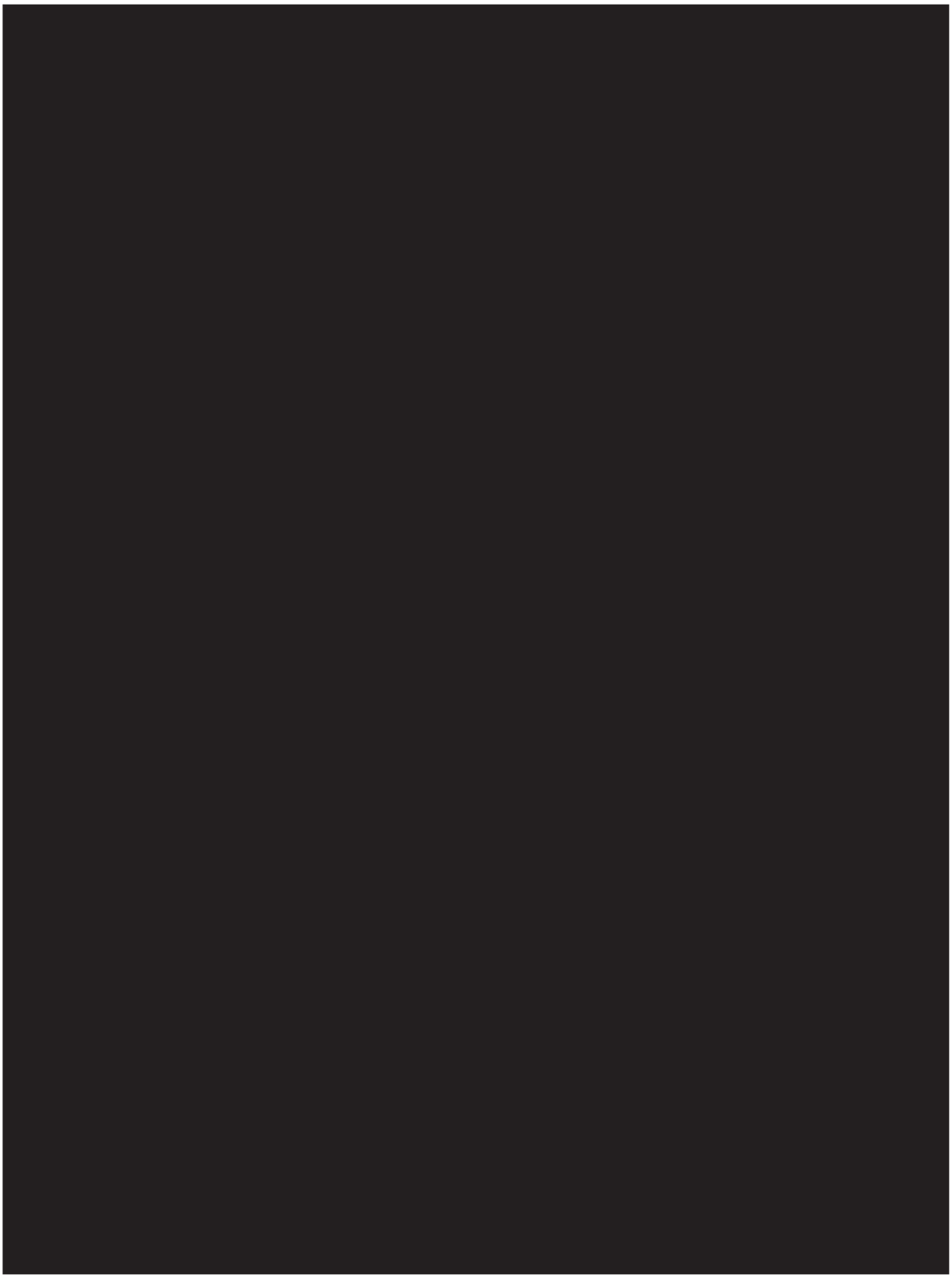
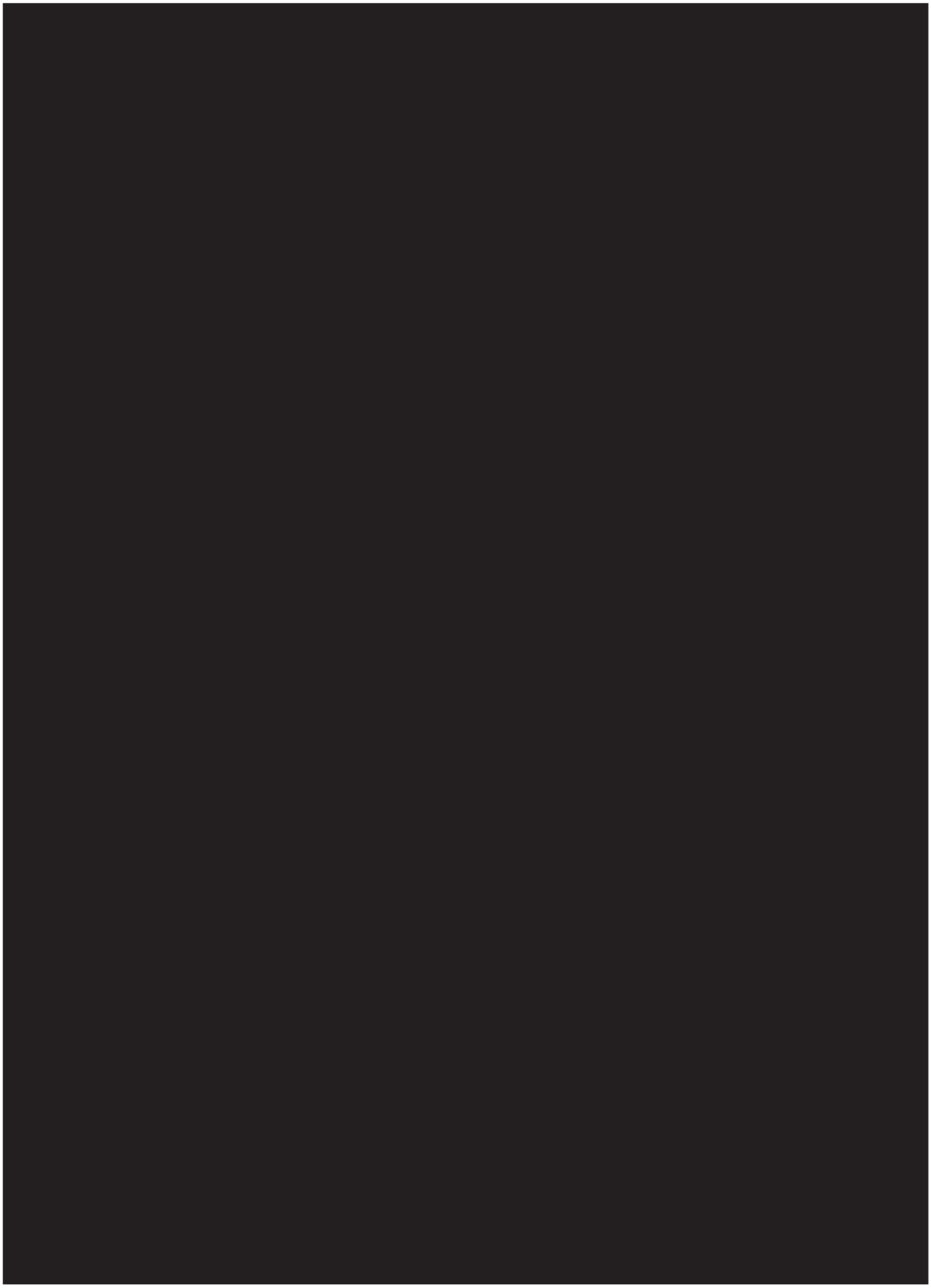










APPENDIX K: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer." **(HER2CLIMB-02)**

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX L: DOCUMENT HISTORY

Version	Date
Original	24-Apr-2019
Amendment 1	13-Aug-2019
Amendment 1.1	20-Dec-2019

SUMMARY OF CHANGES IN AMENDMENT 1.1

Section(s)	Change	Rationale
Cover page	EudraCT number was added.	Documents the assigned study identifier in the European Union. Update was made to enable clinical trial applications in Europe.
Synopsis	Included the Secondary Endpoint - Evaluate the duration of response (DOR) by BICR per RECIST v1.1 between treatment arms	To be consistent with the body of the protocol.
Section 5.2	The minimum time allowed between whole-brain radiotherapy and the initiation of study treatment was changed from ≥21 days to ≥14 days	Correction

Protocol Number:	ACCRU-GI-1617, SGNTUC-017
Version:	Amendment 9 [10-Sep-2020]
Protocol Title:	MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer
Investigational Product:	Tucatinib
Brief Title:	Tucatinib plus Trastuzumab in Patients with HER2+ Colorectal Cancer
Phase:	2
IND Number:	134840
EudraCT Number	2020-000540-60
ClinicalTrials.gov Identifier	NCT03043313
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	Michael Stecher, MD Tel: [redacted] Email: [redacted]
SAE Email or Fax:	See email or fax number specified on the SAE report form.

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Number:	ACCRU-GI-1617, SGNTUC-017
Protocol Title:	MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer
Investigational Product:	Tucatinib
Version:	Amendment 9 10-Sep-2020

The sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the clinical trial is conducted and data are generated, documented, and reported in compliance with this protocol, accepted standards of good clinical practice, and all applicable federal, state, and local laws, rules, regulations, requirements, and guidelines (including all foreign laws and governmental requirements as applicable) relating to the conduct of the clinical trial.

The individuals signing below have reviewed and approve this protocol.

Michael Stecher, MD Senior Medical Director	Date

PROTOCOL SYNOPSIS

Protocol Number ACCRU-GI-1617, SGNTUC-017 **Version** Amendment 9; 10-Sep-2020 **Phase** 2	**Product Name** Tucatinib **Sponsor** Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer

Study Objectives

This study consists of 3 cohorts:

- Cohort A = ~40 subjects dosed with tucatinib and trastuzumab
- Randomized cohorts:
  - Cohort B = ~40 subjects dosed with tucatinib and trastuzumab
  - Cohort C = 30 subjects dosed with tucatinib monotherapy

Primary Objectives

- To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by confirmed objective response rate (cORR, per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria), according to blinded independent central review (BICR) assessment

Secondary Objectives

Efficacy

- To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment
- To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment
- To assess the duration of response (DOR) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment
- To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment
- To assess the progression-free survival (PFS) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment
- To assess the overall survival (OS) in subjects treated with tucatinib given in combination with trastuzumab, in Cohorts A+B

Safety

- To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B
- To assess the safety and tolerability of tucatinib monotherapy, in Cohort C

Exploratory Objectives

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study Endpoints

Primary endpoints

- cORR (confirmed complete response [CR] or partial response [PR]), per RECIST 1.1, according to BICR assessment, in pooled Cohorts A+B.

Secondary endpoints

Efficacy

- ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohorts A+B
- ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohort C
- DOR (RECIST 1.1), according to BICR assessment, in Cohorts A+B.
- DOR (RECIST 1.1), according to BICR assessment, in Cohort C
- PFS (RECIST 1.1), according to BICR assessment, in Cohorts A+B
- OS, in Cohorts A+B

Safety

- Frequency and severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria, of all treatment-emergent adverse events (TEAEs) and treatment-related TEAEs, in Cohorts A+B
- Frequency and severity, according to CTCAE v4.03, of all TEAEs and treatment-related TEAEs, in Cohort C
- Frequency of serious adverse events (SAEs) and deaths due to adverse events (AEs), in Cohorts A+B
- Frequency of SAEs and deaths due to AEs, in Cohort C
- Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B

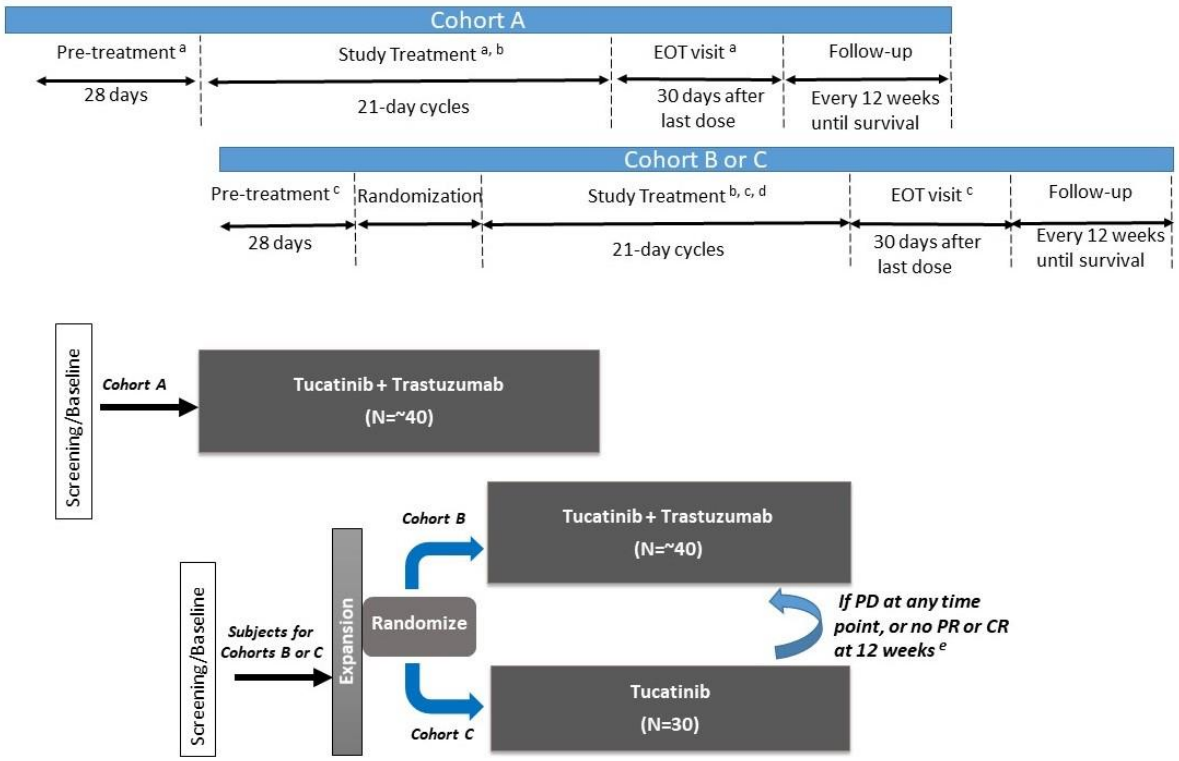
- Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohort C
- Frequency and severity of laboratory abnormalities, in Cohorts A+B
- Frequency and severity of laboratory abnormalities, in Cohort C
- Vital signs and other relevant safety variables, in Cohorts A+B
- Vital signs and other relevant safety variables, in Cohort C

Exploratory endpoints

[redacted]

Study Population

Patients with HER2+, RAS wild-type, unresectable or metastatic colorectal cancer (mCRC) who, unless contraindicated, have previously received systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb); patients whose disease has deficient mismatch repair (dMMR) proteins or is microsatellite instability-High (MSI-H) must also have received anti-PD-(L)1 mAb, if indicated.



Note: Subjects enrolled in Cohort A or Cohort B will be treated with tucatinib and trastuzumab doublet combination therapy, and subjects enrolled in Cohort C will be treated with tucatinib monotherapy.
CR = complete response, EOT = end of treatment, PD = progressive disease, PR = partial response

a For Cohort A, radiological disease assessments (computerized tomography [CT] or magnetic resonance imaging [MRI] scans of chest, abdomen, and pelvis) and carcinoembryonic antigen (CEA) tumor marker assays will be performed at the screening/baseline, every 9 weeks/3 cycles (±14 days) during study treatment (every 12 weeks/ 4 cycles [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

b For Cohorts A and B, treatment will be administered in 21-day cycles. Tucatinib will be administered at 300 mg BID plus trastuzumab IV infusion at a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 21 days.

c For Cohorts B and C, radiological disease assessment (CT or MRI of chest, abdomen, and pelvis) and CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatement for clinical benefit will not require continued disease assessments after discontinuing treatment.

d For Cohort C, treatment will be administered in 21-day cycles. Tucatinib will be administered at 300 mg BID.

e Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy if they experience radiographic progression at any time point, or if they have not achieved a PR or CR by the Week 12 assessment. In order to assess radiographic response to the doublet therapy, subjects in Cohort C must have a new baseline RECIST assessment prior to crossover from monotherapy to doublet therapy using the Week 12 scans or the first PD scans as applicable.

Inclusion Criteria

Subjects must meet the following criteria to be eligible for the study:

1. Have histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is metastatic and/or unresectable
2. Unless otherwise contraindicated, subjects must have received and failed regimens containing the following agents: fluoropyrimidines (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF mAb (bevacizumab, ramucirumab, or ziv-aflibercept), and an anti-PD-(L)1 therapy (nivolumab or pembrolizumab) if the tumor has dMMR proteins or is MSI-H
3. Have progression of unresectable or mCRC after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Have RAS wild-type in primary or metastatic tumor tissue, based on expanded RAS testing including KRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and NRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)
5. Subjects must be willing and able to provide the most recently available tissue blocks (or slides, with Medical Monitor's approval), obtained prior to treatment initiation, to a sponsor-designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion is required
6. Have confirmed HER2-positive mCRC, as defined by having tumor tissue tested at a Clinical Laboratory Improvement Amendments (CLIA)-certified or International Organization for Standardization (ISO)-accredited laboratory, meeting at least one of the following criteria:
    a. HER2+ overexpression (3+ immunohistochemistry [IHC]) by an FDA-approved or Conformité Européenne (CE)-marked HER2 IHC test following the package insert's interpretational manual for breast cancer
    b. HER2 2+ IHC is eligible if the tumor is amplified by an FDA-approved or CE-marked HER2 in situ hybridization assay (fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH]) following the package insert's interpretational manual for breast cancer
    c. HER2 (*ERBB2*) amplification by CLIA-certified or ISO-accredited Next Generation Sequencing (NGS) sequencing assay
7. Age ≥18 years at time of consent
8. Have radiographically measurable disease assessable by RECIST 1.1, with at least one site of disease that is measurable and that has not been previously irradiated; or, if the subject has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation
9. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1, or 2
10. Life expectancy greater than 3 months, in the opinion of the investigator
11. Have adequate hematological, hepatic, renal, coagulation, and cardiac function as defined below, obtained ≤7 days prior to the first study treatment:
    a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$
    b. Platelet count $\geq 75 \times 10^3/\mu L$
    c. Hemoglobin ≥8.0 g/dL

d. Total bilirubin ≤1.5 × upper limit of normal (ULN). Subjects with known history of Gilbert's Syndrome and normal direct bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are eligible

e. AST and ALT ≤2.5 × ULN (≤5 × ULN if liver metastases are present)

f. Calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault formula

g. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless on medication known to alter INR and/or aPTT

h. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan documented ≤28 days prior to study treatment.

12. For subjects of childbearing potential, the following stipulations apply:

    a. Must have a negative serum pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of study treatment. A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.

    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study drug administration

    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study drug administration

    d. May choose to practice complete abstinence, if consistent with the subject's preferred lifestyle, as an acceptable form of contraception

    e. If sexually active in a way that could lead to pregnancy, must consistently use highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration.

13. For subjects who can father children, the following stipulations apply:

    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final study drug administration

    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

14. Subject must provide signed informed consent that has been approved by an institutional review board/independent ethics committee (IRB/IEC) prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease

15. Subject must be willing and able to comply with study procedures

Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

1. Have previously been treated with anti-HER2 targeting therapy
2. Have received treatment with any systemic anticancer therapy (including hormonal and biologic therapy), non-central nervous system (CNS) radiation, or experimental agent ≤3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial
3. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Alopecia and neuropathy, which must have resolved to ≤ Grade 2
    - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
    - Anemia, which must have resolved to ≤ Grade 2
    - Decreased ANC, which must have resolved to ≤ Grade 2
4. Have clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension, as determined by the investigator
    - Any history of symptomatic CHF, left ventricular systolic dysfunction or decrease in ejection fraction
    - Severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy
    - Presence of ≥ Grade 2 corrected QT interval (QTc) prolongation on screening electrocardiogram (ECG)
5. Have known myocardial infarction, unstable angina, cardiac or other vascular stenting, angioplasty, or cardiac surgery within 6 months prior to first dose of study treatment
6. Major surgical procedure, open biopsy, or significant traumatic injury ≤28 days prior to enrollment (≤56 days for hepatectomy, open thoracotomy, or major neurosurgery) or anticipation of need for major surgical procedure during the course of the study
7. Serious, non-healing wound, ulcer, or bone fracture
8. Known to be positive for hepatitis B by surface antigen expression
9. Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks
10. Known to be positive for human immunodeficiency virus (HIV)
11. Subjects who are pregnant, breastfeeding, or planning a pregnancy

12. Inability to swallow pills or any significant gastrointestinal disease which would preclude the adequate oral absorption of medications
13. Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP2C8 or CYP3A4 inducer within 5 days prior to first dose of study treatment.
14. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
15. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)
16. Subjects with known active CNS metastasis (irradiated or resected lesions are permitted, provided the lesions are fully treated and inactive, subject is asymptomatic, and no steroids have been administered for at least 30 days)
17. Have a hypersensitivity to tucatinib or any of its excipients, to trastuzumab or any of its excipients, or to murine proteins.

Number of Planned Subjects

Approximately 110 subjects will be enrolled and treated in this study: 80 subjects treated in the tucatinib + trastuzumab cohorts (Cohorts A+B) and 30 subjects in the tucatinib monotherapy cohort (Cohort C).

Study Design

This is a multicenter, randomized, open-label, Phase 2 study of tucatinib, administered as monotherapy and in combination with trastuzumab, in patients with HER2-positive, RAS wild-type, unresectable or metastatic CRC. Eligible patients are required to have previously received and failed, unless contraindicated, systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients with dMMR or MSI-H disease must also have received an anti-PD-(L)1 mAb, if indicated. The study initially consisted of Cohort A, which includes approximately 40 subjects treated with the doublet regimen. As of Protocol Amendment 8, the study is expanded to include approximately 40 additional subjects (Cohort B) treated with the tucatinib + trastuzumab doublet (for a total of 80 subjects in Cohorts A+B), and 30 subjects treated with tucatinib monotherapy (Cohort C).

Treatment will be administered in cycles of 21 days each. All subjects enrolled in the expansion portion of the trial will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment will continue until 30 subjects have been randomized to Cohort C, and approximately 40 subjects have been randomized to Cohort B.

Treatment will be administered in cycles of 21 days each. Subjects in Cohorts A and B will be treated with tucatinib at a dose of 300 mg orally twice daily (PO BID) and trastuzumab at a loading dose of 8 mg/kg intravenous (IV) followed by a dose of 6 mg/kg IV every 3 weeks.

Subjects randomized to Cohort C will be treated with tucatinib at a dose of 300 mg PO BID.

Subjects enrolled in Cohort A and those randomized to Cohort B will continue on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure. Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy if they experience radiographic progression at any time point, or if they have not achieved a PR or CR by the Week 12 assessment. Subjects in Cohort C must have a new baseline RECIST assessment prior to crossover from monotherapy to doublet therapy using the Week 12 scans or the first PD scans as applicable.

The primary efficacy analysis set will comprise subjects randomized to Cohort B pooled with subjects enrolled in Cohort A.

The primary endpoint of the study is the confirmed ORR. Radiographic response will be assessed by a BICR, according to RECIST 1.1, with confirmation of response required ≥4 weeks from the first documentation of response.

Secondary efficacy endpoints include duration of confirmed response, PFS and OS for all subjects enrolled on the doublet regimen (Cohort A+B). In addition, in order to assess the contribution of tucatinib to the doublet regimen, ORR by 12 weeks will be assessed in Cohorts A+B, as well as in Cohort C; however [redacted]

Investigational Product, Dose, and Mode of Administration

All Cohorts

Tucatinib 300 mg PO BID on Days 1 to 21 of each 21-day cycle.

Cohorts A and B; Subjects from Cohort C Who Crossover to Doublet Therapy

Trastuzumab 8 mg/kg will be administered by IV infusion over 90 minutes on Day 1 of Cycle 1. In subsequent cycles, trastuzumab 6 mg/kg will be administered IV over 30 minutes on Day 1 of each cycle, except in specific circumstances where 2 mg/kg may be given weekly or 4 mg/kg every 2 weeks to compensate for modifications in treatment schedule. Subjects who are crossing over from Cohort C will be able to start doublet combination therapy as soon as the formal crossover process occurs, even if it entails abruption in a previous cycle.

On days when trastuzumab is administered, the tucatinib dose may be taken before, during, or after the trastuzumab infusion.

Duration of Treatment

Subjects in Cohorts A or B may continue on study treatment until progressive disease (PD), death, AEs that are considered intolerable and unmanageable, lost to follow-up, treatment-related adverse events which do not resolve to Grade ≤2 within 6 weeks, request by regulatory agencies, dosing delay greater than 6 weeks, investigator decision, protocol noncompliance, withdrawal of consent, start of a subsequent anticancer therapy, pregnancy or breastfeeding, or study termination by the sponsor. All efforts should be made to continue treatment until unequivocal evidence of radiographic progression occurs.

Subjects randomized to Cohort C, who have experienced radiographic progression at any time point, or if they have not achieved a PR or CR by the Week 12 assessment, may crossover to receive doublet therapy. Subjects in Cohort C must have a new baseline RECIST assessment prior to crossover from monotherapy to doublet therapy using the Week 12 scans or the first PD scans as applicable.

Subjects with signs of clinical benefit (e.g., mixed response, symptom improvement, demonstrable slowing of progression, progression rate of <20% over 6 months) who are tolerating treatment may be allowed to continue treatment past formal radiologic progression (per RECIST 1.1) if such treatment is considered in the subject's best interest by the subject, the treating physician, and the Medical Monitor. In this scenario, subjects may continue until clinical progression.

Efficacy Assessments

Radiological disease assessments (computerized tomography [CT] or magnetic resonance imaging [MRI] scans of chest, abdomen, and pelvis) and carcinoembryonic antigen (CEA) tumor marker assays will be undertaken on the following schedule:

1. Cohort A: at screening/baseline, every 9 weeks (±14 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the end of treatment (EOT) visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until PD, death, withdrawal of consent, study closure, or alternative therapy.
2. Cohorts B and C: at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until PD, death, withdrawal of consent, study closure, or alternative therapy.

Note: Subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST 1.1. Disease assessments will be evaluated by both the BICR and investigators. The investigator will make treatment decisions based on site assessments of scans. For Cohort A, confirmation of response was initially not required per protocol. For the purposes of the primary analysis, the disease assessment timepoint after the first response documented by the BICR will be used to determine confirmed response. For Cohort A, responses (CR or PR) will be confirmed at the next re-staging timepoint, 9 weeks (±14 days) after first documentation of response. For Cohorts B and C, responses (CR or PR) will be confirmed at the next re-staging timepoint, 6 weeks (±7 days) after first documentation of response. Subjects will be followed for survival every 12 weeks (±14 days) up to 5 years from treatment initiation in a long-term follow-up phase of the study.

[redacted]

[redacted]

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, including SAEs, physical examination findings, vital signs, concomitant medications, pregnancy testing, and laboratory tests. Assessment of cardiac ejection fraction will be performed by MUGA scan or ECHO.

Concomitant Therapies

Use of investigational drugs and devices, anticancer (including but not limited to chemotherapy and hormonal therapy) and radiation therapy (except for palliative radiotherapy at focal non-CNS sites which are not considered target lesions per RECIST 1.1) should be prohibited during the study. Tucatinib must be held 7 days prior to and 7 days post radiation therapy. Strong CYP2C8 inhibitors and strong CYP2C8 or CYP3A4 inducers are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment. Concomitant use of a sensitive CYP3A substrate should be avoided 1 week prior to the first dose of study treatment and during the study. Use of moderate or weak inhibitors of CYP2C8 are permitted but should be used with caution.

Statistical Methods

Safety and efficacy endpoints will be summarized with descriptive statistics.

Data collected in this study will be presented using summary tables, subject data listings, and figures. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Confidence intervals (CI), 95% 2-sided, will be presented where needed to gauge the strength of evidence for a

corresponding estimated treatment effect. For time-to-event endpoints, the median survival time will be estimated using the Kaplan Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation. Subjects from the initial and randomized to Cohort B during the expansion will be analyzed together (Cohorts A+B) and by cohort (Cohort A, Cohort B, and Cohort C).

The primary analysis of efficacy endpoints will be performed per BICR assessment using RECIST 1.1 criteria. Supportive analysis per investigator assessments will also be performed. Discordance between the BICR and investigator's assessment will be evaluated.

Sample Size Considerations

Cohort A

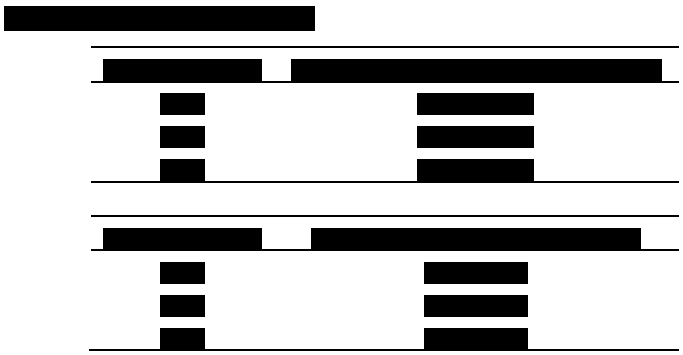
Cohort A used a Fleming 2-stage phase 2 design, with a null hypothesis of 20% unconfirmed ORR for tucatinib+trastuzumab, an alternative hypothesis of 40%, a one-sided significance level of 0.1153, and a power of 83.54%. Ten evaluable subjects were to be treated in the first stage; if ≤1 response is observed the regimen would be considered ineffective in this subject population; if ≥5 successes are observed the null hypothesis will be rejected; otherwise Cohort A proceeds to the second stage. Fifteen evaluable subjects were to be treated in the second stage; if a total of ≤7 responses are observed in the first 25 evaluable subjects, the regimen will be considered ineffective; if ≥8 responses are observed the regimen may merit further evaluation. Based on interim efficacy results, Cohort A has been expanded to approximately 40 subjects.

Cohorts B and C

The expansion Cohort B is designed to increase the size of the study population exposed to the doublet regimen in order to allow more precise estimation of the confirmed ORR in subjects receiving tucatinib with trastuzumab, as well as to furnish supplementary safety data. The primary efficacy analysis will be performed by providing the point estimate and the 2-sided 95% exact Clopper-Pearson CI for the confirmed ORR (pooled Cohorts A and B).

The addition of Cohort C is intended to better characterize the antitumor activity of tucatinib when used as a monotherapy in this patient population.

For illustration purposes, a summary of the expected 95% CIs for subjects treated in Cohorts A+B and subjects treated in Cohort C at the proposed sample sizes of 80 and 30, respectively.



Efficacy Analyses

The primary endpoint of this study is the confirmed ORR per RECIST 1.1 according to BICR assessment. The ORR is defined as the proportion of subjects with confirmed CR or PR. The ORR and its exact 2-sided 95% CI, using the Clopper-Pearson method, will be calculated.

The final analysis of cORR and DOR will be conducted when all treated subjects have been followed for [redacted] (or all responders have been followed for [redacted] after their initial response, whichever comes first), have discontinued from the study, or had [redacted] safety follow-up after disease progression, whichever comes first. PFS and OS will also be analyzed at the time of the final ORR and DOR analyses; additional analysis of these time-to-event endpoints may be undertaken when mature progression and survival data become available.

ORR, DOR, and PFS according to investigator assessment will also be analyzed; discordance between the BICR and investigator's assessment will be summarized descriptively.

Interim Futility Efficacy Analyses

Interim futility efficacy analyses of the Cohort A will be undertaken after the first 10 subjects have undergone disease assessment (first stage of Fleming design), and after the first 25 subjects have undergone disease assessment (second stage of Fleming design).

[redacted]

Safety Analyses

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG PS, and changes in cardiac ejection fraction results. AEs will be classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE v4.03 criteria. Separately, all SAEs and AEs of special interest (e.g., any drug-induced liver injury, and asymptomatic left ventricular systolic dysfunction) will also be listed.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	twice daily
BSD	Baseline sum of diameters BSD
CBC	complete blood count
CCG	Case Report Form Completion Guidelines
CE	Conformité Européenne
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration observed
CNS	central nervous system
cORR	confirmed objective response rate
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
dMMR	deficient mismatch repair
DOR	duration of response
ED	emergency department
EEA	European Economic Area
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
EU	European Union

FDA	Food and Drug Administration
FFPE	formalin fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GLP	Good Laboratory Practice
hERG	human ether a-go-go related gene
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IC_{50}	half maximal inhibitory concentration
IEC	independent ethics committee
IHC	immunohistochemistry
IM	intramuscular
IND	Investigational New Drug
INR	international normalized ratio
ISO	International Organization for Standardization
IRB	institutional review board
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous
HR	hazard ratio
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mAb	monoclonal antibody
mCRC	metastatic colorectal cancer
MRI	magnetic resonance imaging
MSD	minimum sum of the diameters
MSI-H	Microsatellite instability-High
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NGS	Next Generation Sequencing
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
PBSD	Post-Baseline Sum of the Diameters
PD	progressive disease
PET	positron emission tomography
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
QTc	corrected QT interval

RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic oxoloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMC	Safety Monitoring Committee
SOC	System Organ Class
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse events
TGI	tumor growth inhibition
TKI	tyrosine kinase inhibitor
TTP	time-to-progression
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor

1 INTRODUCTION

1.1 HER2+ Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (US), with nearly 50,000 deaths annually (Jemal 2010). Based on current treatment algorithms, survival for patients with metastatic CRC (mCRC) is approximately 2-3 years (Van Cutsem 2011; Douillard 2013a; Douillard 2013b; Cremolini 2015). Nearly half of all patients with mCRC have *KRAS* or *NRAS* (RAS) wild-type tumors (Douillard 2013a). In unselected patients, the prevalence of *ERBB2* amplification is 3.5% (Cancer Genome Atlas 2012); however, among patients with *KRAS*/*NRAS*/*BRAF* wild-type CRC tumors, the prevalence of *ERBB2* amplification increases to 6-10% (Siena 2015; Raghav 2016). There are currently no approved therapies for patients with *ERBB2* amplified metastatic CRC.

Encoded by the *ERBB2* gene, HER2 is part of a family of 4 related receptor tyrosine kinases, which include HER1 (also known as epidermal growth factor receptor [EGFR]), HER2, HER3 and HER4. HER1-4 are single-pass transmembrane glycoprotein receptors containing an extracellular ligand binding region and an intracellular signaling domain. HER2 has no known ligand, but it is the preferred dimerization partner for the other HER family receptors. HER2 homo- or heterodimerization results in the activation of multiple signaling cascades, including the Ras/Raf/MEK/MAPK, PI3K/AKT, Src, and STAT pathways. These signaling pathways lead to cell proliferation, inhibition of apoptosis, and metastasis (Riese 1998; Olayioye 2000; Yarden 2001; Schlessinger 2002; Holbro 2004; Hynes 2005)

1.2 Treatment of HER2+ CRC

Anti-HER2 therapies are active in patients with heavily pre-treated, HER2+ mCRC (Table 1-1). In a single-arm, phase 2 trial conducted in patients with refractory HER2+ mCRC, dual HER2-blockade with lapatinib and trastuzumab resulted in a 30% response rate, and a nearly 5 month median time-to-progression (TTP) (Sartore-Bianchi 2016). In addition, the MyPathway basket trial, which evaluated trastuzumab plus pertuzumab in patients with HER2+ mCRC, reported a 32% response rate (Hainsworth 2016) and a 2.9 month median progression-free survival (PFS) (Meric-Bernstam 2019). “Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): An Updated Report from a Multicenter, Open-label, Phase 2a, multiple basket trial.”(4):518-530. doi: 10.1016/S1470-2045(18)30904-5. Despite these favorable results, access to anti-HER2 therapies is restricted to clinical trials and off-label use.

Table 1-1: Anti-HER2 clinical trials in patients with refractory HER2+ mCRC

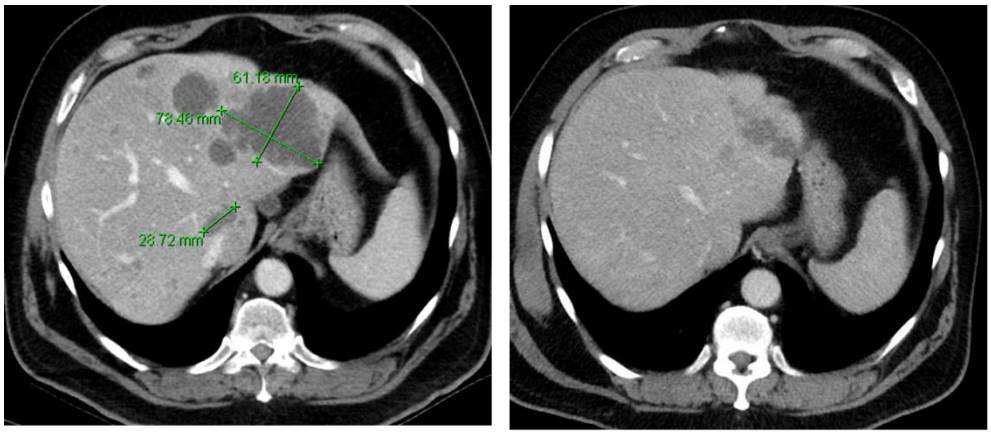
Clinical Trial	Therapies	Patients (N)	Response Rate	TTP/PFS (median)
HERACLES	Lapatinib+Trastuzumab	27	30%	4.9 months
MyPathway	Pertuzumab+Trastuzumab	57	32%[a]	2.9 months

TTP = time-to-progression; WT = wild-type

a ORR 32%; ORR 40% (17/43) in KRAS WT; ORR 8% (1/13) in KRAS mutated

As part of an investigator-initiated trial at Duke University (NCT02008383), comprehensive molecular profiling is being performed on patients with EGFR-refractory, RAS wild-type mCRC. Three out of the first 24 patients (12.5%) had ERBB2 amplification confirmed by fluorescence in situ hybridization (FISH). One of these heavily pretreated patients received off-label lapatinib and trastuzumab and experienced significant clinical response (See Table 1-1).

Figure 1-1: Subject with ERBB2 amplified, EGFR-refractory metastatic CRC treated with off-label lapatinib and trastuzumab



Baseline (8/12/2015) | After 6 cycles lapatinib + trastuzumab (12/23/2015)

With mounting evidence that *ERBB2* amplified tumors are resistant to anti-EGFR therapies (Vlacich 2011; Yonesaka 2011; Bertotti 2015), HER2 testing for patients with mCRC is increasingly routine. Increased access to anti-HER2 clinical trials will further facilitate HER2 testing and personalized treatment strategies.

1.2.1 Ongoing Medical Need in HER2+ Metastatic CRC

After progression on first and second line chemotherapy (FOLFOX and FOLFIRI), the clinical benefit of approved therapies is limited. For patients with RAS wild-type mCRC, antibodies targeting EGFR offer a monotherapy response rate of approximately 20% and a PFS of 4 months (Price 2014). Nonetheless, since *ERBB2* amplification is considered a driver of primary EGFR treatment resistance (Bertotti 2011; Martin 2013b; Raghav 2016), the role for anti-EGFR therapies in the HER2+ CRC patient population is increasingly questioned (Schmoll 2016).

Once patients with mCRC have progressed on all standard chemotherapy and biological therapies, current approved treatment options include regorafenib and trifluridine/tipiracil (TAS-102). Both therapies offer a response rate less than 2%, and a survival benefit of less than 2 months compared to placebo (see Table 1-2) (Grothey 2013; Mayer 2015). To improve clinical outcomes, efforts are needed to identify and treat patients with actionable genomic alterations.

Table 1-2: Clinical trials in patients with treatment refractory mCRC

Clinical Trial	Therapies	Patients (N)	ORR (%)	Median PFS (months)	Median OS (months)
CORRECT	Regorafenib	505	1.0%	1.9	6.4
	Placebo	255	0.4%	1.7	5.0
RECOURSE	TAS-102	534	1.6%	2.0	7.1
	Placebo	266	0.4%	1.7	5.3

1.3 Tucatinib

1.3.1 Product Description and Mechanism of Action

Tucatinib (previously known as ONT-380 and ARRAY-380) is an oral, potent, HER2-specific tyrosine kinase inhibitor (TKI) that is being developed by Seattle Genetics (Bothell, WA). Unlike other small molecule inhibitors of HER2, including lapatinib, neratinib, and afatinib, all of which are dual-inhibitors of both EGFR and HER2, tucatinib selectively inhibits HER2 (Table 1-3). This enables tucatinib to provide potent inhibition of HER2 while minimizing many of the EGFR-related side effects including severe skin rash and gastrointestinal toxicity.

1.3.2 Overview of Nonclinical and Clinical Pharmacology Studies

The pharmacokinetics (PK), toxicokinetics, distribution, metabolism, excretion, and PK drug interactions of tucatinib were assessed in *in vitro* systems, and *in vivo* in mice, rats, and cynomolgus monkeys. Metabolism and excretion studies were also conducted in humans. In addition, multiple clinical trials have been completed, or are currently enrolling to evaluate tucatinib in subjects with HER2+ metastatic breast cancer.

1.3.2.1 Preclinical Studies

For full details of preclinical studies of tucatinib, refer to the tucatinib Investigator's Brochure. One of the key features of tucatinib is the highly potent and selective inhibition of the receptor tyrosine kinase HER2. A combination of biochemical and cell biological assays have been used to demonstrate the selective inhibition of HER2 with limited activity against structurally related protein kinases, including EGFR and human epidermal growth factor receptor 4 (HER4).

Using a panel of 223 protein kinases, the only enzymes inhibited by tucatinib by 75% when tested at either 1 or 10 µM were members of the ErbB kinase family (HER2, EGFR, HER4). Further analysis of this family of kinases using biochemical assays demonstrated that tucatinib inhibited HER2 with a half maximal inhibitory concentration (IC_{50}) of 22 nM and was less active against EGFR (IC_{50} = 94 nM) and HER4 (IC_{50} = 370 nM). The selectivity of tucatinib for HER2 is better exemplified in assays designed to measure the inhibition of HER2 and EGFR autophosphorylation using tumor derived cell lines. In the HER2 overexpressing cell line BT-474, tucatinib inhibited the phosphorylation of HER2 with an

IC_{50} = 8 nM and inhibited the phosphorylation of Akt, a downstream effector of HER2, with an IC_{50} = 3 nM. Consistent with the potent inhibition of HER2 phosphorylation in this cell line, tucatinib blocked the proliferation of BT-474 cells with an IC_{50} = 11 nM. In contrast, tucatinib only weakly inhibited the phosphorylation of EGFR in the overexpressing cell line A431, producing an IC_{50} = 4000 nM and only inhibited proliferation of A431 cells at drug concentrations greater than 1 mM. These data demonstrate a high degree of selectivity (500-fold) for HER2 relative to EGFR and are consistent with the idea that tucatinib has the capacity to block HER2 signaling without the contributing toxicities of EGFR inhibition.

Table 1-3: HER2 and HER1 Inhibition

	HER2 IC_{50} (nM)	HER1 (EGFR) IC_{50} (nM)	Truncated p95 HER2 IC_{50} (nM)
Tucatinib	8	>1000	7
Neratinib	7	8	Not tested
Lapatinib	49	31	25

In Vivo Pharmacology

Tucatinib has been studied in a variety of nonclinical pharmacology studies to measure its efficacy as a single-agent and in drug combinations using HER2-driven tumor models. As a single-agent, tucatinib inhibited tumor growth when dosed at 25, 50 and 100 mg/kg.

At each of these dose levels, tucatinib significantly inhibited tumor growth in subcutaneous tumor models derived from BT-474 (human breast carcinoma) and N87 (human gastric carcinoma) cells. In the BT-474 model, tumor growth inhibition (TGI) by tucatinib was 81% at 50 mg/kg and was greater than the TGI observed with trastuzumab (20 mg/kg). In the N87 model, tucatinib inhibited tumor growth more than 70% when dosed at 50 mg/kg.

Tucatinib has also been evaluated in combination with trastuzumab or docetaxel in subcutaneous HER2 tumor models. In these combination studies, the drug doublets were well-tolerated and more efficacious than any single-agent. When tucatinib was combined with trastuzumab (20 mg/kg) in the BT-474 model, the antitumor activity exceeded either drug when dosed as a single-agent. Similarly, the combination of tucatinib with docetaxel (10 mg/kg) in the BT-474 model was also more effective than either single-agent.

Nonclinical Safety

Good Laboratory Practice (GLP) toxicology, safety pharmacology, and tolerability studies with tucatinib have been conducted in rats and cynomolgous monkeys to extrapolate the safety of administering the drug to humans. Taken together, these studies have demonstrated that tucatinib has a satisfactory safety profile and presents limited risk in humans. In GLP toxicology studies conducted by administration of tucatinib daily over a 28-day period, doses of 30 mg/kg BID in rats and 10 mg/kg BID in monkeys were generally well-tolerated over the testing period. Safety pharmacology studies were conducted to examine the effect of

tucatinib on cardiovascular function using in vitro human ether a-go-go-related gene (hERG) inhibition assays, and by in vivo telemetry using cynomolgous monkeys. Titration of tucatinib in the hERG assay produced an IC_{50} = 13.5 μM and there were no significant effects noted in mean arterial blood pressure, heart rate or electrocardiogram (ECG) waveforms or in QT and corrected QT (QT_c) measurements in the in vivo study. There were also no effects noted in GI (secretion and propulsion), neurobehavioral, or respiratory function studies performed in rats.

In addition to these preclinical safety assessments, tucatinib was also shown to have a low risk of mutagenicity. In vitro studies demonstrated tucatinib is non-mutagenic when tested using bacterial reverse mutation (Ames test) or L5178Y/TK+/- mouse lymphoma cell assays. In addition, at doses up to 2000 mg/kg, tucatinib was negative for the induction of micronucleated polychromatic erythrocytes in mice.

1.3.2.2 Absorption, Distribution, Metabolism, and Excretion Studies

Tucatinib was metabolized by cytochrome P450 2C8 (CYP2C8) and CYP3A in hepatic in vitro systems. Clinical drug-drug interaction (DDI) studies (ONT-380-012, ONT-380-008) and physiologically based pharmacokinetic (PBPK) modeling (PBPK Report) indicate CYP2C8 is the primary route of metabolism (~70%), whereas CYP3A plays a minor role (~10%) in tucatinib metabolism.

In vitro, tucatinib was shown to be a competitive inhibitor of CYP2C8, CYP2C9, and CYP3A with K_i values of 0.170, 4.57, and 0.805 μM, respectively, and caused metabolism-dependent inactivation of CYP3A with K_I value of 0.54 μM. Clinical DDI studies indicated tucatinib is a weak inhibitor of CYP2C8 and a strong inhibitor of CYP3A but not an inhibitor of CYP2C9.

Tucatinib is a substrate and an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), with IC50 values of 10 μM to ~ 30 and ~9 μM, respectively. Clinical DDI studies (ONT-380-012) indicate tucatinib is a weak inhibitor of P-gp. Tucatinib inhibited kidney proximal tubule transporters OCT2, MATE1 and MATE2-K mediated transport of metformin and creatinine in vitro. Results from a clinical drug interaction study (ONT-380-020) with metformin showed that co-administration of tucatinib with metformin increased the metformin plasma exposure by 48% and caused transient increase in serum creatinine level without impacting renal function.

The clinical and non-clinical data indicate that there are no circulating metabolites of tucatinib that exceed 10% of total drug-related exposure in healthy volunteers and metastatic breast cancer patients. In clinical studies, the potency adjusted exposure of the predominant metabolite of tucatinib (ONT-993) was <10%, indicating the pharmacology of tucatinib is primarily driven by the parent drug.

Plasma protein binding of tucatinib was 97.1% at 1 µM (480 ng/mL) and was consistent between 0.1 and 50 µM.

1.3.2.3 Clinical Studies

A summary of completed and ongoing clinical studies, which provide information on the PK and pharmacodynamic properties of tucatinib, is provided in the Investigator's Brochure.

The pharmacokinetics (PK) of tucatinib have been evaluate in multiple Phase 1 and Phase 2 studies in healthy volunteers and in subjects with metastatic breast cancer. At the recommended phase 2 dose (RP2D) (300 mg BID), tucatinib as administered as a tablet was rapidly absorbed with a median time of maximum concentration observed (T_{max}) of 2 hours (range 1 to 4 hours), and a half-life of approximately 8 hours. Tucatinib exhibited less than 2-fold accumulation after multiple dosing to steady-state. Evaluation of the impact of food on the PK of tucatinib indicated co-administration with food increased the exposure area under the curve (AUC) less than 2-fold with no effect on maximum concentration observed (C_{max}).

A radiolabeled mass balance study has indicated that after a single dose, the majority of total radioactivity was recovered in the feces, whereas less than 5% of total radioactivity was recovered in the urine (ONT-380-008). A thorough QT study indicated tucatinib has no effect on QT prolongation (ONT-380-011). Clinical DDI studies have indicated that tucatinib is a strong inhibitor of CYP3A and a weak inhibitor of CYP2C8, P-gp and MATE1/2-K (see Section 5.3.5).

The data from a completed DDI study (ONT-380-012) indicate that co-administration of multiple doses of tucatinib (300 mg BID) with midazolam (a sensitive CYP3A substrate) increased the geometric mean midazolam exposure (AUC) approximately 5.85-fold (90% CI 5.14, 6.66) in healthy subjects, compared with administration of midazolam alone. The findings indicate a potential safety risk to humans exposed to tucatinib who are taking concomitant medications that are sensitive CYP3A substrates, as administration of tucatinib may potentially increase exposure to the concomitant medication. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided (see APPENDIX H). Consider using an alternate medication which is not a sensitive CYP3A substrate. If the use of sensitive CYP3A substrates is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Multiple clinical trials have been conducted, or are ongoing with tucatinib in subjects with HER2+ metastatic breast cancer. Tucatinib has been studied as a single agent in Study ARRAY-380-101, a Phase 1, open-label, dose-escalation and expansion study of tucatinib given as a daily oral (PO) regimen to patients with advanced solid tumors. Two Phase 1b studies were completed to investigate tucatinib as a potential new treatment for patients with advanced HER2+ breast cancer, with a focus on combination with other cancer therapeutics,

including combination with ado-trastuzumab emtansine (T-DM1, Study ONT-380-004), and capecitabine, trastuzumab or capecitabine and trastuzumab (Study ONT-380-005). In addition, Study ONT-380-206 is an ongoing, Phase 2, randomized, double-blinded, placebo-controlled clinical trial that compares tucatinib versus placebo in combination with capecitabine and trastuzumab in patients with progressive, unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1. This trial recently reported topline results which showed a 46% reduction in the risk of disease progression or death (hazard ratio [HR]=0.54; p<0.00001), an improvement in overall survival with a 34% reduction in the risk of death (HR=0.66; p=0.0048) and a 52 percent reduction in the risk of disease progression or death in patients with brain metastases at baseline (HR=0.48; p<0.00001). Finally, a randomized, double-blind, Phase 3 study of tucatinib versus placebo in combination with T-DM1 for patients with unresectable locally advanced or metastatic HER2+ breast cancer has recently been initiated (SGNTUC-016).

1.3.3 Summary of tucatinib

Overall, tucatinib has been well-tolerated and has demonstrated single-agent antitumor activity, including partial response (PR) in subjects who had progressed after 2 prior HER2-directed therapies. Notably, toxicities associated with dual EGFR/HER2 inhibitors have been uncommon, with Grade 3 diarrhea and rash reported in only 1 subject each in the single-agent study (ARRAY-101). The data from 2 phase 1b clinical trials demonstrated that the doublet combination of tucatinib with T-DM1 (ONT-380-004) and the triplet combination with capecitabine and trastuzumab (ONT-380-005) was well-tolerated, demonstrating preliminary activity with acceptable toxicity, in subjects with HER2+ metastatic breast cancer, including subjects with brain metastases. Based upon the preclinical and clinical profile observed to date, tucatinib may be able to address some of the unmet needs in the treatment of HER2+ cancers, particularly with regard to combination approaches with other HER2 agents.

1.4 Trastuzumab

Trastuzumab is a humanized anti-HER2 antibody that binds to subdomain intravenous (IV) of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2-cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand independent, HER2-mediated mitogenic signaling (Arteaga 2012).

HER2 is a validated target in multiple solid tumors, with anti-HER2 biologics (including trastuzumab) and small-molecule drugs approved for patients with HER2+ breast and gastric cancers. In these tumor types, amplification of the HER2-gene or overexpression of its protein is common.

Trastuzumab is not approved for use in CRC. Clinical trial data in HER2+ mCRC patients (see Section 1.6) do support a category 2B recommendation for the treatment of patients with HER2-amplified, RAS wild-type mCRC with either pertuzumab + trastuzumab or lapatinib + trastuzumab in the 2L or 3L setting within the widely adopted national (US) guidelines for the treatment of colon cancer.

1.5 Nonclinical Rationale for combination of tucatinib with trastuzumab

Data from xenograft models across multiple tumor types, including CRC, provide strong preclinical evidence supporting the increased activity of tucatinib + trastuzumab relative to the individual agents. Overall, these models demonstrated tumor regression rates in the tucatinib and trastuzumab monotherapy arms of 27% and 17%, respectively, compared to 67% when administered in combination (see Investigator's Brochure). Similar trends have been observed in preclinical models of other agents (pertuzumab, lapatinib, trastuzumab, and neratinib) comparing monotherapy with dual HER2-inhibition (Haque 2012; American Cancer Society (ACS) 2018).

1.6 Clinical Rationale for combination of tucatinib with trastuzumab

Single-agent clinical activity of trastuzumab in HER2+ mCRC has not been established, as dual inhibition approaches have been chosen in clinical trials to date based upon existing clinical data favoring combination approaches. However, historical data for both anti-HER2 monotherapy and dual trastuzumab-containing therapy is available in the setting of HER2+ breast cancer, where greater activity has been seen in the setting of dual inhibition.

HER2+ Metastatic Breast Cancer setting

Historical data for trastuzumab monotherapy in breast cancer demonstrate modest radiographic response rates of 14% (Cobleigh 1999; Burstein 2008; Cortes 2012; Martin 2013a).

However, when anti-HER2 agents such as lapatinib or pertuzumab are added to trastuzumab-based regimens in HER2+ breast cancer, response rates not only increase (24%–31%), but significant gains in PFS and OS are also achieved (Baselga 2012; Johnston 2018).

HER2+ mCRC setting

As discussed above (see Section 1.2), dual HER2-inhibition with trastuzumab-containing regimens have been examined in the setting of HER2+ mCRC, and the response rates seen in the HERACLES and MyPathway trials (Table 1-1) have led to a change in the widely adopted national (US) guidelines for the treatment of colon cancer, which now recommend (Category 2B) dual HER2-inhibition for treatment of HER2-amplified, RAS wild-type, mCRC patients. While there are no monotherapy arms included in the HERACLES and

MyPathway trials (Table 1-1), it is worth noting that response rates are higher than what has historically been observed with anti-HER2 agents used as monotherapy in metastatic breast cancer, and compare favorably with response rates seen with dual inhibition in that setting.

Interim data from the initial 26 subjects enrolled in the current MOUNTAINEER protocol (tucatinib + trastuzumab) was recently presented at the European Society for Medical Oncology 2019 Congress. The investigators reported an objective response rate (ORR) of 52.2% (12 of 23 subjects; 95% CI: 30.6, 73.2) that consisted of 12 PRs in 23 evaluable subjects, 11 of which were confirmed at a second assessment timepoint (Strickler 2019). Additionally, the median duration of response was 10.4 months (6.0-NE), with a median PFS of 8.1 months (3.8-NE) and a median OS of 18.7 months (12.3-NE).

1.7 Study Rationale

Patients with HER2+ mCRC have limited access to anti-HER2 therapies. Tucatinib is a potent HER2-specific TKI that is active in metastatic breast cancer as a single-agent and in combination with trastuzumab (Borges 2013; Hamilton 2014). Additionally, trastuzumab is approved as a single-agent and in combination with either chemotherapy or pertuzumab.

The activity of tucatinib monotherapy in HER2+ metastatic breast cancer patients that had failed prior HER2 directed therapies has been examined, with an ORR of 14% observed. Tucatinib has also shown single-agent activity in HER2+ CRC preclinical tumor models. However, the activity of tucatinib monotherapy in patients with mCRC is currently unknown. Therefore, a tucatinib monotherapy cohort has been included in order to explore this activity.

In patient-derived xenografts of *ERBB2* amplified metastatic CRC, increased antitumor activity with dual HER2 blockade versus single-agent activity has been described (Bertotti 2011). Furthermore, non-randomized studies conducted in patients with HER2+ metastatic CRC have confirmed the efficacy and tolerability of dual HER2- blockade (Douillard 2013a; Sartore-Bianchi 2016). This trial is designed to establish the efficacy of tucatinib in combination with trastuzumab in patients with HER2+ mCRC.

1.8 Rationale for Selection of Doses

Selection of the tucatinib dosing regimen for the current study was based upon the following:

- PK studies (ARRAY-380-102 and ARRAY-380-103)
- Results of the Phase 1 dose-escalation study of single-agent tucatinib in subjects with advanced solid tumors (ARRAY-380-101)
- Results of a Phase Ib study of tucatinib combined with T-DM1 (ONT-380-004)

- Results of a Phase Ib study of tucatinib combined with either capecitabine and/or trastuzumab (ONT-380-005); this study declared a RP2D of 300 mg BID in the tablet formulation, equivalent to the single-agent dose of tucatinib

Trastuzumab will be given at the dose approved for single-agent use when administered on a Q3 week cycle. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV or Q2 week basis at 4 mg/kg IV, but only in circumstances where the trastuzumab infusion schedule has been interrupted or suspended, and these infusions are required to resynchronize the cycle length to 21 days.

2 OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of tucatinib given in combination with trastuzumab in patients with human epidermal growth factor receptor 2 positive (HER2+), RAS wild-type, unresectable or metastatic CRC who have previously received and failed, unless contraindicated, systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb); patients whose disease has deficient mismatch repair (dMMR) proteins or is Microsatellite instability-High (MSI-H) must also have received an anti-programmed death ligand 1 (PD-[L]1) mAb, if indicated. Specific objectives and corresponding endpoints for the study are summarized in Table 2-1.

Table 2-1: Objectives and corresponding endpoints

Objective	Corresponding Endpoint[a]
Primary	
• To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by confirmed objective response rate (cORR, per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria), according to blinded independent central review (BICR) assessment	• cORR (confirmed complete response [CR] or partial response [PR]), per RECIST 1.1, according to BICR assessment, in pooled Cohorts A+B
Secondary Efficacy	
• To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohorts A+B
• To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohort C
• To assess the duration of response (DOR) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohorts A+B
• To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohort C
• To assess the progression-free survival (PFS) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment	• PFS (RECIST 1.1), according to BICR assessment, in Cohorts A+B
• To assess the overall survival (OS) in subjects treated with tucatinib given in combination with trastuzumab, in Cohorts A+B	• OS, in Cohorts A+B

Objective	Corresponding Endpoint[a]
Secondary Safety	
• To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B	• Frequency and severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria, of all treatment-emergent adverse events (TEAEs) and treatment-related TEAEs, in Cohorts A+B • Frequency of serious adverse events (SAEs) and deaths due to adverse events (AEs), in Cohorts A+B • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B • Frequency and severity of laboratory abnormalities, in Cohorts A+B • Vital signs and other relevant safety variables, in Cohorts A+B
• To assess the safety and tolerability of tucatinib monotherapy, in Cohort C	• Frequency and severity, according to CTCAE v4.03, of all TEAEs and treatment-related TEAEs, in Cohort C • Frequency of SAEs and deaths due to AEs, in Cohort C • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohort C • Frequency and severity of laboratory abnormalities, Cohort C • Vital signs and other relevant safety variables, in Cohort C
Exploratory	
[redacted]	[redacted]

Objective	Corresponding Endpoint[a]
[redacted]	[redacted]

a For the definitions of study endpoints refer to Section 9.2.

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is a Phase 2, randomized, open-label, multicenter study of tucatinib administered as monotherapy and in combination with trastuzumab in patients with HER2-positive, RAS wild-type, unresectable or metastatic CRC. Eligible patients are required to have previously received and failed, unless contraindicated, systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients whose disease has dMMR proteins or is MSI-H must also have received an anti-PD-(L)1 mAb, if indicated. The study initially consisted of Cohort A, which includes approximately 40 subjects treated with the doublet regimen. As of Protocol Amendment 8, the study is expanded to include approximately 40 additional subjects (Cohort B) treated with the tucatinib + trastuzumab doublet (for a total of 80 subjects in Cohorts A+B), and 30 subjects treated with tucatinib monotherapy (Cohort C).

All subjects enrolled in the expansion portion of the trial will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment will continue until 30 subjects have been randomized to Cohort C, and approximately 40 subjects have been randomized to Cohort B.

Treatment will be administered in cycles of 21 days each. Subjects in Cohorts A and B will be treated with tucatinib at a dose of 300 mg PO BID and trastuzumab at a loading dose of 8 mg/kg IV followed by a dose of 6 mg/kg IV every 3 weeks. Subjects randomized to Cohort C will be treated with tucatinib at a dose of 300 mg PO BID.

Subjects enrolled in Cohort A and those randomized to Cohort B will continue on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure. Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy, if they experience radiographic progression at any time point, or if they have not achieved a PR or CR by the Week 12 assessment (for details see Section 6.3.6).

Dose modifications of tucatinib will be allowed. Dose modifications of trastuzumab will not be allowed; if trastuzumab cannot be restarted after being held for an AE, it must be discontinued. If trastuzumab is discontinued, the subject can continue to receive tucatinib monotherapy. Notify the sponsor of any changes made to the subject's study treatment.

The primary endpoint of the study is a point estimate of confirmed ORR. Radiographic response will be assessed by a BICR (per RECIST 1.1), with confirmation of response required ≥4 weeks from the first documentation of response. The primary efficacy analysis set will be comprised of subjects previously enrolled in Cohort A pooled with subjects randomized to Cohort B (Cohorts A+B).

Secondary efficacy endpoints include duration of confirmed response, PFS, and OS for all subjects enrolled on the doublet regimen (Cohort A+B). In addition, in order to assess the contribution of tucatinib to the doublet regimen, ORR by 12 weeks will be assessed in Cohorts A+B, as well as in Cohort C [redacted]

[redacted]

[redacted]

A study schema is provided in Figure 3-1. See APPENDIX A for a schedule of events.

3.1.1 Data & Safety Monitoring

Assessment of safety will be performed by collecting and evaluating information regarding AEs and laboratory test results. A Safety Monitoring Committee (SMC) will evaluate the safety of combination therapy and monotherapy over the course of the study. Periodic cumulative data review meetings will be held every 6 months. The meetings will serve to evaluate aggregate safety data of all subjects (Cohorts A+B+C) and provide a forum for decisions regarding whether to continue with the study as-is, to continue the study with modifications, to suspend enrollment, or to terminate the study.

3.1.2 Stopping Criteria

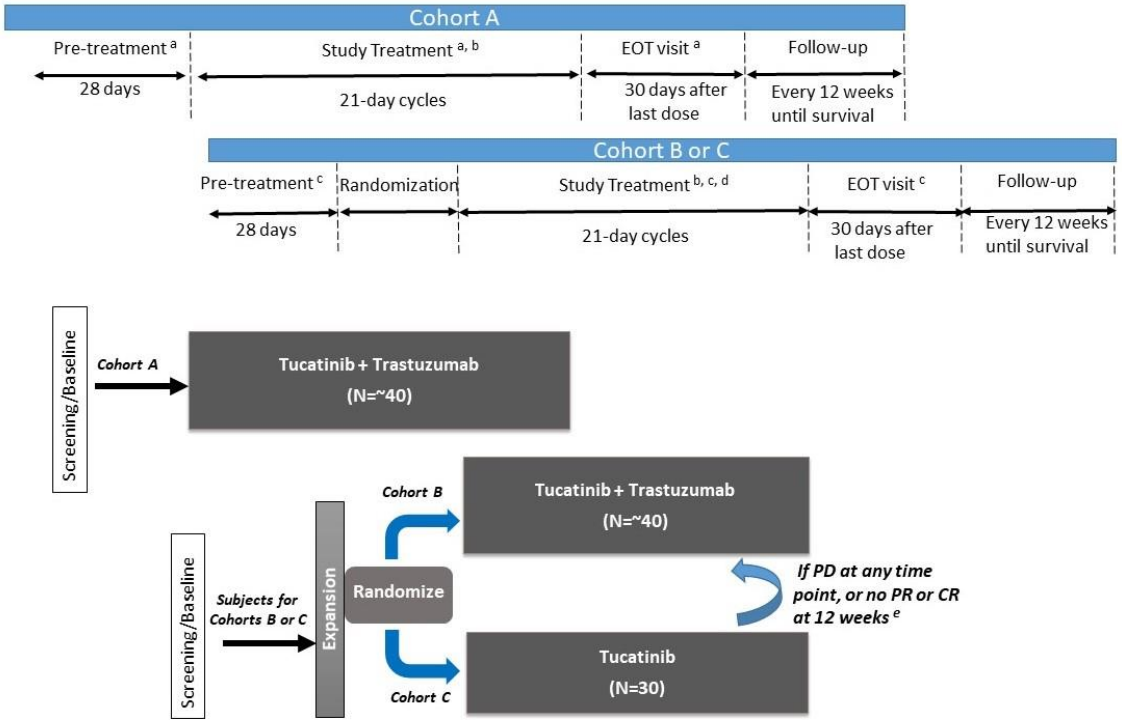
Reasons for prematurely terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects, either through a safety review by the sponsor or an SMC.
- Subject enrollment is unsatisfactory.

3.1.3 End of Study

The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.4.1).

Figure 3-1: Study schematic



Note: Subjects enrolled in Cohort A or Cohort B will be treated with tucatinib and trastuzumab doublet combination therapy, and subjects enrolled in Cohort C will be treated with tucatinib monotherapy.
CR = complete response, EOT = end of treatment, PD = progressive disease, PR = partial response

a For Cohort A, radiological disease assessments (computerized tomography [CT] or magnetic resonance imaging [MRI] scans of chest, abdomen, and pelvis) and carcinoembryonic antigen (CEA) tumor marker assays will be performed at the screening/baseline, every 9 weeks/3 cycles (±14 days) during study treatment (every 12 weeks/ 4 cycles [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

b For Cohorts A and B, treatment will be administered in 21-day cycles. Tucatinib will be administered at 300 mg BID plus trastuzumab IV infusion at a loading dose of 8 mg/kg followed by a maintenance dose of 6 mg/kg every 21 days.

c For Cohorts B and C, radiological disease assessment (CT or MRI of chest, abdomen, and pelvis) and CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

d For Cohort C, treatment will be administered in 21-day cycles. Tucatinib will be administered at 300 mg BID.

e Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy if they experience radiographic progression at any time point, or if they have not achieved a PR or CR by the Week 12 assessment. In order to assess radiographic response to the doublet therapy, subjects in Cohort C must have a new baseline RECIST assessment, as described in Section 6.3.6, prior to crossover from monotherapy to doublet therapy using the Week 12 scans or first PD scans as applicable.

More details on the schedule of events are reported in Table 11-1.

3.2 Discussion and Rationale for Study Design

3.2.1 Rationale for Selection of Doses and Regimen

Response rates to dual HER2-blockade among previously-treated subjects with HER2+, refractory, mCRC of 30% and 35% have been reported, while anti-EGFR monotherapy results in a response rate of 20% among these subjects (Olayioye 2000; Holbro 2004; Hurwitz 2016). The addition of tucatinib to trastuzumab in Cohorts A and B will provide dual-inhibition of HER2 with the potential to improve efficacy and provide benefit over single-agent blockade for subjects previously treated in 3L+ regimens for mCRC.

Selection of the tucatinib dosing regimen for the current study was based upon the RP2D derived from two Phase 1b studies in HER2+ metastatic breast cancer that evaluated tucatinib in combination with T-DM1 (ONT-380-004), or capecitabine and trastuzumab (ONT-380-005). In those studies, tucatinib 300 mg was generally well-tolerated, and AEs were manageable by protocol-specified dose modifications and dose reductions. In addition, the efficacy and safety of tucatinib is currently being explored in a pivotal study in HER2+ metastatic breast cancer (ONT-380-206), at 300 mg BID in combination with capecitabine and trastuzumab and an additional pivotal study in 2L metastatic breast cancer (SGNTUC-016) at 300 mg BID in combination with T-DM1.

Interim data from the initial 26 subjects enrolled in the current MOUNTAINEER protocol (tucatinib + trastuzumab) was recently presented at the European Society for Medical Oncology 2019 Congress. An ORR of 52.2% (12 of 23 subjects; 95% CI: 30.6, 73.2) was observed in the evaluable population. Combination treatment with tucatinib + trastuzumab appears to be efficacious and well-tolerated in the subjects enrolled to date. There is an unmet medical need in HER2+ mCRC patients who have failed prior therapy. The AE profile of tucatinib given in combination with trastuzumab in this setting is expected to be adequately managed by protocol-specified dose modifications and dose reductions.

The dose of trastuzumab administered on a q 21-day cycle is the full dose approved for single-agent use in breast cancer.

4 STUDY POPULATION

Patients with HER2-positive, RAS wild-type, unresectable or metastatic CRC who, unless contraindicated, have previously received systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients whose disease has dMMR proteins or is MSI-H must also have received an anti-PD-(L)1 mAb, if indicated.

Patients must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

Subjects must meet the following criteria to be eligible for the study:

1. Have histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is metastatic and/or unresectable.
2. Unless otherwise contraindicated, subjects must have received and failed regimens containing the following agents: fluoropyrimidine (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF mAb (bevacizumab, ramucirumab, or ziv-aflibercept), and an anti-PD-(L)1 therapy (nivolumab or pembrolizumab) if the tumor has dMMR proteins or is MSI-H.
3. Have progression of unresectable or metastatic CRC after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Have RAS wild-type in primary or metastatic tumor tissue, based on expanded RAS testing including KRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and NRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)
5. Subjects must be willing and able to provide the most recently available tissue blocks (or slides, with Medical Monitor's approval), obtained prior to treatment initiation, to a sponsor-designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion is required.
6. Have confirmed HER2-positive mCRC, as defined by having tumor tissue tested at a Clinical Laboratory Improvement Amendments (CLIA)-certified or International Organization for Standardization (ISO)-accredited laboratory, meeting at least one of the following criteria:
    a. HER2+ overexpression (3+ immunohistochemistry [IHC]) by an FDA-approved or Conformité Européenne (CE)-marked HER2 IHC test following the package insert's interpretational manual for breast cancer
    b. HER2 2+ IHC is eligible if the tumor is amplified by an FDA-approved or CE-marked HER2 in situ hybridization assay (FISH or chromogenic in situ

hybridization [CISH]) following the package insert's interpretational manual for breast cancer

c. HER2 (*ERBB2*) amplification by CLIA-certified or ISO-accredited Next Generation Sequencing (NGS) sequencing assay.

7. Age ≥18 years at time of consent
8. Have radiographically measurable disease assessable by RECIST 1.1, with at least one site of disease that is measurable and that has not been previously irradiated; or, if the subject has had previous radiation to the target lesion(s), there must be evidence of progression since the radiation
9. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0, 1, or 2.
10. Life expectancy greater than 3 months in the opinion of the investigator
11. Have adequate hematological, hepatic, renal, coagulation, and cardiac function (APPENDIX D) as defined below, obtained ≤7 days prior to the first study treatment:

    a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$

    b. Platelet count $\geq 75 \times 10^3/\mu L$

    c. Hemoglobin ≥8.0 g/dL

    d. Total bilirubin ≤1.5 × upper limit of normal (ULN). Subjects with known history of Gilbert's Syndrome and normal direct bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are eligible

    e. AST and ALT ≤2.5 × ULN (≤5 × ULN if liver metastases are present)

    f. Calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault formula

    g. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless on medication known to alter INR and/or aPTT

    h. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan documented ≤28 days prior to study treatment

12. For subjects of childbearing potential, as defined in Section 4.3, the following stipulations apply:
    a. Must have a negative serum pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to the first dose of study treatment. A subject with a false positive result and documented verification that the subject is not pregnant is eligible for participation.
    b. Must agree not to try to become pregnant during the study and for at least 7 months after the final dose of study drug administration

c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study drug administration
d. May choose to practice complete abstinence, if consistent with the subject's preferred lifestyle, as an acceptable form of contraception
e. If sexually active in a way that could lead to pregnancy, must consistently use highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration. For the full list of highly effective methods of birth control and guidance on contraception refer to APPENDIX C.

13. For subjects who can father children, the following stipulations apply:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final study drug administration
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use a barrier method of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration
14. Subject must provide signed informed consent document that has been approved by an institutional review board/independent ethics committee (IRB/IEC) prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease
15. Subject must be willing and able to comply with study procedures

4.2 Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

1. Have previously been treated with anti-HER2 targeting therapy
2. Have received treatment with any systemic anticancer therapy (including hormonal and biologic therapy), non-central nervous system (CNS) radiation, or experimental agent ≤3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial
3. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Alopecia and neuropathy, which must have resolved to ≤ Grade 2

- Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
- Anemia, which must have resolved to ≤ Grade 2
- Decreased ANC, which must have resolved to ≤ Grade 2

4. Have clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension, as determined by the investigator
    - Any history of symptomatic CHF, left ventricular systolic dysfunction or decrease in ejection fraction
    - Severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy
    - Presence of ≥ Grade 2 QTc prolongation on screening ECG
5. Have known myocardial infarction, unstable angina, cardiac or other vascular stenting, angioplasty, or cardiac surgery within 6 months prior to first dose of study treatment
6. Major surgical procedure, open biopsy, or significant traumatic injury ≤28 days prior to enrollment (≤56 days for hepatectomy, open thoracotomy, or major neurosurgery) or anticipation of need for major surgical procedure during the course of the study
7. Serious, non-healing wound, ulcer, or bone fracture
8. Known to be positive for hepatitis B by surface antigen expression
9. Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks
10. Known to be positive for human immunodeficiency virus (HIV)
11. Subjects who are pregnant, breastfeeding, or planning a pregnancy
12. Inability to swallow pills or any significant gastrointestinal disease which would preclude the adequate oral absorption of medications
13. Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP2C8 or CYP3A4 inducer within 5 days prior to first dose of study treatment (see APPENDIX E and APPENDIX F).
14. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
15. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

16. Subjects with known active CNS metastasis (irradiated or resected lesions are permitted, provided the lesions are fully treated and inactive, subject is asymptomatic, and no steroids have been administered for at least 30 days)
17. Have a hypersensitivity to tucatinib or any of its excipients, to trastuzumab or any of its excipients, or to murine proteins.

4.3 Childbearing Potential

A person of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male who has testes and who has not undergone surgical sterilization (e.g. vasectomy followed by a clinical test proving that the procedure was effective).

4.4 Removal of Subjects From Therapy or Assessment

Seattle Genetics 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 case report form (CRF).

4.4.1 Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- PD (per RECIST 1.1), as assessed by investigator
- Clinical disease progression
- AE
- Pregnancy or begins breastfeeding while on trial
- Investigator decision (other)
  Note: Ensure that subjects who are recommended to stop treatment **because of an AE or disease progression** are not included in this rationale.
- Subject decision, non-AE
  Note: Ensure that subjects who decide to stop treatment **because of an AE or disease progression** are not included in this rationale.
- Study termination by sponsor
- Other, non-AE

NOTE: Subjects with signs of clinical benefit (e.g., mixed response, symptom improvement, demonstrable slowing of progression, progression rate of <20% over 6 months) who are tolerating treatment may be allowed to continue treatment past formal radiologic progression (i.e., RECIST 1.1) if such treatment is considered in the subject's best interest by the subject, the treating physician, and the Medical Monitor. In this scenario, subjects may continue until clinical progression.

Subjects who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

4.4.2 Subject Withdrawal From Study

Any subject may be withdrawn from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

Subjects in the study will receive doublet combination therapy of tucatinib with trastuzumab (Cohorts A and B) or tucatinib monotherapy (Cohort C). For Cohorts A and B, tucatinib will be given on a 21-day cycle, with trastuzumab on day 1 of each cycle. For Cohort C, tucatinib will be given on a 21-day cycle. Subjects in Cohort C are allowed to crossover to start doublet combination therapy with Medical Monitor's approval, if, by investigator assessment (per RECIST 1.1), they experience radiographic progression at any time point, or if they have not achieved PR or CR by the 12-week assessment, at which point the monotherapy-cycle will be abrupted and the combination therapy-cycle will start (for details see Section 6.3.6).

Table 5-1: Treatment schedule

Agent	Dose Level	Route	Day(s)	Cycle(s)	Frequency	Drug Administration in Each Cohort (Y/N) Cohort A	Cohort B	Cohort C
Tucatinib	300 mg	PO	Days 1-21	All	Twice daily	Y	Y	Y
Trastuzumab[a]	8 mg/kg body weight	IV	Day 1	Cycle 1 (loading dose)	Once	Y	Y	N
Trastuzumab[ab]	6 mg/kg body weight	IV	Day 1	Cycle 2 and beyond	Once	Y	Y	N

a Use actual weight or estimated dry weight if fluid retention

b Trastuzumab may also be given on a weekly basis at 2 mg/kg IV or Q2 week basis at 4 mg/kg IV, but only in circumstances where the trastuzumab infusion schedule has been interrupted or suspended, and these infusions are required to resynchronize the cycle length to 21 days.

It is a requirement of the nurse to perform instruction on tucatinib administration techniques and drug diary prior to Cycle 1 Day 1 (C1D1) (APPENDIX G). The nurse will need to ensure that the subject understands these instructions before granting treatment independence. It is not a requirement that the first dose be given in clinic.

5.1.1 Investigational Study Drug (Tucatinib)

Tucatinib, the investigational agent under study in this protocol, is a kinase inhibitor that selectively inhibits HER2, and displays limited activity against the related kinase EGFR.

Tucatinib is supplied as yellow oval (150 mg) or round (50 mg) capsule-shaped tablets for oral administration.

Detailed information describing administration, handling and storage of the investigational study drug (tucatinib) is located in the Pharmacy Instructions.

5.1.1.1 Description

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The

tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

5.1.1.2 Method of Procurement

The investigational study drug (tucatinib) will be provided by the sponsor.

5.1.1.3 Dose and Administration

The investigational study drug (tucatinib) will be administered PO BID and may be taken with or without food. Dose modifications of tucatinib are described in Section 5.2. Subjects will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, subjects will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

Subjects will be instructed to take tucatinib tablets twice each day (once in the morning, and once in the evening) approximately 8 to 12 hours between doses in the same calendar day. It is recommended that if a subject misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose.

Complete dosing instructions will be provided to the pharmacist prior to the initiation of the study. Complete dosing instructions will also be provided to study subjects and will include the minimum times between doses, dosing in relation to meals, and instructions for missed doses. Subject compliance with investigational study drug dosing instructions will be assessed with the use of subject diaries and study drug accountability.

5.1.1.4 Storage and Handling

Tablets of tucatinib are packaged in round, high-density polyethylene bottles containing a desiccant, with an induction sealed liner and child-resistant plastic closure cap. Bottles of tucatinib tablets are to be stored under refrigeration at 2–8°C in a secure, access-limited location.

The tablets are coated with a non-hazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the Pharmacy Instructions for more information.

5.1.1.5 Packaging and Labeling

Each bottle of investigational study drug will be labeled in compliance with applicable regulatory requirements.

5.1.1.6 Study Drug Accountability

Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib tablets are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty bottles, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study according to the Study Operations Manual. All used and unused bottles of tucatinib should be handled according to the sponsor's instructions and disposed according to the Pharmacy Instructions.

5.1.2 Trastuzumab

5.1.2.1 Description

Trastuzumab is a humanized IgG-1 kappa monoclonal antibody which binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2); it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which over express HER2 protein.

5.1.2.2 Method of Procurement

The investigational study drug (trastuzumab) will be provided by the sponsor.

5.1.2.3 Dose, Preparation, and Administration

Trastuzumab will be given as a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q 7 days, but only in the circumstance that trastuzumab infusion has been delayed, and weekly infusions are required to resynchronize the cycle length to 21 days, after discussion with the Medical Monitor. Trastuzumab infusion rates will be per institutional guidelines. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose of 8 mg/kg should be given per approved dosing instructions.

Single-dose vial (150 mg/vial) as a lyophilized sterile powder for reconstitution is commercially available and should be prepared and administered per instructions in the trastuzumab (Herceptin®) package insert for administration instructions. Trastuzumab will be administered IV under the direction of the investigator.

Trastuzumab should be stored according to the package insert.

5.1.2.4 Risk Associated with Trastuzumab

Risks associated with trastuzumab include fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia,

myalgia, and CHF. Please see the trastuzumab (Herceptin®) package insert/national prescribing information for more details.

- Management of cardiac, gastrointestinal, and skin/subcutaneous tissue disorders may require temporary interruption or treatment discontinuation of trastuzumab as per guidelines provided in the package insert and of infusion-related reactions (IRR) in Table 5-3.

5.1.2.5 Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials containing trastuzumab. Follow the package insert for more information.

5.1.2.6 Packaging and Labeling

Each vial of trastuzumab will be labeled in compliance with applicable regulatory requirements.

5.1.2.7 Study Drug Accountability

Trastuzumab used during the course of the study should be handled according to its package insert. Trastuzumab vials are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty vials, should be tracked.

The sponsor or designee will conduct drug accountability monitoring during the course of the study. All used and unused vials of trastuzumab should be handled according to the sponsor's instructions.

5.2 Dose Modifications

5.2.1 Tucatinib Dose Reductions

Refer to Table 5-2 for the tucatinib dose reduction levels. Dose reductions larger than those required by these tables may be made at the discretion of the investigator. Up to 3 dose reductions of tucatinib are allowed, but dose reductions to below 150 mg BID are not allowed. Patients who, in the opinion of the investigator, would require a dose reduction to <150 mg BID, or who would require a potential fourth dose reduction of tucatinib, should discontinue study treatment.

The dose of tucatinib should not be re-escalated after a dose reduction is made. For further guidelines regarding dose modification of tucatinib due to AEs, please see Table 5-4.

Table 5-2: Tucatinib: Recommended dose reduction schedule for AEs

Dose Reduction Schedule	Tucatinib Dose Level
Starting dose	300 mg PO BID
1st dose reduction	250 mg PO BID
2nd dose reduction	200 mg PO BID
3rd dose reduction	150 mg PO BID
Requirement for further dose reduction	Discontinue treatment

Note: Tucatinib dose levels are based on AEs listed in Table 5-4. Dose reductions of greater increments than those listed in this table (i.e., more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator. However, tucatinib may not be dose reduced below 150 mg BID

5.2.2 Trastuzumab Dose Modifications

There are no dose reductions for trastuzumab. Guidelines regarding dose delays and discontinuation of trastuzumab due to AEs are given in Table 5-4 and Table 5-6.

Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q 7 days or biweekly at 4mg/kg IV, but only in the circumstance that trastuzumab infusion has been delayed, and these infusions are required to resynchronize the cycle length to 21 days, after discussion with the Medical Monitor. If trastuzumab cannot be restarted at the same dose after being held for an AE, it must be discontinued. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose of 8 mg/kg should be given per approved dosing instructions. As trastuzumab may be given as an IV infusion, infusion-related reactions (IRRs), may occur.

5.2.2.1 Infusion-related Reaction and its Management

An IRR is characterized by an adverse reaction to the infusion of pharmacological or biological substances. IRRs occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain and/or hypotension (Kang 2007).

IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRR.

IRR related to trastuzumab have been observed. Refer to Table 5-3 for IRR-specific dose modification of trastuzumab. If a significant IRR occurs, the infusion should be interrupted and appropriate medical therapies should be administered (see Table 5-3). Permanent discontinuation should be considered in subjects with severe IRR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction. The severity of IRRs should be graded according to NCI CTCAE v4.03 guidelines.

No standard premedication is required for future treatments if subjects have developed an infusion syndrome. Subjects may be given acetaminophen prior to treatments. Serious

reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids, and withdrawal of study agent as indicated.

Table 5-3 Dose modifications for infusion-related reactions for trastuzumab

Infusion-related reactions	Dose Modification
Grade 2	INTERRUPT trastuzumab infusion immediately. Subjects should be treated according to the following guidelines, or according to institutional guidelines, at discretion of the study physician: Stop infusion and notify physician. Assess vital signs. Administer acetaminophen 650 mg PO. Consider administration of meperidine 50 mg intramuscular (IM) or equivalent, diphenhydramine 50 mg IV, ranitidine 50 mg IV or cimetidine 300 mg IV, dexamethasone 10 mg IV or famotidine 20 mg IV. If vital signs stable, RESTART trastuzumab at the same dose. No standard premedication is required for future treatments if subjects have developed an infusion syndrome. Subjects may be given acetaminophen prior to treatments. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of study agent as indicated.
≥ Grade 3	INTERRUPT infusion immediately Administer appropriate medical therapies. DISCONTINUE treatment.

5.2.2.2 Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE v4.03). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of trastuzumab. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, i.e., a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain and/or hypotension.

5.2.2.3 Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death. (NCI CTCAE v4.03 and Rosello 2017).

If anaphylaxis occurs, administration of trastuzumab should be immediately and permanently discontinued.

5.2.3 Dose Modifications for Adverse Events

General dose modification guidelines for tucatinib and trastuzumab are provided in Table 5-4 for clinical AEs. Dose modifications for hepatotoxicity and left ventricular dysfunction are provided in Table 5-5 and Table 5-6, accordingly.

AEs ≥ Grade 3 not specifically mentioned in the following tables but that are assessed as being related to tucatinib or trastuzumab should be managed by HOLDING treatment until event resolution to ≤ Grade 1 or pre-treatment level. Treatment should be RE-STARTED at next lower dose level.

Table 5-4 Dose modifications for clinical AEs related to either tucatinib or trastuzumab

	Tucatinib	Trastuzumab
Clinical Adverse Event	Related to tucatinib	Related to trastuzumab
≥ Grade 3 AEs other than Grade 3 fatigue lasting ≤ 3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤ Grade 1 within 7 days	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITH optimal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 vomiting, or diarrhea regardless of use of anti-emetics or anti-diarrheals	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.	Do not administer until severity ≤ Grade 1. Restart without dose reduction.
Grade 3 rash WITHOUT maximal use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 rash WITH maximal use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reductions.

a No dose modifications are required for alopecia

5.2.3.1 Dose Modifications for Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities. For dose modifications of tucatinib for liver function abnormalities see Table 5-5. Dose modification of trastuzumab is not required but dosing can be held at investigator's discretion. For subjects with documented Gilbert's disease, please contact the Medical Monitor for guidance regarding dose modifications in these subjects.

Table 5-5 Dose modifications of tucatinib for liver function abnormalities

Liver Function Abnormalities	Action for tucatinib, Regardless of Relationship to Drug
Grade 3 elevation of ALT and/or AST (> 5 to 20 × ULN)	Hold until severity ≤ Grade 1 or until return to pretreatment level in subjects with known liver metastases Restart at next lowest dose level
Grade 4 elevation of ALT and/or AST (> 20 × ULN)	Discontinue drug
Elevation of ALT and/or AST (> 3 × ULN) AND Bilirubin (> 2 × ULN)	Discontinue drug
Grade 3 elevation of bilirubin (> 3 to ≤ 10 × ULN) and both ALT and AST <3.0 × ULN	Hold until severity ≤ Grade 1 or until return to pretreatment level in subjects with known liver metastases Restart at next lowest dose level
Grade 4 elevation of bilirubin (> 10 x ULN)	Discontinue drug

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

5.2.3.2 Dose Modifications for Left Ventricular Dysfunction

Trastuzumab dose modification guidelines for left ventricular dysfunction are provided in Table 5-6.

Table 5-6: Dose modifications guidelines for left ventricular dysfunction

Symptomatic CHF	LVEF < 40%	LVEF 40% to ≤45% and decrease is ≥10% points from baseline	LVEF 40% to ≤ 45% and decrease is < 10% points from baseline	LVEF > 45%
Discontinue trastuzumab.	Do not administer trastuzumab. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue trastuzumab.	Do not administer trastuzumab. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue trastuzumab.	Continue treatment with trastuzumab. Repeat LVEF assessment within 3 weeks.	Continue treatment with trastuzumab.

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

5.3 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (pre-dose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.3.1 Potential Concomitant Drug Interactions

5.3.1.1 Tucatinib

Tucatinib is cleared predominantly by CYP2C8 and to a lesser extent by CYP3A4. Strong CYP2C8 inhibitors and strong CYP2C8 or CYP3A4 inducers are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment.

Tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Concomitant use of tucatinib with digoxin, a P-gp substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

Treatment with tucatinib is associated with mild increases in serum creatinine which were reversible upon treatment discontinuation. A dedicated DDI study demonstrated no impact on renal function.

5.3.1.2 Trastuzumab

Please refer to the package insert for trastuzumab potential drug interactions.

Trastuzumab, a monoclonal antibody therapeutic, in PK studies, trastuzumab did not alter the plasma concentrations of other small molecule therapeutics such as paclitaxel, docetaxel or doxorubicin. It is therefore very unlikely that trastuzumab would have an effect on the pharmacokinetics of tucatinib. There was no DDI between tucatinib and trastuzumab observed in Study ONT-380-005, a combination study of tucatinib with capecitabine and trastuzumab.

5.3.2 Required Concomitant Therapy

There is no required concomitant therapy.

5.3.3 Allowed Concomitant Therapy

Subjects may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria. However, efforts should be made to maintain stable doses of concomitant medications during the course of study treatment.

- During study treatment, subjects may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management
- Supportive care medications such as anti-diarrheals, anti-emetics, antacids, and laxatives are permitted. Prophylactic use of anti-diarrheals are permitted at the discretion of the investigator
- Prophylactic and symptomatic treatment of nausea and vomiting may be used per standard-of-care
- Thoracentesis or paracentesis may be performed, if needed for comfort
- If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor), these interventions should be avoided if clinically feasible until after the second response assessment and the Medical Monitor should be consulted prior to the intervention occurring.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline (Smith 2006).
- Subjects should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as anti-diarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea free (maximum 16 mg/day).
- In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and anti-diarrheals.
- If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Subjects with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

5.3.4 Concomitant Therapies to be Used with Caution

Subjects on anti-coagulant treatment should be closely monitored during study treatment.

Sensitive substrates of CYP3A (APPENDIX H); tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Moderate CYP2C8 inhibitors should be used with caution.

Concomitant use of tucatinib with digoxin, a P-gp substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

5.3.5 Prohibited Concomitant Therapy

The following therapies are prohibited during the study (unless otherwise noted):

- Investigational drugs and devices
- Anti-cancer therapy, including but not limited to chemotherapy and hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal non-CNS sites which are not considered target lesions per RECIST 1.1, which may be given after consultation with the Medical Monitor. Radiation therapy directed at target lesions per RECIST 1.1 requires prior approval by the Medical Monitor. Tucatinib must be held 7 days prior to and 7 days post radiation therapy.
- Vaccination with live vaccines
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of study treatment (see APPENDIX E)
- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment (see APPENDIX F)
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (see APPENDIX H). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study.

5.4 Management of Overdose

In the event of an overdose of tucatinib, defined as any dose greater than the prescribed dose, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of tucatinib administered, subject weight) and AEs, if any.

Overdose events (with or without associated AEs) are to be captured on the AE electronic case report form (eCRF) and within the safety database. All overdose events should also be reported using the procedures detailed in the Reporting of Serious Adverse Events (Section 7.7.1.2).

Refer to the package insert for overdose information for trastuzumab.

5.5 Treatment Compliance

Study drug administration will be documented in source documents and the CRF.

Study-drug compliance will be assessed on a subject-by-subject basis using subject diaries. The pharmacist or designee will record the number of tucatinib tablets dispensed to each individual subject, and the number of tablets returned to the clinic at the end of each cycle.

Data regarding the administration and dose of trastuzumab 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 CRF.

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (pre-dose) through the safety reporting period (see Section 7.7.1.3). Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, liver function tests (LFTs), complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.7.3], urinalysis, physical exam, weight, and performance status) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Tumor biopsies performed during the study should be made available to the sponsor if feasible (see Section 7.1).

A schedule of events is provided in APPENDIX A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2 Screening Period

6.2.1 Screening Visit (Days [-28] to [-1])

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Documented disease history (See Section 7.1)
- Radiological Disease Assessment (CT/MRI)
- Blood Tumor Marker (carcinoembryonic antigen [CEA])
- Hepatitis B and C screening (anti-HCV will only be collected for Cohorts B and C)
- Concomitant medications
- AEs
- ECHO/MUGA
- Formalin fixed paraffin-embedded (FFPE) Tumor Specimen collection*

  *Confirm availability of archival tissue for submission to central laboratory (see Section 7.1). If archival tissue blocks which meet requirements are not available, a fresh tumor biopsy must be obtained and submitted for HER2 testing (see Section 7.1).

[redacted]

6.2.2 Baseline Visit (Days [-7] to [-1])

- Physical examination, including height
- Vital signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)

- ECOG PS (APPENDIX B)
- Urinalysis
- Blood samples for laboratory testing (as listed in Section 7.7.3)
  - Blood chemistries and LFTs
  - CBC with differential and platelets
  - Coagulation panel (including INR, prothrombin time (PT), and aPTT)
- For persons of childbearing potential, serum β-hCG pregnancy test within 7 days of first study treatment
- 12-lead ECG
- Concomitant medications
- AEs
- Submit Eligibility Worksheet to sponsor for approval to enroll
- With sponsor's approval, access randomization system for treatment assignment (Cohorts B and C only)

6.3 Treatment Period (21-day cycles)

6.3.1 Cycle 1 Pre-dose Day 1

- Physical Examination (pre-dose, may not be performed if done within 1 day prior to C1D1)
- Vital signs: weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation (pre-dose, may not be performed if done within 1 day prior to C1D1)
- Drug Diary Review
- [redacted]
- [redacted]
- ECOG PS (pre-dose, may not be performed if done within 1 day prior to C1D1)
- Concomitant medications
- AEs
- [redacted]
- Blood chemistries and LFTs (pre-dose, may not be performed if done within 7 days prior to C1D1)
- CBC with differential and platelets (pre-dose, may not be performed if done within 7 days prior to C1D1)
- Serum pregnancy test (pre-dose, may not be performed if done within 7 days prior to C1D1)
- Trastuzumab administration (for Cohorts A, B, and subjects from Cohort C who crossover to dual combination therapy)*
- Tucatinib administration and dispensation (all cohorts)*

* Study drugs may be administered in any order and can be given simultaneously

6.3.2 Cycle 1 Days 8 & 15 (±3 days)

- Blood chemistry and LFTs
- CBC with differential and platelets
- [redacted]
- [redacted]
- Concomitant medications
- AEs

6.3.3 Cycle 2 (and All Subsequent Cycles) Day 1 (±3 days)

- Physical Examination
- Vital Signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)
- Drug Diary Review
- ECOG PS
- Concomitant medications
- AEs
- Blood chemistries and CBC with differential and platelets
- Serum β-HCG pregnancy test for females of childbearing potential
- PK samples for Cohorts B and C only (pre-dose Cycles 2, 3, 4, 5, & 6 and post-dose Cycle3) (Table 11-3)
- Only on Cycles 2, 3, and 4; and every 3 cycles thereafter
  - [redacted]
  - [redacted]
- [redacted]
- Trastuzumab administration (Cohorts A, B, and subjects from Cohort C who crossover to dual combination therapy)*
- Tucatinib administration and dispensation (all cohorts) *

*Study drugs may be administered in any order and can be given simultaneously.

6.3.4 Cycle 2 (and All Subsequent Cycles) Every 6 or 9 weeks (±7 days)

- Radiological Disease assessment:
  - Cohort A: every 9 weeks (±14 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.

- Cohorts B and C: every 6 weeks (±7 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.
- Subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

- Blood Tumor Marker (CEA)

6.3.5 Every 12 weeks (±14 days)

- ECHO/MUGA

6.3.6 Subjects Crossing-Over to Doublet Regimen

Subjects randomized to tucatinib monotherapy (Cohort C) will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy, if they experience radiographic progression at any time point (as determined by investigator assessment using RECIST 1.1), or if they have not achieved a PR or CR by the Week 12 assessment.

- Submit Request for Approval to Change Treatment Regimen form to sponsor
- With sponsor's approval, access randomization system to register the change in treatment assignment

Immediately proceed with new study treatment regimen and continue to follow study procedures outlined in Section 6.3.3.

Investigators must do a new baseline RECIST assessment on Cohort C subjects who crossover from monotherapy to doublet therapy. Investigators must use the RECIST scans that were used to qualify the subject for crossing over (Week 12 scans or first PD scans as applicable) to establish a new baseline. Investigators must select target and non-target lesions per RECIST v1.1 guidance. Selection of target and non-target lesions will be based solely upon the crossover scans, and, therefore, may include new lesions that appeared while the subject was on monotherapy. Establishing a new baseline at the time of crossover will allow these subjects to achieve an objective response (CR/PR) per RECIST while on doublet therapy, which is relative to the new baseline. Subjects that have radiographic progressive disease while on doublet therapy per the new baseline should discontinue therapy unless the investigator believes the subject has signs of clinical benefit, as described in Section 7.7.7.1.

6.4 End of Treatment Visit (30 to 37 days After Last Dose of Study Drug)

EOT visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy.

If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Physical Examination
- Vital Signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)
- ECOG PS
- CBC with differential and platelets
- Serum blood chemistries
- Coagulation tests
- ECHO/MUGA (may not be performed if done on-treatment 12 weeks previously)
- Radiological Disease Assessments
- CEA
- [redacted]
- [redacted])
- Concomitant medications
- AEs
- [redacted]
  - [redacted]
  - [redacted]

6.5 Follow-up (Every 12 weeks ±14 days)

- Further anti-cancer therapy and survival

6.6 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.

The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.4.1).

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only subjects who meet all inclusion and exclusion criteria specified in Section 4.1 and Section 4.2 will be enrolled in this study.

Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing (by an FDA-approved or CE-marked HER2 IHC test following the package insert's interpretational manual for breast cancer). Confirmatory HER2 testing may be performed on archival tissue or a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated.

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

A physical exam, height, vital signs, CT with contrast/MRI scan for baseline response efficacy assessment, biopsy collection, CBC with differential and platelets, urinalysis, ECHO/MUGA, Hepatitis B and C screening, biomarker serum chemistry panel, coagulation tests including, INR, PT, and aPTT, ECOG PS, ECG and serum pregnancy test (for females of childbearing potential) are required for all subjects at screening and/or baseline as described in Section 6.2 and APPENDIX A.

Tissue Collection

The availability of archival tissue is to be confirmed at screening. If archival tissue blocks which meet requirements are not available, a fresh tumor biopsy must be obtained and submitted for HER2 testing. For fresh tissue, core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate.

7.2 Response/Efficacy Assessments

The determination of antitumor activity will be based on confirmed objective response assessments made by a BICR according to the RECIST 1.1 (Eisenhauer 2009). Treatment decisions will be based on objective response assessments made by the investigator. Clinical response of CR, PR, SD, or PD will be determined at each assessment. In addition, images will be collected by an independent review facility.

Measures of anticancer activity will be assessed by either CT with contrast or MRI scans at protocol-specified time points. **Subjects must be evaluated using the same imaging method throughout the study for efficacy assessments.**

For Cohort A, responses (CR or PR) will be confirmed at the next re-staging timepoint, 9 weeks (±14 days) after first documentation of response. For Cohorts B and C, responses (CR or PR) will be confirmed at the next re-staging timepoint, 6 weeks (±7 days) after first

documentation of response. Tumor imaging should also be performed whenever disease progression is suspected.

Subjects that discontinue for reasons other than documented PD will continue to have disease assessments (CT/MRI scans) approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy (see APPENDIX A). However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.2.1 Schedule of Events

For the purposes of this study, subjects should be re-evaluated as follows:

Cohort A: at screening/baseline, every 9 weeks (±14 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until PD, death, withdrawal of consent, study closure, or alternative therapy.

Cohorts B and C: at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments every 9 weeks until PD, death, withdrawal of consent, study closure, or alternative therapy.

Subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

7.2.2 Definitions of Measurable and Non-Measurable Disease

1. Measurable Disease

   - A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with computed tomography (CT) scan, CT component of a positron emission tomography (PET)/CT, or MRI.
   - A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended
   - A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm).
   - Tumor lesions in a previously irradiated area are not considered measurable disease.

2. Non-Measurable Disease

- All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.
- NOTE: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

7.2.3 Guidelines for Evaluation of Measurable Disease

1. Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For subjects having only lesions measuring ≥1 cm to <2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

2. Acceptable Modalities for Measurable Disease

- Conventional CT and MRI
- This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤5 mm. If CT scans have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT

- If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

3. Measurement at Follow-up Evaluation

   In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 9 weeks (see Section 7.2.4.3).

7.2.4 Measurement of Effect

Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 7.2.2) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (see Section 7.2.2), where ≤2 lesions are from the same organ and ≤2 malignant nodal lesions are selected. NOTE: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline sum of diameters (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of diameters (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Diameters (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the PBSD. If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is <0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

Non-Target Lesions & Non-Target Lymph Nodes
Non-measurable sites of disease (see Section 7.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accordance with Section 7.2.4.2.

7.2.4.1 Evaluation of Target Lesions

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 7.2.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

- CR: All of the following must be true:
  - Disappearance of all target lesions.
  - Each target lymph node must have reduction in short axis to <1.0 cm.
- PR: At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 7.2.4).
- PD: At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (see Section 7.2.4). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the MSD.

7.2.4.2 Evaluation of Non-Target Lesions & Non-Target Lymph Nodes

Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

- CR: All of the following must be true:

- Disappearance of all non-target lesions.
- Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- PD: At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

7.2.4.3 Overall Objective Status

The overall objective status for an evaluation is determined by combining the subject's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

Table 7-1: Evaluation of overall objective status

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated[a]	No	PR[b]
SD	CR Non-CR/Non-PD Not All Evaluated[a]	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[a]	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated[a]	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[a]	Yes	PD

a See Section 7.2.4.1

NOTE: This study uses the protocol RECIST 1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the protocol RECIST 1.1 template as of 2/16/2011 and to match RECIST 1.1 requirements.

[redacted]

[redacted]

7.5 Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of antibody-drug conjugate sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

[redacted]

7.7 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, vital signs, and pregnancy testing recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Safety of all cohorts will be monitored over the course of the study by an SMC. Periodic cumulative data (AEs and laboratory results) review meetings will be held every 6 months. The meetings will provide a forum for decisions regarding whether to continue with the study as-is, to continue the study with modifications, to suspend enrollment, or to terminate the study.

The site principal investigator is responsible for reporting any/all AEs to the sponsor as described within the protocol. Refer to Section 7.7.1 for detailed information.

7.7.1 Adverse Events

7.7.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing pre-dose on study Day 1 that increase in CTCAE grade should be recorded.

- Medical conditions present or ongoing pre-dose on study Day 1 that worsen in severity, increase in frequency, become related to study drug, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant/important:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.1.2 for the definition of potential DILI.)

Adverse Event Characteristics

Adverse event monitoring and reporting is a routine part of every clinical trial.

AE characteristics should be defined using the following criteria:

a. Identify the severity grade of the event (Section 7.7.1.1).

b. Determine if the AE is related to the study intervention (agent, treatment or procedure)

c. Determine if AE is serious or non-serious (Section 7.7.1.1).

d. Determine the appropriate timeframe and mechanism of reporting (Sections 7.7.1.3 and 7.7.1.4).

Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are defined by Seattle Genetics as a potential safety problem identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs MUST be undertaken at each treatment evaluation. Development of one of these AESIs (≥ Grade 1 unless otherwise noted) MUST be reported in terms of CTCAE v4.03 grade and attribution.

The AESIs will need to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours.

AESIs for this study are:

1. Potential drug-induced liver injury

Any potential case of drug-induced liver injury as assessed by laboratory criteria for Hy's Law will be considered as a protocol-defined event of special interest. The following laboratory abnormalities define potential Hy's Law cases:

AST or ALT elevations that are > 3 X ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 X the ULN, except in subjects with documented Gilbert's syndrome. Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology.

2. Asymptomatic left ventricular systolic dysfunction

In general, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and must be reported as an AE to the sponsor ≤1 business day of discovery of the event.

Adverse Event Severity

AE severity should be graded using the NCI CTCAE v4.03. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in Section 7.7.1.1.

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib and trastuzumab) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by

standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease”, or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. Symptomatic clinical deterioration due to disease progression as determined by the investigator will not be reported as an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 7 months after the last dose of study drug(s) including any pregnancies that occur in the partner of a study subject who is able to father a child. Only report pregnancies that occur in a subject’s partner if the estimated date of conception is after the subject’s first study drug dose. Email or fax to the sponsor’s Drug Safety Department within 48 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of data on the CRF

All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential drug-induced liver injury (DILI) in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a serious adverse event (SAE) and reported promptly to the sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening. Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

Dosing Errors

All tucatinib overdoses (any dose higher than the prescribed dose), medication errors, or cases of abuse or misuse should be immediately reported to sponsor Drug Safety, following the SAE reporting process (see Section 5.4).

Left Ventricular Ejection Fraction Decreased

For asymptomatic declines in LVEF leading to a change in study treatment or discontinuation of study treatment, the term "ejection fraction decreased" should be used, and severity Grades 2 to 4 used to report asymptomatic LVEF decrease.

For symptomatic CHF, the term "heart failure" should be used, and severity Grades 2 to 5 used to report symptomatic CHF.

7.7.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (pre-dose) through 30 days after the last study treatment (tucatinib or trastuzumab). However, all study protocol-related 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.

7.7.1.4 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's causality assessment

The completed SAE form is to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form).

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

7.7.2 Vital Signs

Vital sign measurements are to include weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation. Vital signs should be measured after the subject has been sitting/resting.

7.7.3 Clinical Laboratory Tests

The following laboratory assessments will be performed by the local laboratory to evaluate safety at scheduled timepoints (see APPENDIX A) and make clinical decisions during the course of the study:

- The serum chemistry panel is to include the following tests: albumin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, calculated creatinine clearance using Cockcroft-Gault (at baseline and as clinically indicated), glucose, potassium, sodium, total protein.
- Hepatitis B and C screening (anti-HCV will only be collected for Cohorts B and C only)
- LFTs include ALT/serum glutamic pyruvic transaminase (SGPT), AST/ serum glutamic oxoloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin (and direct bilirubin when total bilirubin is >ULN)
- The CBC with differential is to include the following tests: CBC with differential that includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with 5-part differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- The coagulation panel is to include the following tests: INR, PT, and PTT
- The urinalysis is to include the following tests: color, appearance, pH, protein, glucose, ketones, blood, specific gravity, bilirubin, leukocyte esterase, nitrites, urobilinogen
- A serum β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) for subjects of childbearing potential

7.7.4 Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. For adult subjects only, measurements of height obtained within the prior 12 months may be utilized.

7.7.5 Pregnancy Testing

For subjects of childbearing potential, a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline and within 7 days prior to Day 1 of each treatment cycle. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations.

7.7.6 Cardiac Function

7.7.6.1 MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

7.7.6.2 Electrocardiogram

ECGs will be performed at baseline. To correct for heart rate, QT intervals should be calculated using the Fridericia formula.

7.7.7 Treatment/Follow-up Decision at Evaluation of Subject

7.7.7.1 Treatment

Subjects will continue to receive study treatment per protocol until discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation from trial will be recorded.

NOTE: Subjects with signs of clinical benefit (e.g., mixed response, symptom improvement, demonstrable slowing of progression, progression rate of <20% over 6 months) who are tolerating treatment may be allowed to continue treatment past formal radiologic progression (i.e., RECIST 1.1) if such treatment is considered in the subject's best interest by the subject, the treating physician, and the Medical Monitor.

Reasons for subject discontinuation may include, but are not limited to, the following:

- Death
- PD/treatment failure without ongoing clinical benefit

- Significant noncompliance by subject or treating physician
- AEs that are considered intolerable and unmanageable (relation to all drugs should be noted)
- Investigator determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 7 months following discontinuation of study treatment
- Women who become pregnant or are breast feeding
- Treatment-related adverse events which do not resolve to Grade ≤2 within 6 weeks, in which case the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefiting
- Dosing delay greater than 6 weeks
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Withdrawal of consent
- Study termination by sponsor

7.7.7.2 Observation and Follow-up (Cohort A)

Observation

If subject discontinues treatment because of disease progression, they will have 1 Observation visit 30 (±7) days post last study intervention. After this time, subject will enter follow-up.

For subjects who go off study treatment with no documented disease progression and no subsequent anticancer treatment, the subject will be observed every 12 weeks (±14 days) or as clinically indicated until PD, at which time they will enter follow-up. Subjects remaining in observation for ≥5 years from first study treatment will go off study without entering follow-up.

Follow-up

Subjects in follow-up will have status evaluation every 12 weeks (±14 days) until PD, death, or it has been ≥5 years from first study treatment. Evaluation may be by telephone call,

email, or in-person assessment. Review of medical records may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful.

Follow-up is the time period when the subject is no longer following the protocol test schedule. During follow-up, the data collection schedule is dictated by the protocol, but the subject visit schedule is determined by clinical practice at each participating site.

During the follow-up phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death.

Subjects cannot be required to return to the consenting site for study-related reasons or be required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

Progression of Disease (PD)

Subjects in Cohort A who develop PD at any time will have one observation visit 30 (±7) days post last study intervention and then to follow-up. These subjects should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

7.7.7.3 Follow-up Disease Assessment

Subjects in all cohorts will undergo:

- Further anti-cancer therapy and survival

7.8 Appropriateness of Measurements

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

Response will be assessed according to RECIST 1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and subject inconvenience associated with CT and PET scanning.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and clinical laboratory data will be graded using standardized criteria for oncology (NCI CTCAE v4.03).

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, Seattle Genetics or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, randomization, study procedures, and withdrawal processes
- Current Investigator's Brochure/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Screening and enrollment
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seattle Genetics representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is

suitable for inspection by Seattle Genetics or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

Seattle Genetics will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant medications, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

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

8.5 Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seattle Genetics as part of the written record.

8.6 Data Handling and Record Keeping

Refer to the Case Report Form Completion Guidelines (CCG) for the methods of data collection.

8.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seattle Genetics, whichever is longer. The investigator must contact Seattle Genetics prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seattle Genetics.

8.7 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

For purposes of timing of the Results Reporting, the estimated completion date for the Primary Endpoint of this study is approximately 50 months after the study opens to enrollment.

The definition of "Primary Endpoint Completion Date" for this study is 8 months from the time the last subject is registered.

9 DATA ANALYSIS METHODS

An overview of study outcome measurements is provided in Table 9-1.

Table 9-1: Overview of study outcome measurements

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
Primary			
• To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by cORR (per RECIST 1.1), according to BICR assessment	• cORR (confirmed CR or PR), per RECIST 1.1, according to BICR assessment, in pooled Cohorts A+B	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
Secondary Efficacy			
• To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohorts A+B	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohort C	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the duration of response (DOR) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohorts A+B	• DOR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohort C	• DOR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• To assess the PFS in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment b	• PFS (RECIST 1.1), according to BICR assessment, in Cohorts A+B	• PFS, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the OS in subjects treated with tucatinib given in combination with trastuzumab, in Cohorts A+B	• OS, in Cohorts A+B	• OS	• Up to approximately 5 years
Secondary Safety			
• To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B	• Frequency and severity, according to CTCAE v4.03 criteria, of all TEAEs and treatment-related TEAEs, in Cohorts A+B • Frequency of SAEs and deaths due to AEs, in Cohorts A+B • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B • Frequency and severity of laboratory abnormalities, in Cohorts A+B • Vital signs and other relevant safety variables, in Cohorts A+B	• Incidence of AEs • Incidence of dose modification and treatment discontinuation • Incidence of laboratory abnormalities	• Through 1 month following last dose; up to approximately 9 months overall per subject

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• To assess the safety and tolerability of tucatinib monotherapy, in Cohort C	• Frequency and severity, according to CTCAE v4.03, of all TEAEs and treatment-related TEAEs, in Cohort C • Frequency of SAEs and deaths due to AEs, in Cohort C • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohort C • Frequency and severity of laboratory abnormalities, Cohort C • Vital signs and other relevant safety variables, in Cohort C	• Incidence of AEs • Incidence of dose modification and treatment discontinuation • Incidence of laboratory abnormalities	• Through 1 month following last dose; up to approximately 9 months overall per subject
Exploratory			
[redacted]			

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

9.1 Determination of Sample Size

Approximately 110 subjects will be enrolled in the study. Subjects are considered enrolled if they give informed consent and meet all eligibility criteria. Approximately 40 subjects will be enrolled in Cohort A. Approximately 70 subjects, enrolled in the expansion portion of the trial, and will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment will continue until 30 subjects have been randomized to Cohort C and approximately 40 subjects have been enrolled to Cohort B.

The expansion Cohort B is designed to increase the size of the study population exposed to the doublet regimen in order to allow more precise estimation of the confirmed ORR in subjects receiving tucatinib given in combination with trastuzumab, as well as to furnish supplementary safety data. The primary efficacy analysis will be performed by providing the point estimate and the 2-sided 95% exact Clopper Pearson CI for the confirmed ORR (pooled Cohorts A and B).

The addition of Cohort C is intended to better characterize the antitumor activity of tucatinib when used as a monotherapy in this patient population.

For illustration purposes, Table 9-2 summarizes the expected 95% CIs for subjects treated with tucatinib given in combination with trastuzumab (Cohort A+B) and subjects treated with tucatinib monotherapy (Cohort C) at the proposed sample sizes of 80 and 30 respectively. [redacted]

Table 9-2: Estimated ORR

Accrual Time and Study Duration

[redacted]. Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. Subjects will be followed for survival up to 5 years from first study treatment.

The final analysis can begin approximately [redacted] after the trial begins.

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

The primary endpoint in this study is the confirmed ORR per BICR. The ORR is defined as the proportion of subjects with confirmed CR or PR, per RECIST 1.1. Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders.

There have been minimal changes to eligibility criteria for Cohort A and Cohort B, and all patients will be centrally confirmed as being HER2+ with the same testing methodology (IHC/breast criteria), therefore the primary efficacy analysis set will be comprised of subjects previously enrolled in Cohort A pooled with subjects randomized to Cohort B (Cohorts A+B).

9.2.2 Objective Response Rate by Week 12

ORR by Week 12 per BICR is defined as the proportion of subjects with CR or PR by 12 weeks of treatment, and before time of crossover (Cohort C), whichever comes earlier, as determined by BICR assessment per RECIST 1.1. Responses do not need to be confirmed to be scored as responders for the purpose of determining ORR by Week 12. Subjects whose disease response cannot be assessed as CR, PR, or SD by Week 12 or later will be scored as non-responders for calculating the ORR by Week 12.

ORR by Week 12 will be summarized for subjects treated solely with tucatinib monotherapy (Cohort C) and subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B).

9.2.2.1 DOR

The DOR is defined as the time from first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD (per RECIST 1.1) or to death due to any cause, whichever comes first.

DOR will be calculated for the subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B) and subjects treated solely with tucatinib monotherapy (Cohort C).

9.2.2.2 PFS

PFS is defined as the time from start of study treatment (Cohort A) or randomization (Cohorts B and C) to first documentation of tumor progression (clinical progression or PD per RECIST 1.1), as determined by BICR assessment, or to death due to any cause, whichever comes first. PFS data will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, or are removed from study prior to documentation of tumor progression. Subjects lacking an evaluation of tumor response after their start of study treatment (Cohort A) or randomization (Cohorts B and C) will have their event time censored at 1 day.

9.2.2.3 OS

OS is defined as the time from start of study treatment (Cohort A) or randomization (Cohorts B and C) to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. Subjects lacking data beyond their start of study treatment (Cohort A) or randomization (Cohorts B and C) will have their survival time censored at 1 day.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. 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.

9.3.1 General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

Unless otherwise specified, CIs will be calculated at 2-sided 95% level.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Subjects from the initial and randomized to Cohort B during the expansion will be analyzed together (Cohorts A+B) and by cohort (Cohort A, Cohort B, and Cohort C).

9.3.1.1 Randomization and Blinding

All subjects enrolled in the expansion portion of the trial will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Randomization will be stratified by:

- Left sided primary versus all other primary types (i.e., right, transverse, overlapping primary)

Blinding will not be performed.

9.3.1.2 Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

9.3.1.3 Handling of Dropouts and Missing Data

With the exception of time-to-event endpoints, no imputation will be conducted for missing data unless otherwise specified.

9.3.1.4 Multicenter Studies

This study will be conducted at multiple study centers, however it is not anticipated that site-to-site variation will be adjusted in the analyses.

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only 1 primary endpoint will be tested in this single arm study.

9.3.1.6 Data Transformations and Derivations

Time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section. Unless otherwise specified, baseline values used in all analyses will be the most recent nonmissing measurement prior to the first dose of study drug.

9.3.1.7 Analysis Sets

The intent-to-treat (ITT) set will include all enrolled subjects in Cohort A and all randomized subjects in Cohorts B and C. A subject is considered enrolled if he/she has met all criteria for participation in the study.

The all treated subjects set will include all subjects who are enrolled and receive any amount of study treatment.

The safety analysis set will include all subjects who receive any amount of study treatment. The safety analysis set will be used for all safety analyses.

The PK analysis set will include all subjects in Cohorts B and C who received study treatment and from whom at least one PK assessment was reported. The PK analysis set will be used for PK analyses.

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

9.3.1.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

The final analysis of the primary endpoint and secondary endpoints will be conducted when all treated subjects have been followed for [redacted] (or all responders have been followed for [redacted] after their initial response, whichever comes first), have discontinued from the study, or had [redacted] safety follow-up after PD, whichever comes first.

9.3.2 Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3 Subject Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the SAP.

9.3.4 Treatment Compliance

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of therapy (weeks) and the number of cycles per subject will be presented, as well as the number and percentage of subjects who were treated at each cycle and completed each cycle. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

The primary endpoint of this study is the confirmed ORR per BICR. The ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST 1.1. Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders.

The ORR and its exact 2-sided 95% CI, using the Clopper-Pearson method (Clopper 1934), will be calculated.

The primary efficacy analysis will be performed for subjects treated solely with tucatinib in combination with trastuzumab (Cohorts A+B).

9.3.5.2 Secondary Efficacy Analyses

The analyses on secondary endpoint, ORR by 12 weeks of treatment, and the exact 2-sided 95% CIs, using the Clopper-Pearson method (Clopper 1934), will be calculated.

Secondary endpoints, such as DOR per BICR, PFS per BICR, and OS, are time-to-event endpoints, and they will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. Details on the censoring algorithm will be provided in the SAP.

ORR by Week 12 will be summarized for subjects treated solely with tucatinib monotherapy (Cohort C) and subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B).

9.3.5.3 Other Efficacy Analyses

ORR, DOR, and PFS according to investigator assessment will also be analyzed; discrepancies between the BICR and investigator's assessment will be summarized descriptively.

[redacted]

[redacted]

[redacted]

9.3.9 Safety Analyses

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG PS, and changes in cardiac ejection fraction results. AEs will be classified by SOC and preferred term using Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE v4.03 criteria.

9.3.9.1 Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by cohort using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.9.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will

be defined as treatment emergent if they are newly occurring or worsen following study treatment.

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence. The incidence of AEs will be tabulated by preferred term and cohort. AEs leading to premature discontinuation of study drug will be summarized and listed in the same manner.

All collected AE data will be listed by cohort, study site, subject number, and cycle. Separately, all serious AEs and AEs of special interest (e.g., any DILI, and asymptomatic left ventricular systolic dysfunction) will be listed. A separate listing of all on-study deaths will be presented.

9.3.9.3 Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4 Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE v4.03 and flagged when values are outside the normal reference range.

9.3.9.5 Other Safety Analyses

Vital Signs
The frequency and percentage of subjects with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs.

ECOG Status
ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG
ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG, and shifts from baseline may be tabulated.

MUGA or ECHO
Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

9.3.10 Interim Analyses

Cohort A uses a Fleming 2-stage phase 2 design, with a null hypothesis of 20% unconfirmed ORR for tucatinib + trastuzumab, an alternative hypothesis of 40%, a one-sided significance level of 0.1153, and a power of 83.54%. Ten evaluable subjects are to be treated in the first stage; if ≤1 response is observed the regimen will be considered ineffective in this patient population; if ≥5 successes are observed the null hypothesis will be rejected; otherwise the initial cohort proceeds to the second stage. Fifteen evaluable subjects are to be treated in the second stage; if a total of ≤7 responses are observed in the first 25 evaluable subjects, the regimen will be considered ineffective; if ≥8 responses are observed the regimen may merit further evaluation.

[redacted]

10 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); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (World Medical Association 2013), and all applicable regulatory requirements. For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations.

10.1 Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

It is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

10.2 Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.

- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 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.

10.4 Investigator Information

The contact information and qualifications of the principal investigator and sub-investigators and name and address of the research facilities are included in the investigator file.

10.4.1 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of 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 implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

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

10.5 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

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.

10.6 Clinical Trial Agreement

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 trial agreement.

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APPENDIX A: SCHEDULE OF EVENTS

Table 11-1: Schedule of events

Study Period/Treatment Cycle	Screening/Baseline		Treatment					EOT[a]	F/U[b]
			Cycle 1		Cycles >1	Every 6 or 9 wks	Every 12 wks	30 days post last dose	Every 12 wks
Day	D–28 to –1	D–7 to –1	Pre-dose D1	D8 and 15	Pre-dose D1				
Visit Window				±3 days	±3 days	±7 days	±14 days	+7 days	±14 days
Informed consent[c]	X								
Inclusion/exclusion criteria	X								
Document disease history	X								
FFPE Tumor Specimen[d]	X								
Physical examination[e]		X	X		X			X	
Height		X							
Vital signs[f]		X	X		X			X	
Drug Diary review			X		X				
Adverse event collection	Related to study procedures		Collect from C1D1 pre-dose through safety reporting period of study drugs						
Concomitant medication									
ECOG PS		X	X		X			X	
CBC with differential and platelets[g]		X	X	X	X			X	
Blood chemistries and LFTs[h]		X	X	X	X			X	
Coagulation tests[i]		X						X	
Urinalysis		X							
12-lead ECG[j]		X							
ECHO/MUGA[k]	X						X	X[l]	
Serum β-HCG pregnancy test[m]		X[m]	X[m]		X				
Hepatitis B and C screening[n]	X								
Radiological disease assessment[o, u]	X					X[o]		X	
Blood tumor marker – CEA[p]	X					X[p]		X	
[redacted]			X	X	X			X	
Study drug treatment – Tucatinib[r]			X		X				
Study drug treatment – Trastuzumab[s]			X		X				
[redacted]	See Table 11-2 and Table 11-3 for [redacted] collection schedule								
Further anticancer therapy and survival[t]									X

a For Cohort A, if subject discontinues treatment because of PD, they will have 1 Observation visit 30 (±7) days post last study intervention. After this time, subject will enter follow-up. For subjects who go off study treatment with no documented disease progression and no subsequent anticancer treatment, the subject will be observed every 12 weeks (±14 days) or as clinically indicated until PD, at which time they will enter follow-up. Subjects remaining in observation for ≥5 years from first study treatment will go off study without entering follow-up.

b Treatment decisions/patient care for subjects who have discontinued study treatment is at the discretion of the treating physician.

c Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/independent ethics committee (IEC) policies.

d Initiate collection of tissue for submission for confirmatory HER2+ and Biomarker testing. If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment.

e Pre-dose, may not be performed if done within 1 day prior to C1D1

f Vital signs to be collected are weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation. Pre-dose, may not be performed if done within 1 day prior to C1D1.

g If CBC is performed within 7 days prior to C1D1, it does NOT need repeating on C1D1.

h Creatinine, calculated creatinine clearance using Cockcroft-Gault (at baseline and as clinically indicated), total bilirubin (and direct bilirubin when total bilirubin is >ULN), ALT, AST, alkaline phosphatase, albumin, calcium, sodium, potassium, chloride, bicarbonate, BUN, glucose, and total protein. If chemistries are performed within 7 days prior to C1D1, they do NOT need to be repeated on C1D1.

i PT, INR, aPTT

j ECG assessments will be performed with standard 12-lead ECG equipment according to standard institutional procedures. Pre-treatment ECGs should be performed after vital signs are obtained and before any blood draws.

k Cardiac ejection fraction will be assessed by transthoracic ECHO will be performed at screening, every 12 weeks until treatment discontinuation irrespective of dose delays or interruption, and at the EOT visit. ECHO is the preferred modality for assessment of LVEF. If clinically indicated, MUGA scan may be used in place of ECHO. The same method for LVEF assessment should be employed at each assessment.

l The EOT assessment of ECHO does not need to be performed if an on-treatment ECHO had been performed within 12 weeks previously.

m Women of childbearing potential only. If pregnancy test is performed within 7 days prior to C1D1, it does not need to be repeated on C1D1.

n Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV will only be collected for Cohorts B and C).

o CT or MRI of the chest, abdomen, and pelvis to assess sites of measurable disease as per RECIST 1.1. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original schedule. Unless clinically indicated, the same method for tumor assessment should be employed at every restaging. For Cohort A, radiological disease assessment will be performed at the screening/baseline, every 9 weeks/3 cycles (±14 days) during study treatment (every 12 weeks/4 cycles [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. For Cohorts B and C, radiological assessment will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

p CEA assays will be assessed on the same schedule as radiographic scanning. For Cohort A, CEA assays will be performed at the screening/baseline, every 9 weeks (every 3 cycles, ±14 days) during study treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. For Cohorts B and C, CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. If cycles are delayed for any reason or there is an interim unscheduled assessment, CEA assays should continue to be performed according to the original schedule.-

q [redacted] will be administered for Cohorts B and C at: pre-dose C1D1, C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.

r Tucatinib is administered PO BID, on each 21-day cycle.

s Trastuzumab is administered IV, once every 21 days for Cohorts A and B, or subjects in Cohort C who are approved to crossover to doublet treatment.

t Following progression or initiation of further anticancer therapy, subjects will be contacted every 12 weeks (±2 weeks) to obtain information on subsequent anticancer therapy, and survival status until death, study closure, or withdrawal of consent.

u Subjects from Cohort C must have a new baseline RECIST assessment, as described in Section 6.3.6, prior to crossover from monotherapy to doublet therapy using the Week 12 scans or the first PD scans as applicable.

[redacted]

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[redacted]

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	Description	Percent	Description	Score	Description
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

ECOG = Eastern Cooperative Oncology Group

APPENDIX C: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 7 months after the final dose of study drug administration; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

a A person of childbearing potential is defined as anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person born female over age 45 in the absence of other biological, physiological, or pharmacological causes.

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

A Functional and Therapeutic Classification for Prescription of Physical Activity for Cardiac Subjects

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

On-line source: http://www heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX E: CYP3A4 INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP3A4 inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inducers with continued research.

Drug[a, b]	Elimination Half-life [c] (hours)
Strong Inducers	
Barbiturates	Variable
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours[d]

Note: Any additional CYP3A4 inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a. FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#potency)

b. EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c. Drug package insert

d. (Kerb 1996)

APPENDIX F: CYP2C8 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES

CYP2C8 inhibitors and inducers include but are not limited to the following. There could also be additional new drugs and marketed drugs that could be identified as inhibitors/inducers with continued research.

Drug[a, b]	Elimination Half-life[c]
Strong Inhibitors	
Gemfibrozil	1–2 hours
Moderate Inhibitors	
Clopidogrel	6 hours
Deferasirox	8-16 hours
Teriflunomide	18-19 days
Moderate Inducer	
Rifampin	3–5 hours

Note: Any additional CYP2C8 inhibitors/inducers that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

a FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#potency)

b EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

c Drug package insert

APPENDIX G: PATIENT DRUG DIARY

Tucatinib

Cycle:	Patient ID Number:	Name:
Pill strength dispensed:	☐ 50 mg tablets ☐ 150 mg tablets	You will take _____ tablets in the MORNING, and _____ tablets in the EVENING.

ORAL MEDICATION DIARY

Patient Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the time dose was taken on the line under the date.
- Tucatinib tablets should be taken twice each day (once in the morning, and once in the evening) approximately 8-12 hours between doses in the same calendar day. It is recommended that if you miss a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, you should not take the missed dose but should wait and take the next regularly scheduled dose. If you miss a dose, place a check "0" under the date.
- Take tablets by mouth twice daily as prescribed on days 1-21 of each cycle
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose or double up the next dose.

- Store your study drug in the refrigerator at 2-8°C and keep out of the reach of children and pets. If left out of refrigeration for a period of time, please contact your study team. Please do not consume grapefruit, grapefruit juice, star fruit, or Seville oranges while taking tucatinib.
- Pills must be swallowed whole. Do not crush, chew, or dissolve pills in liquid.
- If you vomit a dose, and the pill is visible in the vomit, you can take a replacement pill. If the pill is not visible in the vomit, please wait until your next scheduled time before taking the medication again.

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 8	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 15	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
Each cycle has 21 days. In cases where a patient is unable to return to clinic at the end of a cycle, a 3-day window is allowed in the study. Tucatinib tablets taken during this time will be recorded here.					***+Day 1***	***+Day 2***	***+Day 3***
				Date:			
				Time of Morning Dose	AM	AM	AM
				Time of Evening Dose	PM	PM	PM

APPENDIX H: EXAMPLES OF CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

The following table provides examples of clinical substrates for CYP3A-mediated metabolism and is not intended to be an exhaustive list.

Sensitive (AUC increase ≥5-fold with strong index inhibitor)	Moderate Sensitive (AUC increase 2 to 5-fold with strong index inhibitor)
alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[c], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[d], midazolam, naloxegol, nisoldipine, saquinavir[c], simvastatin[d], sirolimus, tacrolimus, tipranavir[c], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[a], colchicine, eliglustat[b], pimozide, rilpivirine, rivaroxaban, tadalafil
budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[c], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown above the dashed line. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.

DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Hachad 2010).

OATP1B1 = organic anion transporting polypeptide 1B1.

a Listed based on pharmacogenetic studies.

b Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

c Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.

d Acid form is an OATP1B1 substrate

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#table3-1

APPENDIX I: DEFINING LINES OF THERAPY

A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the investigator's opinion, maximum benefit has been achieved. Disease progression can be either clinical or radiographic and does not have to be based on a formal RECIST assessment.

- Maintenance therapy (e.g., continuation of 5-fluorouracil [5FU] after discontinuation of oxaliplatin or irinotecan) does not count as a separate line.

- Hepatic arterial infusion (HAI) pump therapy counts as a separate line.

- Restarting a chemotherapy backbone counts as a line if:
  - There is an addition of a biologic not previously used
  - The patient previously had progressive disease (clinical or radiographic) on this regimen

APPENDIX J: INVESTIGATOR SIGNATURE PAGE

Protocol Number:	Study SGNTUC-017
Protocol Title:	A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer **(MOUNTAINEER)**
Investigational Product:	Tucatinib (ONT-380)
Version:	Amendment 9 10-Sep-2020

Investigator Statement and Signature

I have read the attached protocol entitled "A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer (MOUNTAINEER)"

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature _____ Date _____

Investigator Name, Printed _____

APPENDIX K: DOCUMENT HISTORY

Version*	Date
Original	5 May 2017
Amendment 1	23 June 2017
Amendment 2	20 October 2017
Amendment 3	02 March 2018
Amendment 4	21 September 2018
Amendment 5	19 April 2019
Amendment 6	05 July 2019
Amendment 7	10 September 2019
Amendment 8	01 November 2019
Amendment 8.1	22 November 2019
Amendment 8.2	14 February 2020
Amendment 9	DD September 2020

*Up through "Amendment 6" the investigator-sponosored trial documents were also known as "Addendums" instead of "Amendments."

Summary of Changes in Amendment 1

Protocol section updated	Nature of change
Title Page	• IND number corrected • Draft date removed • Document history updated to reflect Activation/Amendment 1
Protocol Resource Page	• Removed from protocol
Schema	• Correction made to Tucatinib dosing schedule • Clarifications made to study schema
Section 3.0, Patient Eligibility	• Editorial changes • Change to length of birth control requirements
Section 4.0, Test Schedule	• Changes to pre-registration tests and procedures • Correction to Clinical Follow-up and Event Follow-up visits • Clarifications to visit timing • Consolidation of like biospecimen collections • Footnotes updated to reflect above-mentioned edits and to add further clarifications
Section 13.0, Treatment/Follow-up Decision at Evaluation of Patient	• Change to length of birth control requirements
Section 14.0, Body Fluid Biospecimens	• Biospecimen submission table updated to reflect Test Schedule changes • Additional guidelines added to kit instructions
Section 15.0, Drug Information	• IND number corrected • Tucatinib section updated based on Pharmacy review of template • Nursing guidelines added
Section 17.0, Pathology Considerations/Tissue Biospecimens	• Removal of redundant information • Correction of form name
Section 18.0, Records and Data Collection Procedures	• Initial Materials table updated to reflect final forms build • Test Schedule Materials updated to reflect final forms build • Follow-up Materials table updated to reflect final forms build
Appendix I, Informed Consent Template	• Side effects of Tucatinib updated based on Pharmacy review of IB • Side effects of Trastuzumab updated based on Pharmacy review of IB • Change to length of birth control requirements • Risks of TTE removed • Timeframe for reporting of pregnancy of partner of male patient revised
Appendix VII, Patient Drug Diary	• Correction made to drug storage instructions
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 2

Protocol section updated	Nature of change
Title Page	• Editorial and administrative changes have been made regarding the Protocol Resource Page communication.
Schema, Page 3	• Tucatinib and Trastuzumab have been updated with administrative and editorial changes.
Section 3.0, Patient Eligibility	• 3.13 have been updated with an editorial change. • 3.18 have been updated with administrative and editorial changes. • 3.19c has been updated with an editorial change and to define amenorrhea as ≥12 consecutive months. • 3.19d have been updated with administrative and editorial changes.
Section 4.0, Test Schedule	• Under Cycle 1, days 8 & 15 was modified as required. • Under the Active Treatment section, the cycles were modified with editorial changes. • Footnote 10 has been deleted; thus renumbering footnotes 10-13 has changed. • The mandatory tissue sample was moved to the observation section as required.
Section 7.0, Protocol Treatment	• Section 7.1 Treatment Schedule has been updated with an administrative change. • Section 7.2 has been updated with administrative and editorial changes.
Section 11.0, RECIST Measurement Guidelines	• Section 11.1 has been updated with administrative and editorial changes.
Section 14.0, Body Fluid Biospecimens	• Section 14.115 has been deleted regarding the days of shipment for specimens.
Section 15.0, Drug Information	• Section 15.14 has been updated with added information regarding the administration of Tucatinib. • Section 15.16, additional information was added to the Potential Drug Interactions paragraph. • Sections 15.297-98 Nursing Guidelines have been added for Trastuzumab.
Section 18.0, Records and Data Collection Procedures	• Section 18.1 Submission Timetable, the specimen submission tissue for baseline has been moved from the active-monitoring phase to the observation phase and footnotes have been updated to reflect these changes.
Section 19.0, Budget	• Section 19.2 has been updated with editorial changes.
Appendix I, Informed Consent Template	• Pages 7, 8, and 9 have been updated to reflect Tucatinib to be taken twice daily. • Page 10 has been updated with administrative and editorial changes. • Pages 14, 15; Reproductive Risks have been updated with administrative and editorial changes. • Page 18; the verbiage regarding drug cost has been updated. • Page 19; Travel Reimbursement language has been added.
Appendix IV	• Page 1; Administrative and editorial changes have been made.

Protocol section updated	Nature of change
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 3

Protocol section updated	Nature of change
Schema	• Trastuzumab availability has been changed to Biologics.
Section 7.0, Protocol Treatment	• Section 7.3 was updated to clarify that the patient does not necessarily need to get treatment where they signed consent.
Section 9.0, Ancillary Treatment/Supportive Care	• Section 9.5 was updated with an editorial change. • Section 9.9a was updated to clarify radiation and RECIST.
Section 14.0, Body Fluid Biospecimens	• Footnote #2; cycle numbers were corrected.
Section 15.0, Drug Information	• Section 15.13 was updated to clarify the shelf life of Tucatinib. • Section 15.17; More verbiage has been added to the toxicities for Tucatinib. • Section 15.18; Drug procurement language has been added for Tucatinib. • Section 15.19a; Temperature Excursion language has been added to clarify the process for sites. • Section 15.19b; Nursing Guidelines have been changed due to the updated IB for Tucatinib. • Section 15.19c; Drug Accountability has been updated for sites clarity. • Section 15.28 Drug procurement for trastuzumab has been updated to clarify funding and the updated process.
Appendix I, Informed Consent Template	• Appendix I; Pages 3, 5, 6, 8, 9, 10, 11, 18, 19 were updated with an administrative and editorial changes.
Appendix VII, Drug Diary	• The Patient Drug Diary has been updated to clarify instructions for the patient regarding the drug.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 4

Protocol section updated	Nature of change
Title Page	• The IND Holder has been changed from [redacted] to [redacted] • The Statistician's for this trial has been edited.
Index	• The header was changed to reflect Amendment 4.
Schema	• Biologics was changed to [redacted] on the availability for tucatinib and trastuzumab.
Section 1.0, Background	• Administrative and editorial changes were made throughout Section 1.0.
Section 3.0, Patient Eligibility	• Administrative and editorial changes were made throughout Section 3.0.
Section 4.0, Test Schedule	• Footnote #6 was changed for clarification regarding imaging. • Footnote #8 was modified to clarify tissue submission.
Section 8.0, Dosage Modification Based on Adverse Events	• Added language was inserted for clarification regarding Adverse Event-Specific Dose Modifications.
Section 10.0, Adverse Event (AE) Reporting and Monitoring	• Cascadian was changed to Seattle Genetics throughout section 10.0.
Section 13.0, Treatment/Follow-up Decision at Evaluation of Patient	• The follow-up period was changed in section 13.1 for clarification. • Verbiage regarding dosing delays was added for clarification.
Section 15.0, Drug Information	• Section 15.1 Tucatinib; Cascadian was changed to their new name Seattle Genetics. • The temperature excursion email was modified. • Section 15.2 Trastuzumab; had administrative and editorial changes throughout for clarification on Cascadian's name change to Seattle Genetics and based on the package insert. • Section 15.26 language removed from the protocol as it was not related to this study. • Section 15.27 has editorial and administrative changes for clarification.
Section 16.0, Statistical Considerations and Methodology	• Section 16.2 Primary Endpoint; has been edited for clarification. • Section 16.31 Decision Rule; Administrative and editorial changes have been made. • Section 16.34 Power and Significance Level; administrative and editorial changes have been made.
Appendix I, Informed Consent Template	• The header has been changed to reflect Amendment 4 • Cascadian has been changed to Seattle Genetics. • Verbiage regarding study testing was modified for clarification. • Side Effects associated with Trastuzumab were changed based on the package insert. • Tumor assessments have been modified regarding RECIST imaging.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 5

Protocol section updated	Nature of change
Title Page	• Amendment 5 has been added to the title page.
Section 1.0, Background	• Section 1.2 references and language was changed based on new findings. • Section 1.323 was edited based on the trastuzumab package insert.
Section 4.0, Test Schedule	• Footnote 6, language had added language for clarification.
Section 8.0, Dosage Modification Based on Adverse Events	• 8.2; Administrative and editorial edits have been added for clarifications. • Edits have been made to the table regarding Left Ventricular Systolic Dysfunction.
Section 11.0, RECIST Measurement Guidelines	• 11.213; An editorial change was made for clarification regarding measurable disease.
Section 14.0, Body Fluid Biospecimens	• 14.0, Footnote 1 had an administrative change regarding blood collection for C1 day 1.
Section 18.0, Records and Data Collection Procedures	• NGS or FISH/CISH are now added as reports to be uploaded for baseline.
Section 20.0 References	• An outdated reference was removed and replaced.
Appendix I, Informed Consent Template	• Trastuzumab Reproductive Risks; language was added for precautionary measures for pregnant females. • Seattle Genetics was added to receive data for this protocol.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 6

Protocol section updated	Nature of change
Title Page	• Amendment 6 was changed on the Title Page.
Section 1.0, Background	• Section 1.2 was modified with the current reference. • Section 1.2; language was removed and an editorial changes was made. • Section 1.323; CYP language was added for study clarification. • Section 1.6; Administrative changes were made for clarification.
Section 3.0, Patient Eligibility	• Numbering was modified due to insertion and deletion of language. • Administrative and editorial changes were made throughout Section 3.0
Section 4.0, Test Schedule	• Footnote 6 &7 had an editorial changes for study clarification. • The mandatory blood sample on the test schedule was changed from baseline to prior to dosing on Day 1, per the PI.
Section 7.0, Protocol Treatment	• Additional language has been added to the treatment schedule for study purposes.
Section 8.0, Dosage Modification Based on Adverse Events	• Editorial changes were made to Section 8.1 for clarification.
Section 9.0, Ancillary Treatment/Supportive Care	• Additional language was inserted throughout for precautionary measures for this trial regarding medications and CYP substrates.
Section 14.0; Body Fluid Specimens	• Footnote 1; additional language was added for clarification.
Section 15.0, Drug Information	• Section 15.15; an editorial change was made. • Section 15.16; Language was removed and replaced for updated potential drug interactions. • 15.17; an editorial change was made.
Section 16.0, Statistical Considerations and Methodology	• Administrative and editorial changes were made throughout Section 16.0 for study clarification.
Section 17.0, Pathology Considerations/Tissue Biospecimens	• The table and sections were edited to change tissue information needed for study purposes.
Section 20.0, References	• A reference was edited to reflect the most current information.
Appendix I, Informed Consent Template	• Appendix I was edited to reflect the most current amendment.
Appendix VIII, List of Selected Substrates or Inhibitors of P-gp and Substrates of BCRP Oral Drugs	• This appendix was added for study purposes.
Appendix IX, Examples of Clinical Substrates for CYP3A-Mediated Metabolism	• This appendix was added for study purposes.
Appendix X, Drugs Accepted or Possibly Associated with Risk of QT Prolongation or Torsade de Pointes	• This appendix was added for study purposes.
Appendix XI, List of Selected Potential Sensitive Substrates for UGT1A1	• This appendix was added for study purposes.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

Summary of Changes in Amendment 7

Section(s)	Change	Rationale
Throughout	Replaced "ACCRU" with "Seattle Genetics, Inc." or "sponsor"	Sponsor name change
Throughout	Added new protocol number: ACCRU-GI-1617, SGNTUC-017	Added Seattle Genetics protocol number.
Cover Page	• Changed the name of the IND Holder from "[redacted]" to "Seattle Genetics" • Removed study co-chair • Added Sponsor Medical Monitor • Replaced ACCRU Statistician with Seattle Genetics Statistician • Added Seattle Genetics confidentiality statement • Removed the following text: ~~*For any communications regarding this protocol, please contact the person indicated on the Protocol Resource Page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org)*~~Study Chairs ~~√ Study contributor(s) not responsible for patient care.~~ ~~Research Coordinating Center~~ ~~Academic and Community Cancer Research United~~ ~~200 First Street Southwest~~ ~~Rochester, MN 55905~~ ~~FAX# 507-538-0906~~	Updated, as after the IND transfer to Seattle Genetics, the company assumed sponsorship of the study and specific information pertaining to ACCRU processes no longer applies. Added Sponsor Medical Monitor and Sponsor Statistician due to change in responsibilities.
Throughout	Removed references to the ACCRU website.	Removed, to reflect the updated resources.
Throughout	Minor editorial corrections: spelling, formatting, addition of missing items to the TOC (Index) table	To provide more clarity and consistency throughout the document.
Schema	Switched the notes on each side of the Schema diagram: "Off study for Disease Progression, Alternative Therapy, or Withdrawal/Refusal" was moved to the right side and "Off study for any reason other than Disease Progression, Alternative Therapy, or Withdrawal/Refusal" was moved to the left side. Changed "availability" of trastuzumab: ~~[redacted]~~ Seattle Genetics	Corrected mislabeling. Correction made to reflect changes in the drug procurement

Section(s)	Change	Rationale
3.17	ECOG Performance Status (PS) of 0, 1, or 2. ~~(Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index html)~~An example form is available in the Study Operations Manual.	Correction made to specify the designated location (Study Operations Manual) of the updated forms
4.0	In the Test Schedule Table: 1. Removed "Mandatory blood sample – whole blood for pharmacogenomics analysis" row 2. Amended text in the Footnote 8: Submission will be ~~once within 12 months of the analysis of the primary endpoint when requested by study chair or designee~~ done upon enrollment. See section 17.0.	Change made to reflect the reduction in blood collection. The footnote update was also captured in Section 17.11 and was performed to reflect the changes in the process.
6.1	Procedures for registering patients are available in the Study Operations Manual. ~~To register a patient, access the ACCRU web page at https://www.accru.org/accru/group/cra html, go to the Remote Application section, click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).~~ ~~Instructions for the registration/randomization application are available on the above web page under the Remote Application section, "Remote Application Training."~~ ~~Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:~~ ~~• Contact the ACCRU Registration Office (507) 284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.~~ ~~• Refer to "Remote Registration, Installation & Entry Instructions" under "Training Material Manuals."~~	Removed, as specific details about procedures for registering patients are outlined in the Study Operations Manual.

Section(s)	Change	Rationale
6.3	Documentation of IRB approval must be on file with ~~ACCRU~~ the sponsor before an investigator may register any patients. ~~Approvals should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~ In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ~~ACCRU~~the sponsor no less than annually. ~~Approvals should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~ If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved. Annual IRB approval must continue to be submitted to ~~ACCRU~~ the sponsor until site receives notification from ~~ACCRU~~the sponsor that IRB closure can commence and approval of such is granted. ~~IRB approval of study closure should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~	Removed specific information regarding ACCRU electronic regulatory system as it is no longer relevant.
6.4 to 6.9	Removed Sections 6.4 through 6.9. ~~6.4 Prior to accepting the patient registration, the registration application will verify the following:~~ ~~• IRB approval at the registering institution~~ ~~• Patient eligibility~~ ~~• Existence of a signed consent form~~ ~~• Existence of a signed authorization for use and disclosure of protected health information~~ ~~6.5 At the time of registration, the following will be recorded:~~ ~~• Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.~~ ~~• Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.~~	Removed as specific details about registration processes are outlined in the Study Operations Manual, as specified in Section 6.1.

Section(s)	Change	Rationale
	~~6.6 Treatment cannot begin prior to registration and must begin 7 days after registration.~~ ~~6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.~~ ~~6.8 All required baseline symptoms (see Section 10.62) must be documented and graded.~~ ~~6.9a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.~~ ~~6.9b Study drug is available on site.~~ ~~6.9c Blood draw kit is available on site.~~	
10.0	**10.0 Adverse Event (AE) Reporting and Monitoring** The site principal investigator is responsible for reporting any/all adverse events to ~~ACCRU~~the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information. ~~ACCRU is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:~~ ~~• Any suspected adverse reaction that is both serious and unexpected.~~ ~~• Any findings from laboratory animal or in vitro testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.~~ ~~• Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.~~ ~~• Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).~~	Removed specific information regarding ACCRU's processes, as following updated sponsorship, all regulatory authority reporting is performed per Seattle Genetics Standard Operating Procedures (SOPs).
10.1	Removed the following definitions: ~~Suspected Unexpected Serious Adverse Reaction (SUSAR)~~	Removed, as information related to Suspected Unexpected Serious Adverse Reactions (SUSAR), Suspected Adverse Reaction, and

Section(s)	Change	Rationale
	~~A SUSAR is a serious adverse reaction or event, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or package insert). The Investigator must determine the relationship of the event to study agent based on information available at the time of the initial reporting. The initial assessment may be revised as new information becomes available.~~ ~~Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.~~ ~~NOTE: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (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).~~ ~~Suspected Adverse Reaction~~ ~~Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.~~ ~~Expedited Reporting~~ ~~Events reported to sponsor within 24 hours, 5 days, or 10 days of study team becoming aware of the event.~~ ~~Routine Reporting~~ ~~Events reported to sponsor via case report forms~~ ~~Events of Interest~~ ~~Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).~~	Expedited and Routine Reporting are covered by Seattle Genetics SOPs and are outside of the scope of the individual site(s). Removed Events of Interest as ACCRU's definition does not align with Seattle Genetics' definition.
10.2	Added the following text: <u>Diagnosis vs. Signs or Symptoms</u>	Added the Seattle Genetics standard language for more clarity.

Section(s)	Change	Rationale
	In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event. If applicable: Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI Common Terminology Criteria for Adverse Events (CTCAE) terms of "cytokine release syndrome," "acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion related event, each sign or symptom should be recorded separately with its level of severity. Progression of Underlying Malignancy Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or serious adverse event (SAE). The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.	
Prior 10.4	~~10.4 Expectedness~~ ~~Determination of whether an event is expected or unexpected should be determined as outlined below.~~ ~~10.41 Expected events~~	Removed, as assessment of expectedness will not be performed by the clinical sites, but will be performed by Seattle Genetics.

Section(s)	Change	Rationale
	~~Those events described within the Section 15.0 of the protocol, the study-specific consent form, package insert and/or the investigator brochure, or otherwise described in the general investigational plan.~~ ~~10.42 Unexpected adverse events~~ ~~Those events not listed in Section 15.0 of the protocol, the study specific consent form, package insert and/or in the investigator brochure (or are not listed at the specificity or severity that has been observed), or is not consistent with the risk information described in the general investigational plan.~~ ~~Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.~~ ~~10.43 Suspected Unexpected Serious Adverse Reaction (SUSAR)~~ ~~A SUSAR is a serious adverse reaction or event, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or package insert). The Investigator must determine the relationship of the event to study agent based on information available at the time of the initial reporting. The initial assessment may be revised as new information becomes available. SUSARs include any incident, experience, or outcome that meets all of the following criteria:~~ ~~• Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;~~ ~~• Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and~~ ~~• Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.~~	

Section(s)	Change	Rationale
	~~Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.~~ ~~If the event meets the criteria for a SUSAR, submit to your IRB as required by your institutional policies.~~	
10.41	~~Investigational Agents and Commercial Agents on the SAME Arm~~ ~~When commercial agents are used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.~~ ~~These AEs should be assessed as specified in the appropriate IND/IDE Reporting Table in Section 10.822.~~ Relationship of the Adverse Event to Study Treatment The relationship of each AE to each study treatment (tucatinib and trastuzumab) should be evaluated by the investigator using the following criteria: Related: There is evidence to suggest a causal relationship between the drug and the AE, such as: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture) Unrelated: Another cause of the AE is more plausible (e.g., due to underlying disease o occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatmer a causal relationship is considered biologically implausible	Replaced the content of the Section 10.41 (prior 10.51), as relatedness will be reported in relations to each study drug (tucatinib and trastuzumab) in the combination treatment, as opposed to the regimen in general.

Section(s)	Change	Rationale
10.5111	Reportable categories of death: • Death attributable to a CTCAE term • Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life • Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF. • ~~Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5~~ • ~~Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5~~ • ~~Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.~~	Updated the language on death to align with the Seattle Genetics standard language.
10.513	An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.	Added the language on reporting of serious events to align with the Seattle Genetics standard language.
Prior 10.62, 10.621, and 10.622	~~10.62 Non-Serious Events~~ ~~A non-serious adverse event is defined as any of the following that do not meet serious criteria as previously outlined:~~ ~~10.621 Grade 2 AEs deemed possibly, probably, or definitely related to the study treatment or procedure.~~ ~~10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure~~.	Removed, as this definition does not align with Seattle Genetics' definition.
10.62	In general, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and must be	Removed specific information regarding ACCRU's processes to

Section(s)	Change	Rationale
	reported as a serious adverse event to ~~ACCRU~~ the sponsor ≤1 business day of discovery of the event. ~~ACCRU will notify Seattle Genetics ≤1 business day of site notification.~~	reflect the changes associated with the updated sponsorship.
10.7	Removed the table for Reporting Timeframes and Mechanisms and added the following language: 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: ● Patient number ● Date of event onset ● Description of the event ● Study treatment, if known ● Investigator's causality assessment The completed SAE form is to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form). Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.	Removed the table for Reporting Timeframes and Mechanisms and added the updated information on SAEs (per Seattle Genetics standard SAE reporting language) in Section 10.7, on Adverse Events of Special Interest (AESI) in Section 10.73, and on pregnancies in Section 10.83.
10.72 (prior 10.82)	~~Expedited Reporting Timeframe and Mechanism~~ ~~10.821 Expedited Reporting Mechanism~~ ~~For adverse events meeting criteria for expedited reporting and occurring within 30 days of the last dose of investigational agent:~~ ~~• Complete the ACCRU Adverse Event Expedited Report Form, located on the ACCRU website: (https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html) and submit the completed form to the ACCRU SAE Coordinator via fax (507.284.9628) within the timeframe outlined in the table(s) below.~~	Removed the section, as all Expedited Reporting.to regulatory authorities will be performed by Seattle Genetics as per Seattle Genetics SOPs.

Section(s)	Change	Rationale
	• The ACCRU SAE Coordinator will notify Industry Partner via email to Drug.safety@seagen.com and ACCRU IND Coordinator as required. • The ACCRU IND Coordinator will assist ACCRU sponsor-investigator in notifying FDA if required. • Complete all required site-specific reporting procedures.	
Prior 10.822	10.822 Expedited Reporting Timelines for Investigational Agents **FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)** **NOTE:** Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in **ANY** of the following outcomes: 1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). **ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.	Removed the section, as all Expedited Reporting to regulatory authorities will be performed by Seattle Genetics as per Seattle Genetics SOPs.

Section(s)	Change	Rationale

~~**Hospitalization**~~	~~**Grade 1 and Grade 2 Timeframes**~~	~~**Grade 3-5 Timeframes**~~
~~Resulting in Hospitalization ≥24 hrs~~	~~7 Calendar Days~~	~~24 Hour; 3 Calendar Days~~
~~Not resulting in Hospitalization ≥24 hrs~~	~~Not required~~	

~~**Expedited AE reporting timelines are defined as:**~~

- ~~"24 Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.~~
- ~~"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.~~

~~[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:~~

~~**Expedited 24-hour notification followed by complete report within 3 calendar days for:**~~

- ~~All Grade 3, 4, and Grade 5 AEs~~

~~**Expedited 7 calendar day reports for:**~~

1. ~~Grade 2 AEs resulting in hospitalization or prolongation of hospitalization~~

~~[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.~~

~~Effective Date: May 5, 2011~~

Section(s)	Change	Rationale
10.73 (prior 10.84)	~~10.841 AESI Reporting Mechanism~~ Within 24 hours of observing or learning of an event meeting criteria for an AESI (Section 10.7), investigators are to report, email or fax (see email or fax number specified on the SAE report form), the event to the sponsor's Drug Safety Department, regardless of the relationship of the event to the study treatment regimen. ~~For events meeting criteria for adverse event of special interest (AESI) reporting and occurring within 30 days of the last dose of investigational agent (Section 10.7):~~ ~~1. Complete the ACCRU Adverse Event Expedited Report Form, located on the ACCRU website: (https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html) and submit the completed form to the ACCRU SAE Coordinator via fax (507.284.9628) within the timeframe outlined below.~~ ~~2. The ACCRU SAE Coordinator will notify Industry Partner via email to Drug.safety@seagen.com within the timeline outlined below.~~ ~~NOTE: For events that meet criteria for both an AESI and a severe adverse event (Section 10.61), only the SAE reporting mechanism and timeline should be used.~~ ~~10.842 AESI Reporting Timeline~~ ~~3. Events meeting criteria for AESI should be reported to ACCRU within 21 days of learning of them.~~ 4. ~~ACCRU will forward all AESI forms to Seattle Genetics within 24 hours of their receipt.~~	Updated the language on reporting of AESIs to align with Seattle Genetics standard language.
10.83	The investigator should report, email or fax (see email or fax number specified on the SAE report form), all pregnancies, including those of the partners of male patients, within 24 hours to ~~ACCRU~~the sponsor's Drug Safety Department using Pregnancy Report form. ~~The funding sponsor will be notified by ACCRU within 2 business days.~~ The sponsor may ask for follow up evaluation of the pregnancy, fetus, and child.	Updated the information on reporting of pregnancies.
Throughout	Replaced CTCAE v4.0 to CTCAE version 4.03	Updated the version of CTCAE.
13.1	NOTE: Subjects with signs of clinical benefit (e.g., mixed response, symptom improvement, demonstrable slowing of progression, progression rate of <20% over 6 months) who are tolerating treatment may be allowed to continue treatment past formal radiologic progression (i.e. RECIST) if such treatment is considered in the subject's best	Updated, to reflect the changes in the process.

Section(s)	Change	Rationale
	interest by the subject, the treating physician, and the ~~ACCRU study chair~~Sponsor Medical Monitor.	
13.7	A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. ~~On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.~~ The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.	Removed, as the specific instructions on which forms to complete for this population are provided in CCGs.
14.1	14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol: 1. Removed "Mandatory - EDTA K2 (purple) - Whole Blood" row 2. Changes in the footnote: 4. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions found in the Central Laboratory Manual ~~(see Section 14.2 for detailed shipping instructions.)~~	Updated, to reflect the reduction in the blood collection and location of shipping instructions.
14.111 to 14.114	~~14.111~~ The kit contains supplies and instructions for collecting, processing, and shipping specimens. Refer to the Central Laboratory Manual for instructions regarding the kit supply, re-ordering, specimen collection, processing, and shipping. ~~14.112 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. A small but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed of per institution policy. Do not send unused kits back to BAP. Supply Order Forms must be filled in completely and legibly for quick processing.~~ ~~14.113 Kits will be sent via FedEx Ground at no cost to the participating institutions. Allow up to two weeks to receive the kits. Kits will arrive inside the shipping boxes.~~ ~~14.114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx account number or alternate billing number for express service. ACCRU will not cover the cost for rush delivery of kits.~~	Removed, as the specific instructions on procurement of kits is listed in the Central Laboratory Manual.

Section(s)	Change	Rationale
14.2	14.2 Shipping and Handling Refer to the Central Laboratory Manual for details on shipping and handling. ~~14.21 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit, and specimen collection labels are completed and filled in correctly.~~ ~~14.22 Specimens must be shipped the same day they are drawn.~~ ~~14.23 Ship tubes with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.~~ ~~14.24 Ship specimens via Priority Overnight service, Monday – Thursday, to BAP Freezer according to kit instructions. Do not send samples on weekends or just prior to federal holidays. If a patient can only be seen on Fridays, email the Biospecimen Manager (found on resource page) with the sample information and FedEx tracking number.~~ ~~14.25 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Freezer.~~ ~~14.26 BAP Freezer will receive the samples and immediately forward specimens to the ACCRU Research Base BAP Shared Resource, Hilton SL 21, Attention: BAP Supervisor.~~	Removed specific information regarding shipping and handling of body fluid biospecimens as the updated information is provided in the Central Laboratory Manual.
[redacted]	[redacted]	Change made to reflect the reduction in blood collection. Analyses of biospecimens will be performed by the central laboratory and no longer by the Duke Phase I Biomarker Laboratory.

Section(s)	Change	Rationale
	[redacted]	
15.0	Investigator brochure will be provided to participating sites ~~and stored on the ACCRU website~~.	Removed, to reflect the administrative changes.
15.18	An initial supply of tucatinib will be auto-shipped to participating sites upon ~~receipt by ACCRU of signed Pharmacy Contact Form and initial IRB approval~~site activation by the sponsor. Thereafter, each participating ~~ACCRU~~ treating location will order the drug from Seattle Genetics. Email the ~~Drug Order Request~~ Investigational Drug Request/Shipment Record Form (found in the ~~forms packet~~ Pharmacy Binder) to: ~~IST@seagen.com~~ mountaineer@seagen.com Each participating ~~ACCRU~~ treating location will be responsible for monitoring the supply of tucatinib and will use the ~~Drug Order Request~~ Investigational Drug Request/Shipment Record Form to order additional supplies as needed. ~~Outdated~~Expired or remaining drug is to be destroyed on-site as per procedures in place at each institution. Contact the sponsor prior to destroying investigational product.	Updates made to reflect the administrative changes in the process of drug procurement.
15.19a	Temperature Excursions Temperature excursions that occur at the site should be reported by the site using the Investigational Product Quality Complaints and Temperature Excursions Form ~~insert~~	Updates made to reflect the administrative changes in the process of drug procurement

Section(s)	Change	Rationale
	~~sponsor deviation/temperature excursion form name~~ found ~~on the ACCRU web site for this study~~ in the Pharmacy Binder~~and emailed to: IST@seagen.com~~	
15.28	~~Seattle Genetics will provide funding for the procurement of trastuzumab by [redacted] Each participating ACCRU treating location will order the drug from [redacted] Fax the Drug Order Request Form (found on the ACCRU web site) to:~~ [redacted] ~~Each participating ACCRU treating location will be responsible for monitoring the supply of trastuzumab and will use the Drug Order Request Form to order additional supplies as needed.~~ Each participating treating location will be responsible for monitoring the supply of trastuzumab and will use the Investigational Drug Request/Shipment Record Form (found in the Pharmacy Binder) to order additional supplies as needed. ~~Outdated~~Expired or remaining drug is to be destroyed on-site as per procedures in place at each institution. Contact the sponsor prior to destroying the investigational product.	Updates made to reflect the administrative changes in the process of drug procurement
16.51	The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. ~~The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.~~	Removed specific information regarding ACCRU's processes of data monitoring to reflect the administrative changes associated with the updated sponsorship.
16.73	Based on prior ~~ACCRU~~ studies involving similar disease sites, ~~we expect about~~ it is estimated that 10% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:	Reworded for clarity.
17.0 and 17.11	• Added language to Section 17: Refer to the Central Laboratory Manual for instructions on preparation and submission of tissue biospecimens. • Changes made to the Summary Table of Tissue Biospecimens for This Protocol (Section 17.11): • To the "Type of tissue biospecimen to submit" column: FFPE tissue block ~~with corresponding H&E slide or up to fifty (50) 5-micron, unstained slides and up to three (3) corresponding H&E slides~~ from **primary tumors present prior to**	Updates made to reflect the changes in the processes.

Section(s)	Change	Rationale
	study entry (if available). If no primary tumor tissue is available, metastatic biopsies should be used. • To the "when to submit" column: ~~Within 12 months of the analysis of the primary endpoint when requested by study chair or designee~~Upon enrollment	
17.2, 17.21 to 17.29	17.2Paraffin Embedded Tissue Blocks~~/Slides~~ ~~17.21~~ Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original surgery at the time of diagnosis. Biopsy material obtained at the time of metastatic diagnosis may be submitted. ~~A corresponding H&E slide for each submitted block must be provided to permit quality assessment of each tissue block. The H&E slide for each block should be reviewed by the institution's pathologist to assess tissue quality prior to submission.~~ If there is no suitable FFPE block available, contact the medical monitor.~~17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut up to 50 (fifty) 5 micron sections and mount on charged glass slides. Label the slides with ACCRU patient ID number, accession number, and order of sections, and thickness of sections. NOTE: do not place "sticky" labels directly on slides. H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). The H&E slides should be reviewed by the institution's pathologist to assess tissue quality prior to submission. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide should have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides.~~ ~~17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:~~ ~~• Paraffin embedded tissue blocks with corresponding H&E slide(s) (OR up to 50 (fifty) unstained slides with corresponding H&E slide(s).~~ ~~• Specimen Submission: Tissue form~~ ~~• Surgical Pathology Report~~ ~~• Operative Report (optional)~~ ~~NOTE: Please include the ACCRU patient ID number on all materials listed above.~~	Removed, as specific information regarding shipping and handling of tissue specimens is provided in the Central Laboratory Manual, as specified in Section 17.0.

Section(s)	Change	Rationale
	~~17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.~~ ~~17.25 Tissue specimens must be shipped ≤30 days from date of submission request by study chair or designee.~~ ~~17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).~~ ~~17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:~~ ~~ACCRU Operations Office Attn: PC Office (ACCRU-GI-1617) RO_FF_03_24 CC/NW Clinic 200 First Street SW Rochester, MN 55905~~ ~~17.28 When an appropriate request is submitted, the ACCRU Operations Office will forward the block(s) to the ACCRU Research Base PRC, 2915 Valley high Drive, Mayo Clinic Rochester (Attn: PRC Supervisor) for processing as outlined in Section 17.3.~~ ~~17.29 If a corresponding H&E wasn't submitted by the institution with the block, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and will be forwarded to the ACCRU Research Base PRC for review under the research base's protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed. After ACCRU research base pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the ACCRU Operations Office.Operations Office.~~	
17.3	17.31 At the completion of the study, any unused/remaining material will be stored ~~in the ACCRU Central Operations Office or Duke Phase I Biomarker Laboratory (Attn.: Pathology Coordinator)~~ for future research ~~according to the patient consent permission (see Section 6. 5)~~. Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy,	Updated the biospecimen repository information per Seattle Genetics SOPs.

Section(s)	Change	Rationale
	and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval. 17.32 For patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of sensitivity and resistance mechanisms to tucatinib, and the identification of biomarkers of HER2+ metastatic colorectal disease and response/resistance to therapy. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met. ~~Banking of tumor tissue, according to the patient consent permission (see Section 6. 5), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU studies).~~ ~~17.33 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.~~	
18.0	Removed all 3 Submission Timetables: • Initial Material(s) • Test Schedule Material(s) • Follow-up Material(s) Removed tables were replaced with the following language: Refer to the Case Report Form Completion Guidelines (CCG) for the methods of data collection.	Removed, as specific information regarding methods of data collection are provided in the CCG.
Appendix I	• Removed a sample of Informed Consent Template for Cancer Treatment Trials as Appendix I, and • Original Appendices II through XI were renumbered to Appendix I through X. • Added text to the Appendix I (ACCRU-GI-1617, SGNTUC-017 [MOUNTAINEER] Study Assessment) Local laboratories will perform all laboratory tests, and results will be provided to the investigator. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. With the exception of pregnancy testing, results of clinical laboratory tests are to be submitted to the central laboratory. Laboratory results will be reviewed by the investigator for clinical significance.	ICF template was removed from the protocol to provide consistency with Seattle Genetics document development. Added text to reflect the administrative change in the Laboratory Assessment process.

Section(s)	Change	Rationale
Appendix II	Tumor Assessments Tumor response will be assessed using RECIST 1.1 Criteria. Radiographic imaging will be performed with CT or MRI. The same method for tumor assessment should be employed at every assessment. Imaging will be performed every 9 weeks (every 3 cycles). If the patient is clinically stable after ~~two years (34 cycles)~~12 month of treatment, CT or MRI of the chest, abdomen, and pelvis may be performed once every 12 weeks (every 4 cycles +/- 14 days).	Updated for the consistency with Section 4 (Test Schedule).
Appendix VI	•It is recommended that if you miss a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, you should not take the missed dose but should wait and take the next regularly scheduled dose. If you miss a dose, place a check "0" under the date~~, but remember to take your prescribed dose at the next regularly scheduled time~~.	Added text to the Patient Drug Diary to provide more clarity.
Appendix XI	Added appendix XI	Added to align with Seattle Genetics document development.
Appendix XII	Added Summary of Changes for Amendment 2 through 7.	Added to align with Seattle Genetics document development.

Summary of Changes in Amendment 8

Section(s)	Change	Rationale
Title page	Added a brief title.	To align with protocol template
Throughout	Revised ACCRU (IST) language with the standard Seattle Genetics template language	To have the protocol that better reflects company's processes and to accommodate changes due to updated sponsorship (the IND transfer to Seattle Genetics occurred on the 17-Sep-2019), the document was transferred into the Seattle Genetics protocol template
Synopsis	Addition of synopsis	To align with the protocol template. There was no synopsis in the ACCRU template (original protocol through the Protocol Amendment A07)
Synopsis, 2, 3.1, 4	Added indication: • Patients with HER2-positive, RAS wild-type, unresectable or metastatic CRC who, unless contraindicated, have previously received systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients whose disease has dMMR proteins or is MSI-H must also have received an anti-PD-(L)1 mAb, if indicated.	To add clarity
Throughout	Addition of 2 cohorts to the study: tucatinib given in combination with trastuzumab (Cohort B) and tucatinib monotherapy (Cohort C).	Cohort B was added to assess efficacy (confirmed Objective Ressponse Rate [cORR]) and safety of the dual therapy for mCRC subjects. Cohort C was added to better characterize the antitumor activity of tucatinib when used as a monotherapy.
1.3.2 and 1.3.3	Updated the text pertaining to the overview of clinical tucatinib studies.	Reflects the latest updates for tucatinib clinical trials
1.4 and 1.6	Addition of the "widely adopted national (US) guidelines for the treatment of colon cancer".	Reflects an update to the current guidelines for treatment of colon cancer patients
1.6	Addition of the interim data from the current MOUNTAINEER protocol.	Reflects the latest data update for the MOUNTAINEER study
Synopsis, 2, 9	Amendment of the primary objective (to cORR) and addition of new study objectives (secondary, and exploratory) for the combination therapy and monotherapy cohorts of the study as follows: • To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by cORR (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria), according to blinded independent central review (BICR) assessment	Evaluation of tucatinib given in combination with trastuzumab and tucatinib monotherapy

Section(s)	Change	Rationale
	• To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment • To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment • To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment • To assess the safety and tolerability of tucatinib monotherapy, in Cohort C [redacted] Removed clinical benefit rate (CBR) from the objectives. Updated objectives and endpoints to state that all assessments will be done by BICR. Amended endpoints to reflect the objectives.	
Synopsis, 3	Planned enrollment was increased from 40 to 110 subjects. As of Amendment 8, 70 newly enrolled subjects will be randomized to either tucatinib given in combination with trastuzumab (40 subjects randomized to Cohort B) or tucatinib monotherapy (30 subjects randomized to Cohort C).	Evaluation of tucatinib given in combination with trastuzumab and tucatinib monotherapy
3.1.1, and 7.7	As of Amendment 8, safety over the course of the study will be evaluated by safety monitoring committee (SMC).	Reflects transfer of data and safety monitoring function from Study Chair to SMC
3.1.2	Addition of stopping criteria.	Reflects changes to the study design
Synopsis, 3.1.3	Updated the study schematic.	Reflects changes to the study design
3.2.1	Reworded the rationale for selection of doses and regimen.	Clarification
Synopsis, 4.1, 7.1, 7.4, 7.4.3, and APPENDIX A	Specified that: • IHC testing must be done following the package insert's interpretational manual for breast cancer. • Confirmatory HER2 testing will be done in the central laboratory. Added:	Reflects changes to the study design.

Section(s)	Change	Rationale
	• If archived tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion is required.	
Synopsis, 4.1	The baseline platelet count was changed from "≥75,000/mm^3" to "≥100 x 10^3/μL; subjects with stable platelet count from 75-100 × 10^3/μL may be included with approval from medical monitor"	Clarification
Synopsis, 4.1	The baseline laboratory hemoglobin level was changed from "≥8.0 g/dL" to "≥9.0 g/dL"	Added flexibility
Synopsis, 4.1	The inclusion criteria for pregnancy was clarified to include an agreement for females of childbearing potential not to try to become pregnant during the study and for at least 7 months after the final dose of study drug, and agreement to not donate ova, starting at the time of informed consent and continuing through 7 months after the final dose of study drug. Added hormonal methods of contraception. In addition, the timing of males who agreed not to donate sperm during the study was clarified to "starting at the time of informed consent, continuing throughout the study period and for 7 months after discontinuation of study drug."	Added flexibility, clarification, and alignment with the protocol template
Synopsis, 4.2	Added "decreased absolute neutrophil count, which must have resolved to ≤ Grade 2" clause to the Toxicity Related to Prior Cancer Therapies criterion"	Clarification
Synopsis, 4.2, 5.2.2.1, 5.3.4, APPENDIX E and APPENDIX F	Updated the Concomitant Medication Exclusion criterion to as follows: Have used strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a CYP2C8 inducer within 5 days prior to first dose of study treatment. CYP3A4 or CYP2C8 inducers and strong CYP2C8 inhibitors are also prohibited as concomitant medications within 2 weeks of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks before enrollment and during study treatment. Removed "Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)" criterion. Updated information on CYP3A4 and CYP2C8 inhibitors/inducers, Appendix E and Appendix F, respectively.	Reflects the latest updates from tucatinib clinical studies

Section(s)	Change	Rationale
Synopsis, 4.2	Updated the history of another malignancy exclusion criterion from "≤2 years prior to registration which required systemic treatment" to "within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy"	Alignment with the protocol template
Synopsis, 4.2	Updated Hepatitis C exclusion criterion to as follows: Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks	Added flexibility for enrollment
5.1, 5.2	Updated treatment administration to include Cohorts B and C	Reflects changes to the study design
5.2.3	AE-specific Dose Modification table for tucatinib and trastuzumab was modified to reflect the latest updates from the clinical studies and separated into 4 tables: • Table 5-3 Dose modifications for infusion-related reactions for trastuzumab • Table 5-4 Dose modifications for clinical AEs related to either tucatinib or trastuzumab • Table 5-5 Dose modifications of tucatinib for liver function abnormalities • Table 5-6 Dose modifications guidelines for left ventricular dysfunction	Clarification
5.2.3	Dose modification for "Blood bilirubin increased at Grade 2" was removed and at an instance of "Blood bilirubin increased at Grade 3" it is now recommended to "HOLD until severity ≤ Grade 2", instead of "≤ Grade 1".	Changes to the dose modification were performed to reflect the updates to the safety practices
5.3.3, 5.3.4	Updated the language in Concomitant Therapies to be Used with Caution and Prohibited Concomitant Therapies.	Reflects the latest updates from tucatinib clinical studies
5.4, 5.5	Added language for Management of Treatment-Emergent Adverse Events (TEAE) and Treatment Compliance.	Alignment with the protocol template
6, APPENDIX A	Added: [redacted] Added only for Cohorts B and C: • [redacted] • Randomization (At screening)	Reflects changes to the study design

Section(s)	Change	Rationale
	• Antibodies to Hepatitis C (anti-HCV) • [redacted] • Radiological assessment: every 6 weeks (±7 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy Added for all cohorts: • If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment Updated for Cohort A: • Radiological assessment: every 9 weeks during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. • [redacted] Added: "Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy, if they experience radiographic progression at any time point (as determined by investigator assessment using RECIST 1.1), or if they have not achieved a PR or CR by the week 12 assessment."	
7.3, APPENDIX A	[redacted]	Reflects changes to the study design
7.6, APPENDIX A	[redacted]	Reflects changes to the study design
7.7, 7.8, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7	The standard Seattle Genetics template language was incorporated throughout the section.	Alignment with the protocol template
9.1	Added information on determination of sample size of 110 subjects.	Reflects changes to the study design
9.2	Added the definitions for cORR and ORR by Week 12	Reflects changes to the study design
9.3	Added and updated the information on Statistical and Analytical Plans to reflect changes in the objectives.	Reflects changes to the study design

Section(s)	Change	Rationale
10	Added the standard Seattle Genetics language.	Alignment with the protocol template
APPENDIX B	Added the Lansky Performance Status scale	Alignment with the protocol template
APPENDIX C	Added the appendix per Seattle Genetics template.	Alignment with the protocol template
Appendix IX (removed)	Removed the appendix titled Drugs Accepted or Possibly Associated with Risk of QT Prolongation or Torsade De Pointes.	Results from a clinical pharmacology thorough QT study in healthy volunteers evaluating the potential for tucatinib to prolong the QT interval indicated that multiple doses of tucatinib 300 mg BID did not have a significant effect on the QT interval in healthy volunteers.
5.3.3 and Appendix X (removed)	Removed "sensitive substrates for the UGT1A1 transporter" from the list of Concomitant Therapies to be Used with Caution. Removed the appendix titled List of Selected Potential Sensitive Substrates for UGT1A1.	Reflects the latest updates from tucatinib clinical studies
Throughout	Administrative changes made, as necessary	To fix errors and ensure clarity

Summary of Changes in Amendment 8.1

Section(s)	Change	Rationale
Synopsis, 4.2	13. Have used a strong CYP2C8 inhibitor within 5 half-lives of the ***inhibitor, or*** have used a CYP2C8 ***or CYP3A4*** inducer within 5 days prior to first dose of study treatment. ~~CYP3A4 or CYP2C8 inducers and strong~~ ***Strong*** CYP2C8 inhibitors ***and CYP2C8 or CYP3A4 inducers*** are also prohibited ~~as concomitant medications within 2 weeks of~~ ***in the 2 weeks following*** discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks ~~before enrollment~~ ***prior to first dose of study treatment*** and during study treatment.	Clarify the use of concomitant drug that are specific CYP inhibitors or inducers.
Synopsis, 5.3.1.1	Strong ~~inhibitors or inducers of~~ CYP2C8 ***inhibitors and CYP2C8 or CYP3A4 inducers*** are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of tucatinib treatment. ~~Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of study treatment.~~	Clarify the use of concomitant drug that are specific CYP inhibitors or inducers.
5.1.1.6	Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib ***tablets*** are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction.	Clarify the collection of tucatinib tablets
5.1.2.7	Trastuzumab used during the course of the study should be handled according to its package insert. Trastuzumab ***vials*** are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction.	Clarify the collection of trastuzumab vials

Summary of Changes in Amendment 8.2

Section(s)	Change	Rationale
Title page	Added EudraCT number	Administrative change.
Synopsis, 4.1, APPENDIX C	Appendix C was updated. The inclusion criteria number 12 was updated to align with Appendix C. ***d May choose to practice complete abstinence if consistent with the subject's preferred lifestyle, as an acceptable form of contraception*** ~~d.~~***e*** If sexually active in a way that could lead to pregnancy, must consistently use highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration. ***For the full list of highly effective methods of birth control and guidance on contraception r***~~R~~efer to APPENDIX C. ~~for guidance on contraception.~~ ~~Highly effective methods of birth control include:~~ ~~● Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)~~ ~~● Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)~~ ~~● Intrauterine device~~ ~~● Bilateral tubal occlusion/ligation~~ ~~● Vasectomized partner~~ ~~● Sexual abstinence when it is the preferred and usual lifestyle choice of the subject~~	Reflects the latest updates of Seattle Genetics guidance on contraception.

Section(s)	Change	Rationale
Synopsis, 4.1, 7.1, 7.4	HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved ***or CE-marked*** IHC test following the package insert's interpretational manual for breast cancer. 6. Have confirmed HER2-positive mCRC, as defined by having tumor tissue tested at a Clinical Laboratory Improvement Amendments (CLIA)-certified ***or International Organization for Standardization (ISO)-accredited*** laboratory, meeting at least one of the following criteria: a. HER2+ overexpression (3+ immunohistochemistry [IHC]) by an FDA-approved ***or Conformité Européenne (CE)-marked*** HER2 IHC test following the package insert's interpretational manual for breast cancer b. HER2 2+ IHC is eligible if the tumor is amplified by an FDA-approved ***or CE-marked*** HER2 in situ hybridization assay (FISH or chromogenic in situ hybridization [CISH]) following the package insert's interpretational manual for breast cancer c. HER2 (*ERBB2*) amplification by CLIA-certified ***or ISO-accredited*** Next Generation Sequencing (NGS) sequencing assay. Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing (by an FDA-approved ***or CE-marked*** HER2 IHC test following the package insert's interpretational manual for breast cancer). HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved ***or CE-marked*** IHC test following the package insert's interpretational manual for breast cancer.	Added EU-specific language for the local IHC testing.
7.4.2	If at any time, genetic results are obtained that may have clinical relevance, IRB/***IEC*** review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required.	Alligned with the rest of the protocol.

Section(s)	Change	Rationale
1.1, 1.2.1, 1.7, 1.8	Removed US-specific language as appropriate. There are currently no ~~FDA~~ approved therapies for patients with ERBB2 amplified metastatic CRC. After progression on first and second line chemotherapy (FOLFOX and FOLFIRI), the clinical benefit of ~~FDA~~ approved therapies is limited. Once patients with mCRC have progressed on all standard chemotherapy and biological therapies, current ~~FDA~~ approved treatment options include regorafenib and trifluridine/tipiracil (TAS-102). Additionally, trastuzumab is ~~FDA~~ approved as a single-agent and in combination with either chemotherapy or pertuzumab. Trastuzumab will be given at the dose approved ~~by the FDA~~ for single-agent use when administered on a Q3 week cycle.	Removed US-specific language to accommodate the trial expansion in the EU.
3.1.3, 6.6	Updated the End of Study definition ~~The study ends when the last subject completes the last visit, or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first.~~ ***The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.4.1).***	Clarifies the definition of End of Study.
4.3	Menopause is defined clinically as 12 months of amenorrhea in a person ***born female*** over age 45 in the absence of other biological, physiological, or pharmacological causes.	Clarifies the definition of menopause.
Synopsis, 6.3.1, 6.3.2, 6.3.3, 6.4, 7.6, APPENDIX A	Specified that [redacted] apply to Cohorts B and C only. [redacted] will be administered ***for Cohorts B and C*** at: pre-dose Cycle 1 Day 1 (C1D1), C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.	Clarifies the use of questionnaires.
10.0	***For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations***.	Added regulatory considerations for EU/EEA countries.

Summary of Changes in Amendment 9

Section(s)	Change	Rationale
Synopsis, Sections 3.1.3 (Figure 3-1 footnotes a and c), 6.3.4, 7.2, 7.2.1, and Appendix A footnote o.	In these sections text was updated to indicate subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment. In the synopsis this included updated text in the study schema footnotes a and c, and in the "Efficacy Assessments" section.	Procedural clarification describing disease assessments for subjects with documented PD who have continued on study treatment for clinical benefit only. Consistency with detailed updates in Section 6.3.6 about disease assessment procedures.
Synopsis, Sections 3.1.3 (Figure 3-1, footnote e), 7.2.1, and Appendix A footnote u.	In these sections text about requiring new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy was added. In the synopsis this included updates to text in the study schema (footnote e), study design, and duration of treatment sections. In Appendix A, footnote u was added.	Consistency with detailed update about new baseline RECIST assessment added to Section 6.3.6 (see below).
Synopsis, Sections 4.1, and 7.4.3	Inclusion criterion 5 and Section 7.4.3: Added text to indicate subjects must be willing and able to provide most recently available tissue blocks.	To account for instances where latest tissue block is exhausted or not available.
Synopsis, Section 4.1	Inclusion criterion 11 was adjusted as follows: • Platelet count change from 100 to 75 × 10^3/uL and note to contact medical monitor for counts from 75 to 100 × 10^3/uL was deleted as it is no longer relevent. • Hemoglobin values were changed from 9 to 8 g/dL	Adjusted to align with original values used in the investigator-sponsored trial protocol.
Synopsis, Sections 4.2, Section 5.3.1.1, and 5.3.5	Exclusion criterion (EC) 13, Concomitant Therapies (in synopsis), and Sections 5.3.1.1 and 5.3.5 were updated with text about CYP2C8 and CYP3A4 inducers to include the qualifier "strong" and adjusted prohibition of use of strong CYP2C8 inhbitors, strong CYP2C8 or CYP3A4 inducers, or sensitive CYP3A substrates following discontinuation from 2 weeks to 1 week. In Synopsis and Section 4.2 EC 13, removed CYP related text that was covered in Section 5.3.1.1. In Section 5.3.1.1 added text about avoiding sensitive CYP3A substrates 1 week prior to first dose of study treatment and during study treatment. In Section 5.3.5 added new bullet: Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment	Consistency with other tucatinib protocols and current harmonized drug-drug interaction recommendations.

Section(s)	Change	Rationale
	(see APPENDIX H). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.	
Synopsis, Section 4.2	Exclusion criterion 17 was added: Have a hypersensitivity to tucatinib or any of its excipients, to trastuzumab or any of its excipients, or to murine proteins.	New text to align with updates made in tucatinib responses to requests for information.
Sections 3.1, 5.1,	Added cross-reference to Section 6.3.6	Clarification to align with changes made in Section 6.3.6
Section 5.2.3.2	In Table 5-6, removed tucatinib from dose modification guidelines for left ventricular ejection fraction	Based on evaluation of HER2CLIMB data, a causal association between tucatinib and decreased LVEF was not established
Section 5.3.4	Added text indicating moderate CYP2C8 inhibitors should be used with caution.	Consistency with other tucatinib protocols and current harmonized drug-drug interaction recommendations.
Section 5.4	Added text to be consistent with other tucatinib protocols indicating overdose events should be captured on adverse event eCRF per Section 5.4 and reported as discussed in Section 7.7.1.2.	Consistency with other tucatinib protocols
Sections 6.2.2, 6.3.1, 6.3.3, 6.4, 7.7.2, Appendix A footnote f	Aligned vital sign text between these sections.	Consistency between sections
Section 6.3.6 (See Row 2 above as well for related updates)	Added clarification about tucatinib monotherapy and added more detailed text about requiring new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy. As mentioned on Row 2, updates were made throughout the protocol where crossover was discussed to either refer back to this section (Section 6.3.6) and/or to mention requirement for new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy.	Detailed procedural clarifications about new baseline assessments for subjects in Cohort C who crossover from monotherapy to doublet therapy. Consistency with updates in Synopsis, Sections 3.1.3 (Figure 3-1, footnote e), 7.2.1, and Appendix A footnote u.

Section(s)	Change	Rationale
Section 7.7.1.1	Added text to mandate that AESIs be reported within 24 hours to be consistent with other tucatinib studies. Clarified DILI related text – rewrote into text form because table form was potentially ambiguous. Added statement about measuring conjugated and unconjugated bilirubin in cases of hyperbilirubinemia.	Clarifications to be consistent with other tucatinib protocols Clarification only Clarification to assist in determining etiology in cases of hyperbilirubinemia.
Section 7.7.1.2	To "Follow-up for Abnormal Laboratory Results Suggesting Potential DILI", added text about measuring conjugated and unconjugated bilirubin Added text in section called "Dosing Errors" about tucatinib dosing errors and cross-referenced to Section 5.4 Management of Overdose Added text in section called "Left Ventricular Ejection Fraction Decreased" to address reporting for left ventricular ejection fraction decrease and congestive heart failure.	Consistency with updates to Section 7.7.1.1 Consistency with other tucatinib protocols Consistency with other tucatinib protocols
Appendix A	Table 11-2: Added footnote c '[redacted] prior to dosing on Day 1 of Cycle 3 and every 3 cycles thereafter (i.e., Cycle 3, 6, 9 etc.) prior to Protocol Addendum 2 (effective date: 20OCT2017).'	[redacted]
Appendix E	Removed text about CYP3A4 inhibitors	Consistency with other tucatinib protocols
Appendix F	The following changes were made: • Strong Inhibitors list: removed clopidogrel • Moderate Inhibitors List: added clopidogrel, deferasirox, teriflunomide Rifampin was changed to a moderate inducer (instead of strong inducer)	Changes to align with current CYP recommendations.
Appendix G	Added row for 50 and 150 mg pills in Instructions header Added +3 day window for end of cycle clinic visit Clarified text about missing/replacing a dose due to vomiting.	Changes to make the Patient Drug Diary more functional and to clarify missing/replaced doses due to vomiting.
Appendix H	Removed content about P-gp inhibitors (This was in Appendix H content). The former Appendix I "Examples of Clinical Substrates for CYP3A-Mediated Metabolism now becomes Appendix H.	These are no longer prohibited concomitant medications.

Section(s)	Change	Rationale
Appendix I	Added a new appendix to include information about Defining Lines of Therapy. This addition means the Investigator's Signature Page becomes Appendix J	Addition to provide clarifications about protocol specific definitions related to lines of therapy.
Throughout	Administrative changes made, as necessary	To fix errors and ensure clarity