Clinical Study Protocol
Effective Date: 30-Jun-2021

Protocol Title:	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma **(HER2CLIMB)**
Protocol Number:	ONT-380-206
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EudraCT Number:	2015-002801-12
Investigational Product:	Tucatinib (ONT-380)
Version No.	Version 11, 27-Nov-2019, Version 12, 30-Jun-2021 Version 10, 25-Mar-2019; Version 9, 28-Feb-2019; Version 8, 12-Nov-2018; Version 7, 30-Aug-2017, Version 6, 29-Nov-2016, Version 5, 06-Jul-2016, Version 4, 21-Mar-2016, Version 3, 26-Jan-2016, Version 2, 25-Sep-2015, Version 1, 11-Aug-2015
Indication:	Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021
Sponsor Medical Monitor:	PPD Phone: PPD Email: PPD
Serious Adverse Event Reports:	Provided on the SAE report form

Confidentiality Statement

SPONSOR PROTOCOL APPROVAL PAGE

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Version:	Version 12, 30-Jun-2021

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.

PPD

Date

INVESTIGATOR SIGNATURE PAGE

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Version:	Version 12, 30-Jun-2021

By signing this protocol, the investigator confirms that they have read and understood the protocol and agrees to conduct the clinical trial in accordance with this protocol, generally 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. In addition, the investigator agrees to provide the sponsor with such information and certifications as the sponsor shall reasonably request from time to time regarding direct and indirect financial interests and other arrangements between sponsor and investigator, to allow the sponsor to submit complete and accurate certification and disclosure statements as required.

I understand that all documentation provided to me by Seagen or its designated representatives concerning the study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of Seagen and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patient.

Principal Investigator Name (Printed)	Title
Principal Investigator's Signature	Date
Site Address and Telephone Number	

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1 GLOSSARY AND TERMS

5FU	5-fluorouracil
ADL	activities of daily living
AE	adverse event
ALT/SGPT	alanine aminotransferase/serum glutamic-pyruvate transaminase
ANC	absolute neutrophil count
anti-HBc	antibodies to Hepatitis B core
anti-HCV	antibodies to Hepatitis C virus
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
AUC	area under the curve
BICR	blinded independent central review
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum concentration observed
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DCC	Data Coordinating Center
DDI	drug-drug interaction
DFS	disease-free survival
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
ED	emergency department
EGFR	epidermal growth factor receptor
EOI	event of interest
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen

HC	Health Canada
Hct	Hematocrit
HER1	human epidermal growth factor receptor 1
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HIV	human immunodeficiency virus
HR	hazard ratio
IAR	infusion-associated reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
ILD	interstitial lung disease
INR	international normalized ratio
IUD	intrauterine device
IV	Intravenous
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
ITT	Intent-to-Treat
kg	Kilogram
LDH	lactate dehydrogenase
LFT	liver function test
LMD	leptomeningeal disease
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum-tolerated dose
MUGA	multiple-gated acquisition scan
NCI	National Cancer Institute
ONT-380 (tucatinib)	Investigational small molecule inhibitor of HER2
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PIC	powder in capsule
PK	Pharmacokinetics
PO	oral administration
PPE	palmar-plantar erythrodysaesthesia

PR	partial response
PT	prothrombin time
PVP-VA	polyvinylpyrrolidine-vinyl acetate copolymer
QTc	corrected QT
RANO-BM	Response Assessment in Neuro-Oncology – Brain Metastases
RD	recommended dose
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SRS	stereotactic radiosurgery
SUSAR	suspected unexpected serious adverse reaction
T-DM1	ado-trastuzumab emtansine or trastuzumab emtansine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
Tucatinib (ONT-380)	Investigational small molecule inhibitor of HER2
ULN	upper limit of normal
WBRT	whole brain radiation therapy

2 PROTOCOL SYNOPSIS

Protocol Number: ONT-380-206 **Version:** Version 12, 30-Jul-2021 **Phase:** 2	**Product Name:** Tucatinib **Sponsor:** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021
Protocol Title Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma **(HER2CLIMB)**	

Previously, the study sponsor, Seagen, performed the per-protocol primary analysis of this trial. At the time of the primary analysis, the trial met the primary endpoint of progression-free survival (PFS), showing that the addition of tucatinib was superior to trastuzumab and capecitabine alone, with a 46 percent reduction in the risk of disease progression or death (hazard ratio [HR]=0.54 [95% Confidence Interval [CI]: 0.42, 0.71]; p<0.00001). The trial also met the two key secondary endpoints at interim analysis. The tucatinib arm demonstrated an improvement in overall survival (OS), with a 34 percent reduction in the risk of death (HR=0.66 [95% CI: 0.50, 0.88]; p=0.0048) compared to trastuzumab and capecitabine alone. For patients with brain metastases at baseline, the tucatinib arm also demonstrated superior PFS, with a 52 percent reduction in the risk of disease progression or death compared to those who received trastuzumab and capecitabine alone (HR=0.48 (95% CI: 0.34, 0.69); p<0.00001). Due to the statistically significant results, these interim analyses of OS and PFS in patients with brain metastases are considered the final analyses of these endpoints.

Tucatinib in combination with trastuzumab and capecitabine was generally well tolerated with a manageable safety profile. The most frequent adverse events in the tucatinib arm included diarrhea, palmar-plantar erythrodysaesthesia syndrome (PPE), nausea, fatigue, and vomiting. Grade 3 or greater adverse events in the tucatinib arm compared to the control arm included diarrhea (12.9 vs. 8.6 percent), increased aspartate aminotransferase (AST) (4.5 vs. 0.5 percent), increased alanine aminotransferase (ALT) (5.4 vs. 0.5 percent) and increased bilirubin (0.7 vs. 2.5 percent). There was no requirement for prophylactic antidiarrheals. Adverse events leading to discontinuations were infrequent in both the tucatinib arm and the control arm (5.7 and 3.0 percent).

Based on these results, the Sponsor decided to unblind this trial and offer tucatinib to patients on the control arm. Protocol Version 11 established a new Unblinded Phase of the study, and presented study procedures for these 2 distinct phases: the Double-blind Phase and the Unblinded Phase.

An analysis of OS and PFS conducted approximately 2 years after the last patient was randomized to the study demonstrated that the OS benefit with tucatinib was maintained, and PFS per investigator assessment was consistent with the primary analysis (Curigliano 2021). Moreover, the number of OS events observed exceeded the number required for the originally planned final analysis. These data will be included in an addendum to the clinical study report and no additional analyses are planned.

Based on these data, the Sponsor will end the study and a last visit/contact will occur for patients who are still in the study.

Double-blind Phase Study Objectives

Double-blind Phase Primary Objective

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 based on blinded independent central review (BICR)

Double-blind Phase Secondary Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab in patients with brain metastases at baseline, defined as patients with a history of brain metastases, current brain metastases, or equivocal brain lesions at baseline, using RECIST 1.1 based on BICR
- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on OS
- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per RECIST 1.1 based on investigator assessment
- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on objective response rate (ORR) per RECIST 1.1 based on BICR and by the investigator
- To assess the duration of response (DOR) of tucatinib in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR and by the investigator
- To assess the clinical benefit rate (CBR) [stable disease (SD) or non-complete response (CR)/non-progressive disease (PD) for ≥ 6 months, or best response of CR or partial response (PR)] of tucatinib vs. placebo in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR
- To assess the health-related quality of life and health economics associated with tucatinib vs. placebo in combination with capecitabine and trastuzumab based on patient health status collected using the EQ-5D-5L instrument and health resources utilized in patient care

Double-blind Phase Safety Objective

- To assess the safety and tolerability of tucatinib in combination with capecitabine and trastuzumab

Double-blind Phase Pharmacokinetic Objective

- To evaluate the pharmacokinetics of tucatinib and metabolite ONT-993 when administered in combination with capecitabine and trastuzumab

Double-blind Phase Exploratory Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab using RANO-BM by BICR in patients with brain metastases at baseline

- To identify potential biomarkers of response, including human epidermal growth factor receptor 2 (HER2) mutations and other mutations by DNA sequence analyses of ctDNA isolated from plasma samples
- To assess the effect of tucatinib on progression in brain in patients with brain metastases at baseline

Double-blind Phase Endpoints

Double-blind Phase Primary Endpoint

- PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST 1.1), or death from any cause, whichever occurs first

Double-blind Phase Secondary Endpoints

Efficacy

Key Secondary Endpoints

- PFS in patients with brain metastases at baseline using RECIST 1.1 as determined by BICR
- OS

Other Secondary Endpoints

- PFS, defined as the time from randomization to investigator-assessed documented disease progression (per RECIST 1.1), or death from any cause, whichever occurs first
- ORR (RECIST 1.1) as determined by BICR as well as the investigator
- DOR (RECIST 1.1) as determined by BICR as well as the investigator
- CBR (RECIST 1.1) as determined by BICR as well as the investigator

Safety

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab

Pharmacokinetics

- Plasma concentrations of tucatinib and metabolite

Heath Economics and Outcomes

- Cumulative incidence of health resource utilization, including length of stay, hospitalizations and emergency department (ED) visits
- Health-related quality of life / health status using the EQ-5D-5L instrument

Double-blind Phase Exploratory Endpoints

- ORR in brain per RANO-BM as determined by BICR
- Duration of response in brain per RANO-BM as determined by BICR
- Time to brain progression in patients with brain metastases at baseline per RANO-BM as determined by BICR
- Presence of HER2 mutations or other potential biomarkers of response

Unblinded Phase Study Objectives

- To assess the safety and tolerability of tucatinib in combination with capecitabine and trastuzumab
- To assess PFS per RECIST 1.1 by investigator
- To assess OS

Unblinded Phase Endpoints

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab
- PFS per RECIST 1.1 as determined by investigator
- OS

Study Population

Patients with pretreated unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1 (ado-trastuzumab emtansine or trastuzumab emtansine).

Double-blind Phase Eligibility Criteria

Double-blind Phase Inclusion

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

1. Have histologically confirmed HER2+ breast carcinoma, with HER2+ defined by *in situ* hybridization (ISH) or fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) methodology
    a. Tissue blocks or slides must be submitted to confirm HER2 positivity (using ISH or FISH) by a sponsor-designated central laboratory prior to randomization
    b. Centrally confirmed HER2 results (either IHC, ISH, or FISH) from a previous study can be used to determine eligibility for this study with approval from the sponsor
2. Have received previous treatment with trastuzumab, pertuzumab, and T-DM1
3. Have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Have measurable or non-measurable disease assessable by RECIST 1.1
5. Be at least 18 years of age at time of consent
6. Have Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 or 1
7. Have a life expectancy of at least 6 months, in the opinion of the investigator
8. Have adequate hepatic function as defined by the following:
    a. Total bilirubin ≤1.5 X upper limit of normal (ULN), except for patients 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)
9. Have adequate baseline hematologic parameters as defined by:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^3/μL
    b. Platelet count ≥ 100 x 10^3/μL; patients with stable platelet count from 75-100 x 10^3/μL may be included with approval from medical monitor
    c. Hemoglobin ≥ 9 g/dL

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

10. Have creatinine clearance ≥ 50 mL/min as calculated per institutional guidelines or, in patients ≤ 45 kg in weight, a serum creatinine within institutional normal limits

11. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 X ULN unless on medication known to alter INR and aPTT. (Note: Warfarin and other coumarin derivatives are prohibited.)

12. Have left ventricular ejection fraction (LVEF) ≥ 50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) documented within 4 weeks prior to first dose of study treatment

13. If female of childbearing potential, must have a negative result of serum or urine pregnancy test performed within 7 days prior to first dose of study treatment. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Postmenopausal patients with known β-HCG secreting tumors may be eligible when β-HCG-based urine or serum pregnancy tests yield false positive if they meet the definition of postmenopausal state and have a negative uterine ultrasound

14. Women of childbearing potential (as defined above) and men with partners of childbearing potential must agree to use a highly effective birth control method, i.e. methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods 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; intrauterine hormone-releasing system; bilateral tubal occlusion/ligation; vasectomized partner; or sexual abstinence. Male patients with partners of childbearing potential must use barrier contraception. All study patients should practice effective contraception, as described above, starting from the signing of informed consent until 7 months after the last dose of study medication or investigational medicinal product.

15. Patient must provide signed informed consent per a consent document that has been approved by an institutional review board or 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 patient's disease

16. Patients must be willing and able to comply with study procedures

CNS Inclusion – Based on screening contrast brain magnetic resonance imaging (MRI), patients must have **one** of the following:

17. No evidence of brain metastases
18. Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions > 2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment
19. Previously treated brain metastases
    a. 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
    b. Patients 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:
        i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to first dose of study treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to first dose of study treatment, or time since surgical resection is ≥ 28 days
        ii. Other sites of disease assessable by RECIST 1.1 are present
    c. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

Double-blind Phase Exclusion

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

1. Have previously been treated with:
    a. 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)
    b. neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI) at any time previously
2. Have previously been treated with capecitabine (or other fluoropyrimidine [e.g., 5-fluorouracil]) for metastatic disease (except in cases where capecitabine was given for ≤ 21 days and was discontinued for reasons other than disease progression or severe toxicity) Note: Patients who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment are eligible.

3. History of exposure to the following cumulative doses of anthracyclines:
    a. Doxorubicin > 360 mg/m^2
    b. Epirubicin > 720 mg/m^2
    c. Mitoxantrone > 120 mg/m^2
    d. Idarubicin > 90 mg/m^2
    e. Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) > 550 mg/m^2
4. History of allergic reactions to trastuzumab, capecitabine, 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 one of the excipients in the study drugs
5. Have received treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤ 3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies is gonadotropin releasing hormone (GnRH) agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
6. 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; and
    - 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
7. Have clinically significant cardiopulmonary disease such as:
    - ventricular arrhythmia requiring therapy,
    - uncontrolled hypertension (defined as persistent systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg on antihypertensive medications), or
    - any history of symptomatic CHF
    - severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy
    - hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea
    - presence of ≥ Grade 2 QTc prolongation on screening ECG

- conditions potentially resulting in drug-induced prolongation of the QT interval or torsade de pointes:
    a. Congenital or acquired long QT syndrome
    b. Family history of sudden death
    c. History of previous drug induced QT prolongation
    d. Current use of medications with known and accepted associated risk of QT prolongation (see row "Accepted Association" in Appendix H)

8. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
9. Are known carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease
10. Are known to be positive for human immunodeficiency virus (HIV)
11. Are pregnant, breastfeeding, or planning a pregnancy
12. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)
13. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
14. Have used a strong CYP3A4 or CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 days prior to first dose of study treatment (see Appendix C and Appendix D)
15. Have known dihydropyrimidine dehydrogenase deficiency
16. Unable for any reason to undergo contrast MRI of the brain
17. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
18. Have evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment

CNS Exclusion – Based on screening brain MRI, patients must not have any of the following:

19. Any untreated brain lesions > 2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given
20. 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, patients on a chronic stable dose of ≤ 2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor

21. 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 patient (e.g. brain stem lesions). Patients 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 criteria 19b
22. Known or suspected leptomeningeal disease (LMD) as documented by the investigator
23. Have poorly controlled (> 1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Unblinded Phase Crossover Criteria

Crossover Inclusion Criteria

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) must meet the inclusion criteria below at the time of crossover screening to be eligible to crossover to the experimental arm. Prior scans and imaging may be used for crossover inclusion/exclusion criteria and tumor burden if these were collected within 6 weeks prior to the time of the patients signing the crossover consent for this Unblinded Phase of the study.

1. Have measurable or non-measurable disease assessable by RECIST 1.1
2. For patients who were randomized to the control arm and on the long-term follow-up period at the time of the crossover screening: have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
3. Have ECOG PS 0 or 1
4. Have a life expectancy of at least 6 months, in the opinion of the investigator
5. Have adequate hepatic function as defined by:
    a. Total bilirubin ≤1.5 X upper limit of normal (ULN), except for patients 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)
6. Have adequate hematologic parameters as defined by:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x $10^3/\mu L$

b. Platelet count ≥ 100 x 10^3/μL; patients with stable platelet count from 75-100 x 10^3/μL may be included with approval from medical monitor

c. Hemoglobin ≥ 9 g/dL

d. In patients transfused before crossover screening, transfusion must be ≥ 14 days prior to start of crossover treatment to establish adequate hematologic parameters independent from transfusion support

7. Have creatinine clearance ≥ 50 mL/min as calculated per institutional guidelines or, in patients ≤ 45 kg in weight, a serum creatinine within institutional normal limits

8. Have left ventricular ejection fraction (LVEF) ≥ 50% as assessed by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) documented within 6 weeks prior to the time of crossover screening

9. For patients of childbearing potential, 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 starting crossover study treatment. A subject with a false positive result and documented verification that the patient is not pregnant is eligible for starting crossover study treatment.

   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:

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

10. For patients 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

11. Patient must provide signed informed consent per a consent document that has been approved by an institutional review board or 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 patient's disease

12. Patients must be willing and able to comply with study procedures

CNS Inclusion – Based on crossover screening contrast brain magnetic resonance imaging (MRI) within 6 weeks prior to the time of crossover screening, patients must have **one** of the following:

13. No evidence of brain metastases

14. Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions > 2.0 cm on the crossover screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment

15. Previously treated brain metastases

    a. 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

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

        i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to start of crossover (tucatinib) treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to start of crossover (tucatinib) treatment, or time since surgical resection is ≥ 28 days prior to start of crossover (tucatinib) treatment

        ii. Other sites of disease assessable by RECIST 1.1 are present

Crossover Exclusion Criteria

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) will be excluded if they meet any of the exclusion criterion below. Prior scans and imaging may be used for crossover inclusion/exclusion criteria and tumor burden if these were collected within 6 weeks prior to the time of the patients signing the crossover consent for this Unblinded Phase of the study.

1. Discontinuation of study treatment (placebo + trastuzumab + capecitabine) due to an adverse event while on the double-blind phase of the study. If the adverse event leading to discontinuation of study treatment has resolved, the patient may be allowed to crossover with approval from the medical monitor.
2. History of exposure to the following cumulative doses of anthracyclines:
    a. Doxorubicin > 360 mg/m^2
    b. Epirubicin > 720 mg/m^2
    c. Mitoxantrone > 120 mg/m^2
    d. Idarubicin > 90 mg/m^2
    e. Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) > 550 mg/m^2
3. History of allergic reactions to trastuzumab, capecitabine, 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 one of the excipients in the study drugs
4. Have received treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤ 3 weeks prior to start of crossover (tucatinib) treatment or are currently participating in another interventional clinical trial. Ongoing treatment with trastuzumab + capecitabine as part of this trial is not exclusionary. An exception for the washout of hormonal therapies is gonadotropin releasing hormone (GnRH) agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
5. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1 (ongoing treatment with trastuzumab + capecitabine as part of this trial is not exclusionary), 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
6. Have clinically significant cardiopulmonary disease such as:

- ventricular arrhythmia requiring therapy,
- uncontrolled hypertension as determined by investigator,
- any history of symptomatic CHF,
- severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy, or
- hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea

7. Have known myocardial infarction or unstable angina within 6 months prior to start of crossover (tucatinib) treatment
8. Are known carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease
9. Are known to be positive for HIV
10. Are pregnant, breastfeeding, or planning a pregnancy
11. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)
12. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
13. Have used strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a CYP2C8 or CYP3A4 inducer within 5 day prior to start of crossover (tucatinib) treatment. Strong CYP2C8 inhibitors and CYP2C8 or CYP3A4 inducers are also prohibited in the 2 weeks following discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks prior to start of crossover (tucatinib) treatment
14. Have known dihydropyrimidine dehydrogenase deficiency
15. Unable for any reason to undergo contrast MRI of the brain
16. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
17. Have evidence within 2 years prior to start of crossover (tucatinib) treatment of another malignancy that required systemic treatment

CNS Exclusion – Based on crossover screening contrast brain MRI within 6 weeks prior to the time of crossover screening, patients must not have any of the following:

18. Any untreated brain lesions > 2.0 cm in size, unless discussed with medical monitor and approval for crossover enrollment is given
19. 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, patients on a

chronic stable dose of ≤ 2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor

20. 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 patient (e.g. brain stem lesions). Patients who undergo local treatment for such lesions identified by crossover screening contrast brain MRI may still be eligible for crossover enrollment based on criteria described under CNS inclusion criteria 15b
21. Known or suspected leptomeningeal disease (LMD) as documented by the investigator
22. Have poorly controlled (> 1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Study Design

DOUBLE-BLIND PHASE

A Double-blind Phase study schematic is presented in Figure 5-1.

In this phase, the study is a randomized, international, multi-center, double-blind study of tucatinib or placebo in combination with capecitabine and trastuzumab in patients with pretreated unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1. After signing informed consent and meeting all eligibility criteria, patients will be randomized in a 2:1 ratio to receive tucatinib or placebo in combination with capecitabine and trastuzumab.

Randomization will be made using a dynamic hierarchical randomization schema. Stratification factors will include presence or history of treated or untreated brain metastases or brain lesions of equivocal significance (yes/no), ECOG PS (0 vs. 1), and region of world (US vs. Canada vs. Rest of World). Stratification for presence of brain metastases will be based upon medical history and investigator assessment of screening contrast brain MRI.

Treatment will be administered in cycles of 21 days each. Tucatinib 300 mg or placebo will be given orally twice daily (PO BID). Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV) followed by 6 mg/kg once every 21 days, except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule. In instances of subcutaneous trastuzumab use, a fixed dose of 600 mg is administered without a loading dose. Following an IV loading dose of trastuzumab, 6 mg/kg of trastuzumab is administered once every 21 days, except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule. Subcutaneous trastuzumab is given only once every three weeks as there is no allowance for weekly dosing. There is no ability to modify the trastuzumab dose when administered subcutaneously. Dose modifications of tucatinib or placebo and capecitabine will be allowed. Dose holding or discontinuation of tucatinib or placebo, capecitabine, and trastuzumab will also be allowed as needed for patient safety. Patients who discontinue either capecitabine

or trastuzumab (but not both) may remain on study treatment. Patients who discontinue tucatinib or placebo, or both capecitabine and trastuzumab will not be allowed to remain on study treatment but will continue to be followed for efficacy assessments per protocol schedule.

Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. In the absence of clear evidence of disease progression (per RECIST 1.1), development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the patient, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST 1.1.

After discontinuing study treatment, patients may receive further care as determined by their physician. No crossover from placebo to tucatinib will be allowed while patients are on this phase of the study. It is planned that patients will be followed for efficacy endpoints after treatment discontinuation until the protocol specified number of events (both PFS and OS) are observed or the primary and key secondary endpoints are met.

Safety monitoring will be performed by the sponsor throughout the study on a blinded basis. An independent Data Monitoring Committee (DMC) will regularly review all relevant safety data (blinded and unblinded) as outlined in a separate DMC charter. Ad hoc meetings of the DMC may be held upon the request of the sponsor or DMC.

UNBLINDED PHASE

An Unblinded Phase study schematic is presented in Figure 5-2.

With the implementation of protocol version 11, the double-blind phase of the study ended and all patients were unblinded to their treatment assignment.

- Patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine) and are receiving study treatment at the time of unblinding will continue on that treatment arm with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and Appendix A.2). For these patients, the treatment cycle counting will continue from prior to the unblinding, and patients will continue study treatment at the same doses they were given in the double-blind phase of the study.

- Patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine), ended study treatment and are in the long-term follow-up are not eligible for additional treatment on the experimental arm in this study and will remain in long-term follow-up.

- Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are receiving study treatment at the time of unblinding may crossover to the experimental arm if crossover criteria are met.

    - If the patient does not meet crossover criteria, the patient will continue trastuzumab + capecitabine therapy. At the start of the next scheduled cycle, the patient will continue trastuzumab + capecitabine therapy with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and

Appendix A.3). These patients will continue trastuzumab + capecitabine therapy at the same doses they were given in the double-blind phase of the study.

- Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are in long-term follow-up at the time of unblinding may crossover to the experimental arm if crossover criteria are met.
    - If the patient does not meet crossover criteria, the patient will remain in long-term follow-up

Treatments Administered in the Unblinded Phase

In the unblinded phase of the study, tucatinib will be given in combination with trastuzumab and capecitabine. Treatment will be administered in repeating 21-day cycles.

- Patients randomized to the experimental arm will continue tucatinib + trastuzumab + capecitabine at the same doses they were given in the double-blind phase of the study, using a modified schedule of events as outlined in Appendix A.2.
- Patients who were randomized to the control arm and meet crossover criteria will be given:
    - Tucatinib 300 mg orally twice daily (PO BID) every day (Days 1–21) of each 21-day cycle using a modified schedule of events as outlined in Appendix A.3.
    - Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle. For patients who required dose reductions of capecitabine, capecitabine must be given at the same reduced dose most recently given in the double-blind phase of the study.
    - The initial dose of trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV), unless trastuzumab was administered within the prior 4 weeks, then the initial dose of trastuzumab will be administered at a dose of 6 mg/kg. Each trastuzumab dose is given once every 21 days, except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule. Subcutaneous trastuzumab is given only once every three weeks as there is no allowance for weekly dosing. There is no ability to modify the trastuzumab dose when administered subcutaneously.

Dose modifications of tucatinib and capecitabine will be allowed. Dose holding of tucatinib or dose holding and/or discontinuation of capecitabine and trastuzumab will also be allowed as needed for patient safety. Patients who discontinue either capecitabine or trastuzumab may remain on study treatment. In instances where capecitabine and trastuzumab have been discontinued, patients may remain on study treatment with tucatinib alone. Patients who discontinue tucatinib will not be allowed to remain on study treatment. Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

Number of Planned Patients and Investigators/Centers

The study will enroll approximately 600 patients. It will involve approximately 100 sites in North America and approximately 100 sites in the rest of the world, with planned enrollment over approximately 48 months. This study completed enrollment during the Double-blind Phase; no additional patients will be enrolled during the Unblinded Phase.

Study Assessments

DOUBLE-BLIND PHASE

Baseline Assessments

Optional prescreening to confirm HER2 positivity by central review is permitted at any time prior to study screening, after signing a separate pre-screening consent form. There will be a screening period of up to 28 days after patients sign main informed consent. During that time, contrast MRI of the brain will be performed in all patients. All patients will also undergo high quality spiral contrast computed tomography (CT), PET/CT (if high quality CT scan included) and/or contrast MRI scan imaging, including at a minimum the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging). Blood samples for hematology, coagulation, chemistry, and liver function tests will be drawn. Testing for Hepatitis B and C, urinalysis, and ECG will also be performed, along with assessment of cardiac ejection fraction by MUGA or ECHO. Pregnancy testing (except in men or in women of non-childbearing potential) will be performed within 7 days of first study treatment. Patients will also have a blood sample drawn to assess for certain biomarkers of response, including analysis of mutations in circulating tumor DNA (ctDNA).

Safety Assessments

Patients will be assessed throughout the study for safety. Safety assessments including physical exam and collection of AEs and laboratory abnormalities will be performed at a minimum of once every three weeks throughout study treatment and 30 days after the last dose of study drugs. Laboratory assessments will be performed locally. During Cycle 1, an in-person safety assessment will be performed on Days 1 and 12. During Cycle 2, an in-person safety assessment will be performed on Day 1 and liver function tests (AST/ALT and total bilirubin) will be collected on Cycle 2 Day 12. An in-person safety assessment will then be performed on Day 1 of each cycle throughout the remainder of the study or as clinically indicated. 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 irrespective of dose delays or interruption, and 30 days after the last dose of study drugs (unless done within 12 weeks prior to 30-day follow-up visit).

Efficacy Assessments

Efficacy assessments will include measurement of all known sites of metastatic or locally advanced unresectable disease (including at a minimum the chest, abdomen, and pelvis) by high quality spiral contrast CT, PET/CT (if high quality CT scan included) and/or MRI scan as appropriate, as well as appropriate imaging of any other known sites of disease (e.g. skin lesion photography, bone imaging) at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter, irrespective of dose

holdings or interruptions. Efficacy assessments for each patient will continue until a PFS event has been documented. Follow-up for survival will continue until death, withdrawal of consent, or study closure. Contrast MRI of the brain will be required on this same schedule only in those patients with prior history of brain metastases or with brain metastases or equivocal brain lesions at screening. Contrast brain MRI may also be performed in patients without known brain metastases if there is clinical suspicion of new brain lesions. Additional imaging such as nuclear medicine bone scan or other unscheduled scans may be performed at the discretion of the investigator. Treatment decisions will be made based upon local assessment of radiologic scans. Patients in both arms of the study will continue to be followed for OS after completion of study treatment as well as after the occurrence of disease progression.

Pharmacokinetic Assessments

Pharmacokinetic assessments of trough levels of tucatinib and metabolite drug levels will be performed on Day 1 of Cycles 2-6 prior to administration of tucatinib or placebo. On Day 1 of Cycle 3, pharmacokinetic assessments of peak levels of tucatinib and metabolite drug levels will be performed 1–4 hours after administration of tucatinib or placebo.

Health Economic Assessments

The EQ-5D-5L questionnaire will be administered to assess patient health-related quality of life / health status information. Administration will occur at Cycle 1 Day 1 prior to the start of study drug treatment and then every six weeks for 24 weeks and then every 9 weeks until disease progression, death, toxicity, withdrawal of consent or study closure. Additionally, a post-treatment assessment will occur approximately 30-days post end of treatment. Health resource utilization data are also collected, including procedures that occur on study, length of stay, hospitalizations, ED visits, planned and unplanned provider visits, medication use, radiology, and other treatments or procedures.

Assessments after Treatment Discontinuation

A final routine, safety assessment including physical examination and laboratory assessments will be required approximately 30 days after discontinuation of study treatment. For patients who discontinue study treatment for reasons other than disease progression per RECIST 1.1, repeat imaging of all known areas of metastatic or locally advanced unresectable disease will also be requested until disease progression per RECIST 1.1 or death. A repeat contrast MRI of the brain is required in all patients following treatment discontinuation (unless a contrast brain MRI was performed within 30 days of treatment discontinuation or prior documentation of CNS progression while on study). Patients will also have a blood sample drawn to assess for the presence of certain potential biomarkers of response, including analysis of mutations in ctDNA.

Blinding

This phase of the study will be double-blinded. The patients, personnel in contact with study patients, data collection personnel, and others associated with patient procedures or data handling will be blinded to the treatment allocation. The sponsor will have limited access to treatment allocation only in the event of a

suspected unexpected serious adverse reaction (SUSAR) where unblinding for regulatory purposes becomes necessary. All SUSARs will be reported in accordance with local regulatory requirements.

Unblinded data including deaths, discontinuations, dose reductions, AEs, and serious adverse events (SAEs) will be monitored regularly by an independent DMC. Further details will be provided in the DMC charter.

UNBLINDED PHASE

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are receiving study treatment at the time of unblinding will continue trastuzumab + capecitabine treatment at the same doses they were given in the double-blind phase of the study.

Screening for Crossover Criteria

Patients who were randomized to the control arm who wish to crossover to receive tucatinib will undergo a screening period of up to 28 days after signing the revised informed consent. During that time patients will also undergo contrast MRI brain scan imaging in addition to CT, PET/CT, or MRI imaging to include, at a minimum, the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging) for an assessment of tumor burden. Based on this crossover screening imaging, new baseline RECIST lesions will be selected by the investigator.

Cardiac ejection fraction will be assessed by MUGA and ECHO. If an MRI of the brain, systemic imaging for assessment of tumor burden (e.g., CT, PET/CT, or MRI), or cardiac imaging for assessment of ejection fraction have been performed while on the double-blind phase of the study or as part of standard of care within the prior 6 weeks, those assessments can be used for crossover screening purposes. Blood samples for hematology, chemistry, and liver function tests will be drawn. Pregnancy testing (except in men or in women of non-childbearing potential) will be performed within 7 days prior to start of crossover (tucatinib) treatment.

Tumor Response Assessments

The investigator will determine the frequency and method of tumor assessments performed for patient care decisions according to routine clinical practice, with a maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.

Safety Assessments

Patients will be assessed throughout the study for safety. Safety assessments including physical exam and collection of AEs and laboratory abnormalities will be performed at a minimum of once every three weeks throughout study treatment and 30 days after the last dose of study drugs. Cardiac ejection fraction assessments should be continued to be assessed by MUGA scan or ECHO at least once every 12 weeks. Laboratory assessments will be performed locally.

Assessments after Treatment Discontinuation

A final routine, safety assessment including physical examination and laboratory assessments will be required approximately 30 days after discontinuation of study treatment. Patients will continue in long-term follow-up per the schedule of events as outlined in Appendix A.2 and in Appendix A.3, as appropriate.

BOTH the Double-blind and Unblinded Phases

Continuation on Study Treatment After CNS-Only Progression

If a patient is found to have radiographic progressive disease per RECIST 1.1 based on isolated progression in the CNS (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 patient may be eligible to continue on study drugs after completion of local treatment (radiotherapy or surgery) of the brain/dural metastases to allow for clinical benefit. Continuation of study treatment requires discussion with and documented approval from the study medical monitor and may continue until either systemic progression or a second isolated CNS progression. Because this approach approximates common practice off-study in this clinical scenario, the duration of treatment after the CNS-only progression will be analyzed as an exploratory objective. The patient will remain on the same treatment regimen that they were receiving prior to receipt of CNS-directed therapy, and may continue on study provided the following criteria are met and the patient continues to receive clinical benefit:

- The patient is not experiencing any worsening of cancer-related symptoms. Patients who are clinically deteriorating and unlikely to receive further benefit from continued treatment should discontinue study treatment.
- The patient is tolerating study drug
- Approval by the medical monitor
- Patient has no evidence of unequivocal systemic progression
- Patient has not had a previous isolated CNS progression on tucatinib while 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. Oral study drugs (tucatinib/placebo and capecitabine) are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib is unknown. Capecitabine is a known radiation sensitizer and therefore needs to be held prior to CNS-directed radiotherapy. Trastuzumab has been shown not to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study drugs may be re-initiated 7 days or more after completion of SRS/SRT, 21-days or more after WBRT and 28-days or more after surgical resection. Plans for holding and re-initiating study drugs before and after local therapy will require discussion with, and documented approval from, the medical monitor.

Following CNS-directed therapy for isolated CNS disease progression, RECIST 1.1 criteria would continue to measure a CNS target lesion(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.

For patients in the double-blind phase: 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 progressive disease by RECIST 1.1 unless clinically necessary in the opinion of the investigator. The rationale for this is that target lesions, once treated with local CNS therapy, cannot be adequately assessed for subsequent response to systemic therapy. Because of this, if a patient 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 1.1 assessment.

Dose Modifications

Dose modification is required for certain clinical AEs and for significant changes in hepatoxicities or measured cardiac ejection fraction. Dose modification for other toxicity is permitted at the investigator's discretion.

Dose reduction of tucatinib or placebo may be made in 50, 100, or 150 mg/dose steps. Dose reduction of capecitabine must be performed as outlined in the protocol and dose reduction of trastuzumab is not allowed. Doses of any study drug may be held for up to six weeks for toxicity, surgical procedure, or during radiation therapy; longer holds will require approval from the medical monitor.

Prohibited Concomitant Therapies

Use of 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 (for double-blind) or prior to the start of crossover (tucatinib) treatment (see Appendix C and Appendix D). Strong CYP2C8 inhibitors and CYP2C8 or CYP3A4 inducers are also prohibited as concomitant medications during the study and in the 2 weeks following discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks before enrollment (for both double-blind and unblinded phases) and during study treatment. Warfarin therapy, or therapy with other coumarin derivatives is not permitted on the study. The use of corticosteroids at a daily dose of > 2 mg dexamethasone or equivalent for control of symptoms of brain metastases is not permitted at the time of study entry.

Allowed Concomitant Therapy

Standard supportive care measures, including anti-emetics, anti-diarrheal medications, permitted concomitant medications, and hematopoietic support, are permitted but not required.

Statistical Methods

DOUBLE-BLIND PHASE

Data collected in this study will be presented using summary tables, patient 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, 95% 2-sided, will be presented where needed to gauge the strength of evidence for a corresponding estimated treatment effect.

Disease evaluations will be performed both by BICR and by investigators using RECIST 1.1 criteria. Discrepancies between the BICR and investigator's assessment will be summarized descriptively. For the exploratory efficacy endpoints, disease evaluation will be performed using RANO-BM criteria.

Efficacy Analyses

For the primary endpoint of centrally-reviewed PFS, the two treatment groups will be compared using a 2-sided log-rank test. To reflect the method of randomization (dynamic randomization), a re-randomization based procedure will be implemented (Rosenberger 2015) taking into account the stratification factors: [known history of treated or untreated brain metastases (yes/no); ECOG PS (0 vs. 1); and region of world (US vs. Canada vs. Rest of World)]. The first 480 randomized patients 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 analysis methods will be used to analyze the key secondary endpoints of PFS for the subgroup of patients with brain metastases at baseline (PFS_{BM}), as well as for OS in the overall ITT population.

Health-Related Quality of Life

The treatment and placebo group index value changes will be summarized. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes.

Health Care Resource Utilization

Analysis of health utilization by resource utilization category will rely primarily on descriptive summary statistics and confidence intervals.

Pharmacokinetic Analyses

Individual (patient) plasma tucatinib and ONT-993 concentrations at each sampling time will be listed and summarized. Additional exploratory pharmacokinetics analyses may be conducted.

Exploratory analyses investigating the relationship between tucatinib exposure and efficacy and safety endpoints may be conducted.

Safety Analyses

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, 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 Common Toxicity Criteria for Adverse Events (CTCAE v4.03) criteria. Separately, all SAEs and AEs of special interest (e.g., any drug-induced liver injury, asymptomatic left ventricular systolic dysfunction, and/or cerebral edema) will also be listed.

All collected AE data will be listed. All treatment-emergent AEs will be summarized by treatment group, as follows:

- All AEs (regardless of grade)
- All Grade 3/4/5 AEs
- All drug-related AEs (regardless of grade)
- All AEs leading to study drug discontinuations
- All SAEs, including deaths
- All AEs of special interest (regardless of grade)

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

Laboratory values (hematology, chemistry, and liver function) will be summarized by treatment group. Abnormal laboratory values (relative to respective normal ranges) will be flagged in listings.

The frequency and percentage of patients with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs. Cardiac ejection fraction data will also be summarized by treatment group, along with corresponding shift tables.

Extent of exposure for tucatinib, capecitabine, and trastuzumab including frequency of dose holding, dose reductions, and dose discontinuations, as well as treatment compliance (percent of actual to planned dosing) will be summarized by treatment group.

Sample Size Considerations

The sample size for this study was calculated based on maintaining 90% power for the primary endpoint PFS with an alpha of 0.05 and 80% power for OS with an alpha of 0.02.

For PFS, 288 events are required with 90% power to detect a hazard ratio of 0.67 (4.5 months median PFS in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test and alpha of 0.05.

For OS, 361 events are required with 80% power to detect a hazard ratio of 0.70 (15 months median OS in the control arm vs. 21.4 months in the experimental arm) using a 2-sided log-rank test and alpha of 0.02. With 361 OS events, it will provide 88% power using a 2-sided log-rank test and alpha of 0.05.

For PFS_{BM}, 220 events are required with 80% power to detect a hazard ratio of 0.67 (4.5 months median PFS_{BM} in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test at alpha of 0.05. The power will be 74% at 2-sided alpha of 0.03.

Approximately, 600 patients will be randomized in a 2:1 ratio to either the experimental arm or the control arm. Assuming an accrual period of 48 months and a 5% yearly drop-out rate, it is expected that 361 OS events will be observed approximately 59 months after first patient randomized.

UNBLINDED PHASE

Safety data will be summarized for the patients who receive study treatment in the unblinded phase. PFS per RECIST 1.1 by investigator and OS will be summarized at approximately 2 years after the last patient was randomized in this study.

3 BACKGROUND AND RATIONALE

3.1 HER2+ Breast Cancer

Breast cancer is the most common form of cancer in women worldwide (Bray 2017), and the second leading cause of cancer-related death in the United States (U.S. Cancer Statistics Working Group 2010).Approximately 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) [3, 4] 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 therapy or a small molecule tyrosine kinase inhibitor (TKI) has led to significant and ongoing improvements in disease-free survival (DFS), progression-free survival (PFS), and OS in both the adjuvant and metastatic settings (Slamon 2001; Geyer 2006; Baselga 2012b; Verma 2012). Trastuzumab, a humanized anti-HER2 antibody, remains the backbone of treatment in the adjuvant and first-line metastatic settings, usually in combination with a taxane. Anti-HER2 therapy in combination with cytotoxic chemotherapy allows for concurrent treatment with agents having two different mechanisms of action, leading to greater efficacy than with either agent alone (TYKERB Prescribing Information, Novartis Pharmaceuticals Corp., Feb 2021) (Slamon 2001; Vogel 2002).

Despite the improvements in outcomes for early stage HER2+ breast cancer, up to a quarter of all patients treated with anti-HER2 therapy in the adjuvant setting relapse. The development of new HER2 targeted therapies such as pertuzumab and T-DM1 (ado-trastuzumab emtansine or trastuzumab emtansine) for metastatic HER2+ breast cancer has led to a meaningful prolongation in the median survival of these patients; however, essentially all patients in the metastatic setting ultimately progress. Treatment failures may result from primary or acquired resistance to HER2 blockade (Lu 2001; Nahta 2006; Scaltriti 2007; Pohlmann 2009).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 such as trastuzumab 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 through utilization of an alternative mechanism of receptor inhibition. Lapatinib, a dual epidermal growth factor receptor (EGFR)/HER2 oral TKI, has been shown to have increased activity in combination with trastuzumab compared to lapatinib alone, even when given to patients who have previously progressed on prior trastuzumab-based therapy (Blackwell 2010; Blackwell 2012).Use of lapatinib, however, has been limited by the anti-EGFR/human epidermal growth factor receptor 1 (HER1) activity of the drug, which results in toxicities such as rash, diarrhea, and fatigue. There is therefore a need for a

more selective small molecule inhibitor of HER2 that could be combined with other anti-HER2 therapies to improve clinical outcomes.

The current standard of care for patients with HER2+ metastatic disease consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line treatment for metastatic disease, followed by T-DM1 in second line (Giordano 2014). Treatment options for patients who progress after treatment with both pertuzumab and T-DM1 remain relatively limited. Patients are generally treated with a continuation of anti-HER2 therapy (in the form of trastuzumab or lapatinib) in combination with cytotoxic chemotherapy, such as capecitabine. Combined HER2 therapy with trastuzumab and lapatinib can also be considered. However, no single regimen is considered the standard of care in this setting and better options for these patients are needed.

3.1.1 Brain Metastases in HER2+ Breast Cancer

Perhaps the greatest unmet medical need in the post-trastuzumab era is treatment and prevention of brain metastases. Recent data suggest that the incidence of first relapse occurring in the brain is increasing in patients who have received trastuzumab-based adjuvant therapy, (Clayton 2004) and approximately 30-50% of HER2+ patients with metastatic disease will develop brain metastases (Clayton 2004; Goldhirsch 2013; Pestalozzi 2013).The increasing prevalence of brain metastases in HER2+ breast cancer patients may be due to several factors. First, HER2+ breast cancer appears to display tropism for the brain. Second, with better control of non-CNS disease, patients may be living longer allowing brain metastases to become more of a critical clinical issue. Finally, the brain may represent a sanctuary site for HER2+ disease as large molecules, such as trastuzumab, do not penetrate the blood-brain barrier (Lin 2004).

Treatment options for brain metastases are limited. There is no specific systemic treatment regimen approved for brain metastases, and treatment currently relies heavily on the use of local therapies such as whole brain radiation therapy (WBRT), stereotactic radiation (SRS), or surgery. Patients may also receive chemotherapy alone, or capecitabine and either lapatinib or trastuzumab, although brain response rates are generally modest (Ekenel 2007; Ramakrishna 2014). The development of HER2-targeted systemic therapies with clinical benefit in both brain and non-CNS sites of disease could lead to improved clinical outcomes, both by improving overall PFS and OS as well as by avoiding or delaying the use of radiation therapy and its associated toxicities, including neurocognitive impairment.

3.2 Tucatinib

3.2.1 Product Description and Mechanism of Action

Tucatinib is an orally available, reversible HER2 small molecule tyrosine kinase inhibitor that is being developed as a novel treatment for HER2+ breast cancer. One of the key features of tucatinib is its potency and selectivity for HER2 compared to the closely related kinase EGFR. With a >1000 fold increase in potency for HER2 inhibition compared to EGFR, tucatinib has the potential to inhibit HER2 signaling while avoiding known EGFR-related side effects [e.g., severe skin rash and gastrointestinal (GI) toxicity]. This unique feature differentiates tucatinib from other HER2 inhibitors, including neratinib and lapatinib, which inhibit HER2 and EGFR with similar potency and have been associated with side effects associated with EGFR inhibition.

3.2.2 Nonclinical Studies

A detailed description of nonclinical studies can be found in the Investigator's Brochure (IB).

3.2.3 Clinical Studies

See the IB for current data on all tucatinib studies.

3.2.4 Tucatinib in the Treatment of Brain Metastases

Both Study ONT-380-004 (tucatinib + T-DM1) and Study ONT-380-005 (tucatinib + capecitabine, trastuzumab or capecitabine and trastuzumab) have enrolled patients with either previously treated stable brain metastases, untreated brain metastases, or previously treated and progressive brain metastases. Patients were considered evaluable for response in brain if they had brain lesions that had never been treated, or lesions that had clearly progressed after prior local therapy (either WBRT, SRS, or surgical resection). Patients were considered not evaluable for response in brain if they had a history of brain metastases which were previously treated with local therapy, but which were stable or decreased in size since local therapy. Response in brain was evaluated using a modified RECIST 1.1 criteria which assessed response by considering the unidimensional sum of the longest diameters of identified target brain metastases only, as well as considerations for neurological deterioration and steroid use. Refer to the Investigator's Brochure for additional information.

Tucatinib has demonstrated early signs of activity in brain metastases using multiple combinations, including combinations with either capecitabine and/or trastuzumab. In some patients, treatment resulted in radiographic tumor responses as well as prolonged stabilization of disease, even in patients with progressing brain metastases at the time of study entry.

3.3 Potential Risks, Benefits and Rationale for the Combination of Tucatinib with Capecitabine and Trastuzumab in a Phase 2 Study

Overall, tucatinib has been associated with an acceptable safety profile and has demonstrated both single-agent and combination anti-tumor activity, including in patients with progression after multiple prior HER2-directed therapies, and in patients with either untreated or previously radiated brain metastases. The combination of tucatinib with capecitabine and trastuzumab in a Phase 1b study ONT-380-005 has demonstrated acceptable toxicity, with the majority of AEs Grade 1 or 2 in severity. Infrequent Grade 3 or greater AEs and ALT/AST elevations not due to progressive disease have been reversible with interruption of dosing and/or dose reduction.

Given the overall safety profile of tucatinib, and the signs of clinical activity seen in Phase 1 studies, the potential benefits of tucatinib outweigh the risks in patients with progressive, incurable, unresectable locally advanced or metastatic HER2+ breast cancer after prior treatment with standard of care first and second-line therapies. This study proposes to further evaluate the potential benefit of tucatinib by adding tucatinib or placebo to the combination of capecitabine and trastuzumab in a randomized, blinded trial.

3.3.1 Trastuzumab

Trastuzumab is a humanized anti-HER2 antibody that binds to subdomain IV of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2 cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand-independent HER2-mediated mitogenic signaling (Arteaga 2011).

The clinical benefit of trastuzumab in women with metastatic breast cancer has been demonstrated in multiple clinical studies. One large open label randomized Phase 3 study (Slamon 2001), showed that, compared to chemotherapy alone, the addition of trastuzumab significantly increased PFS, ORR, median duration of response, and OS. Based on these data, trastuzumab was approved for use in HER2-overexpressing metastatic breast cancer (MBC) in combination with paclitaxel for first-line treatment and as a single agent for patients whose cancers progressed after prior chemotherapy for metastatic disease.

Since this initial pivotal clinical trial, data have emerged demonstrating efficacy of trastuzumab in the metastatic setting combined with a variety of chemotherapeutic agents as well as other targeted HER2 agents. Data support the use of trastuzumab in multiple lines of treatment in the setting of metastatic disease, even after failure of first line regimens that included trastuzumab and a taxane (Giordano 2014). The value of continued use of trastuzumab was demonstrated in a randomized trial comparing capecitabine vs. capecitabine plus trastuzumab in patients who had progressed through a prior trastuzumab-containing regimen. Patients who received the combination

experienced superior PFS and OS compared to patients assigned to capecitabine alone (von Minckwitz 2009). In a randomized Phase 3 trial comparing lapatinib, an oral EGFR/HER2 TKI, with or without trastuzumab in patients with trastuzumab-refractory breast cancer, the combination was associated with a prolongation of PFS and OS, supporting the concept of dual HER2 blockade, even in the setting of progression on prior trastuzumab-containing regimens (Blackwell 2010; Blackwell 2012).

3.3.2 Capecitabine

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

The clinical benefit of capecitabine in women with metastatic breast cancer has been demonstrated in multiple clinical studies. Use of capecitabine as monotherapy was evaluated in an open-label, single-arm trial in 162 patients with stage IV breast cancer (XELODA Prescribing Information, Genentech, Inc., May 2021). Capecitabine was given at 1250 mg/m^2 BID for 2 weeks followed by a one week rest period. Among patients with measurable disease, there was a response rate of 18.5% (1 CR, 24 PRs, with a median time to progression of 90 days, and a median OS of 306 days). Lower doses, such as 1000 mg/m^2 PO BID, have been studied as monotherapy in metastatic breast cancer, and have shown comparable efficacy with less toxicity (Rossi 2007). Capecitabine has also been approved to be used in combination with the oral HER2/EGFR inhibitor lapatinib at a dose of 1000 mg/m^2 PO BID based on the results of studies showing an increase in PFS by adding lapatinib to capecitabine when compared to capecitabine alone (TYKERB Prescribing Information, Novartis Pharmaceuticals Corp., Feb 2021). In addition, as mentioned above in Section 3.3.1, the addition of capecitabine to trastuzumab in patients who had previously progressed on trastuzumab showed an improvement in efficacy when compared to capecitabine alone. Treatment with capecitabine in combination with trastuzumab has also been shown to result in increased PFS when compared to capecitabine plus lapatinib.

3.3.3 Double-blind Phase Study Rationale

Despite the marked improvements in PFS and OS with the introduction of new agents for the treatment of HER2+ breast cancer, patients with unresectable locally advanced or metastatic breast cancer are not cured with currently available therapy and represent an ongoing medical need.

The standard of care for patients with HER2+ advanced disease currently consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line therapy, followed by T-DM1 as second-line therapy (Blackwell 2012). After patients progress on these

therapies, there is no single preferred regimen that is considered standard of care; treatment generally consists of combining trastuzumab with either a second HER2-targeted agent (lapatinib), or with a cytotoxic agent, such as the combination of trastuzumab and capecitabine. The median PFS and OS in patients receiving third-line therapy after prior pertuzumab and T-DM1 based regimens has not been established. However, in the TH3RESA study, in which patients received T-DM1 vs. physician's choice (including trastuzumab and capecitabine) for progressive disease after prior treatment with trastuzumab- and lapatinib- based treatments, the median PFS for the physician's choice arm was only 3.3 months.

Based on the anti-tumor activity and safety observed to date, tucatinib in combination with capecitabine and trastuzumab has the potential to provide dual HER2 inhibition in the context of a cytotoxic agent. This three drug combination may lead to improved clinical outcomes for HER2+ breast cancer patients who have progressive disease following prior treatment with pertuzumab, trastuzumab, and T-DM1 compared to the combination of capecitabine and trastuzumab alone, potentially establishing a new standard of care for these patients and addressing an ongoing medical need.

Early clinical data also indicate that tucatinib may have activity against brain metastases, particularly when combined with other agents, including capecitabine and trastuzumab. As discussed, up to 50% of patients with HER2+ metastatic breast cancer may develop brain metastases (Pestalozzi 2013). With no approved systemic therapies for treatment of HER2+ brain metastases, treatment options for these patients are limited. An effective HER2-directed systemic treatment that controls both in brain as well as non-brain metastases could help address a significant unmet medical need in the post-trastuzumab era. The combination of tucatinib with capecitabine and trastuzumab has the potential to meet this need and provide a new treatment option for these patients.

The intent of this Phase 2 randomized, double-blinded trial is to determine if tucatinib provides additional benefit to the combination of capecitabine plus trastuzumab in patients with incurable, progressing, unresectable locally advanced or metastatic HER2+ breast cancer who have previously been treated with trastuzumab, pertuzumab, and T-DM1. Control arm patients will be treated with a combination of capecitabine and trastuzumab, a combination recommended in this patient population for whom no single standard of care therapy exists (Giordano 2014). Patients with brain metastases may also be eligible as outlined in the CNS Inclusion/Exclusion Criteria (Sections 6.1 and 6.2).

3.3.4 Unblinded Phase Study Rationale

Previously, the study sponsor, Seagen, performed the per-protocol primary analysis of this trial. At the time of the primary analysis, the trial met the primary endpoint of progression-free survival (PFS), showing that the addition of tucatinib was superior to trastuzumab and capecitabine alone, with a 46 percent reduction in the risk of disease

progression or death (hazard ratio [HR]=0.54 [95% Confidence Interval [CI]: 0.42, 0.71]; p<0.00001). The trial also met the two key secondary endpoints at interim analysis. The tucatinib arm demonstrated an improvement in overall survival, with a 34 percent reduction in the risk of death (HR=0.66 [95% CI: 0.50, 0.88]; p=0.0048) compared to trastuzumab and capecitabine alone. For patients with brain metastases at baseline, the tucatinib arm also demonstrated superior PFS, with a 52 percent reduction in the risk of disease progression or death compared to those who received trastuzumab and capecitabine alone (HR=0.48 (95% CI: 0.34, 0.69); p<0.00001). Due to the statistically significant results, these interim analyses of OS and PFS in patients with brain metastases are considered the final analyses of these endpoints.

Tucatinib in combination with trastuzumab and capecitabine was generally well tolerated with a manageable safety profile. The most frequent adverse events in the tucatinib arm included diarrhea, palmar-plantar erythrodysaesthesia syndrome (PPE), nausea, fatigue, and vomiting. Grade 3 or greater adverse events in the tucatinib arm compared to the control arm included diarrhea (12.9 vs. 8.6 percent), increased aspartate aminotransferase (AST) (4.5 vs. 0.5 percent), increased alanine aminotransferase (ALT) (5.4 vs. 0.5 percent) and increased bilirubin (0.7 vs. 2.5 percent). There was no requirement for prophylactic antidiarrheals. Adverse events leading to discontinuations were infrequent in both the tucatinib arm and the control arm (5.7 and 3.0 percent).

Based on these results, the Sponsor decided to unblind this trial and offer tucatinib to patients on the control arm. Protocol Version 11 established a new Unblinded Phase of the study, and presented study procedures for these 2 distinct phases: the Double-blind Phase and the Unblinded Phase.

4 STUDY OBJECTIVES

4.1 Double-blind Phase

4.1.1 Primary Objective

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per RECIST 1.1 based on blinded independent central review (BICR)

4.1.2 Secondary Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab in patients with brain metastases at baseline, defined as patients with a history of brain metastases, current brain metastases, or equivocal brain lesions at baseline, using RECIST 1.1 based on (BICR)
- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on OS
- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per RECIST 1.1 based on investigator assessment
- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on objective response rate (ORR) per RECIST 1.1 based on BICR and by the investigator
- To assess the duration of response (DOR) of tucatinib in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR and by the investigator
- To assess the clinical benefit rate (CBR) [stable disease (SD) or non-complete response (CR)/non-progressive disease (PD) for ≥ 6 months, or best response of CR or partial response (PR)] of tucatinib vs. placebo in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR and by the investigator
- To assess health-related quality of life and health economics associated with tucatinib vs. placebo in combination with capecitabine and trastuzumab based on patient health status collected using the EQ-5D-5L instrument and health care resources utilized in patient care

4.1.2.1 Safety Objective

- To assess the safety and tolerability of tucatinib in combination with capecitabine and trastuzumab

4.1.2.2 Pharmacokinetic Objective

- To evaluate the pharmacokinetics of tucatinib and metabolite ONT-993 when administered in combination with capecitabine and trastuzumab

4.1.3 Exploratory Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab using RANO-BM based on BICR in patients with brain metastases at baseline
- To identify potential biomarkers of response, including human epidermal growth factor receptor 2 (HER2) mutations and other mutations by DNA sequence analyses of ctDNA isolated from plasma samples
- To assess the effect of tucatinib on progression in brain in patients with brain metastases at baseline

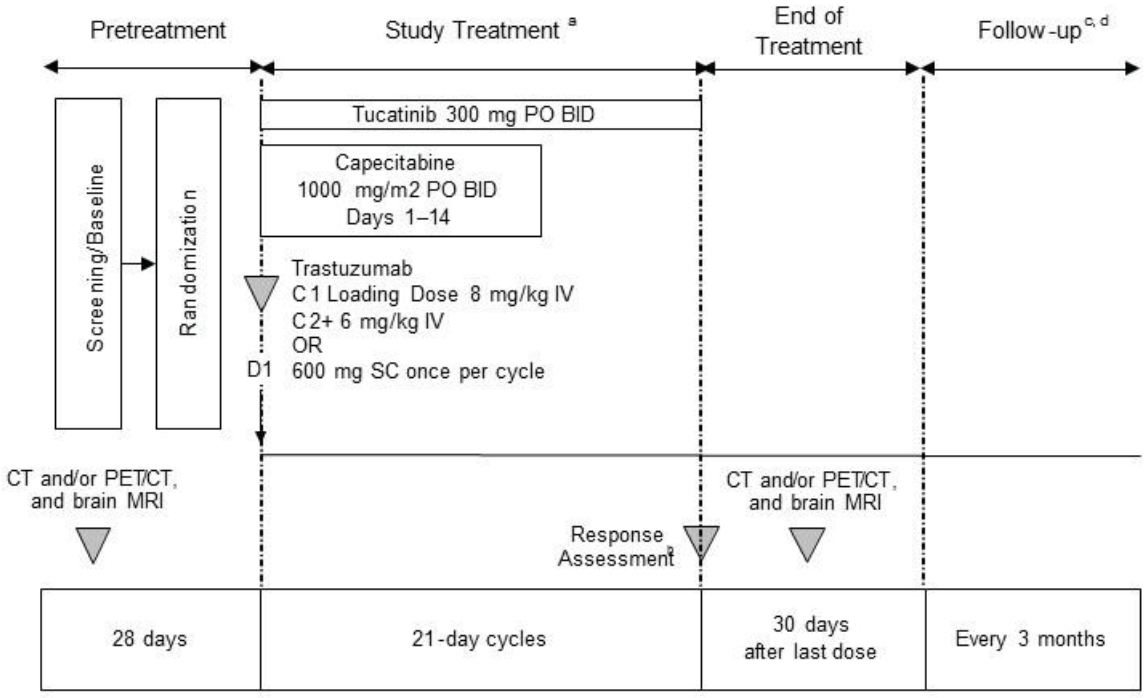
4.2 Unblinded Phase

- To assess the safety and tolerability of tucatinib in combination with capecitabine and trastuzumab
- To assess PFS per RECIST 1.1 by investigator
- To assess OS

5 STUDY DESIGN

5.1 Overview of Study Design

Figure 5-1 Double-blind Study Schematic



a Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. Patients with CNS progression may undergo local therapy to CNS lesions and continue on study treatment with approval from the medical monitor for clinical benefit.

b Contrast CT, PET/CT (CT must be of diagnostic quality), and/or MRI, and brain contrast MRI scan at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter until PD, initiation of a new therapy, withdrawal of consent, or study closure. Patients without brain metastases at baseline do not require brain contrast MRIs while on treatment. A brain contrast MRI is required at the 30-Day Follow-up Visit for all patients.

c Assessment of overall survival and/or disease recurrence, as well as collection of information regarding any additional anti-cancer therapies administered after completion of study treatment.

d. If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death, every reasonable effort will be made to obtain contrast CT, PET/CT and/or MRI, and contrast brain MRI (only in patients with known brain metastases) approximately every 9 weeks until disease progression (per RECIST 1.1), death, withdrawal of consent, or study closure.

5.1.1 Double-blind Phase

In this phase, the study is a randomized, international, multi-center, double-blind study of tucatinib or placebo in combination with capecitabine and trastuzumab in patients with unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab and T-DM1. After signing informed consent and meeting all eligibility criteria, patients will be randomized in a 2:1 ratio to receive tucatinib or placebo in combination with capecitabine and trastuzumab.

Randomization will be made using a dynamic hierarchical randomization schema. Stratification factors will include presence or history of treated or untreated brain metastases or brain lesions of equivocal significance (yes/no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1), and region of world (US vs Canada vs Rest of World). Stratification for presence of brain metastases will be based upon medical history and investigator assessment of screening contrast brain MRI. Patients who have prior brain metastases (treated or untreated) or unequivocal presence of brain metastases on screening MRI will be considered a "Yes" for stratification purposes, and subsequent efficacy assessments. Patients with no prior history of brain metastases and lesions of equivocal significance on screening contrast brain MRI will also be considered a "Yes" for purposes of stratification and follow-up.

Treatment will be administered in cycles of 21 days each. Tucatinib or placebo will be given PO BID. The tucatinib dose will be 300 mg. Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg IV. In instances of subcutaneous trastuzumab use, a fixed dose of 600 mg is administered without a loading dose. Following an IV loading dose of trastuzumab, 6 mg/kg of trastuzumab is administered once every 21 days, except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule. Subcutaneous trastuzumab is given only once every three weeks as there is no allowance for weekly dosing. There is no ability to modify the trastuzumab dose when administered subcutaneously. Dose modifications of tucatinib or placebo and capecitabine will be allowed.

Dose holding or discontinuation of tucatinib or placebo, capecitabine, and trastuzumab will also be allowed as needed for patient safety. Patients who discontinue either capecitabine or trastuzumab (but not both) may remain on study treatment. Patients who discontinue tucatinib or placebo, or both capecitabine and trastuzumab will not be allowed to remain on study treatment but will continue to be followed for efficacy assessments per protocol schedule.

Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure. In the absence of clear evidence of disease progression (per RECIST 1.1), development of CNS symptoms or radiographic changes thought to pose potential immediate risk to patient, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST 1.1.

After discontinuing study treatment, patients may receive further care as determined by their physician. No crossover from placebo to tucatinib will be allowed while patients are in this phase of the study. It is planned that patients will be followed for efficacy endpoints after treatment discontinuation until the protocol specified number of events (both PFS and OS) are observed or the primary and key secondary endpoints are met.

Tumor Response Assessments

Contrast brain MRI will be performed at baseline in all patients regardless of prior history of brain metastases. Efficacy assessments will include measurement of all known sites of metastatic or locally advanced unresectable disease (including at a minimum the chest, abdomen, and pelvis) by high quality spiral contrast CT, PET/CT (if high quality CT scan included) and/or MRI scan as appropriate, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging) at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter. Repeat contrast brain MRI will be required on this same schedule only in those patients with prior history of brain metastases, brain metastases found at screening, or brain lesions of equivocal significance found at screening. Contrast brain MRI may also be performed in patients without known brain metastases if there is clinical suspicion of new brain lesions. Additional imaging such as nuclear medicine bone scan or other unscheduled scans may be performed at the discretion of the investigator. Treatment decisions will be made based upon investigator assessment of radiologic scans. All patients will undergo a repeat contrast MRI of the brain within 30 days of the end of treatment, unless a contrast MRI of the brain has already been performed within 30 days or there is prior documentation of progression in the brain on study. If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1), patients will continue to be followed for progressive disease including submission of subsequent imaging so as to define PFS. All patients in the study will continue to be followed for OS after completion of study treatment. Patients who were randomized but did not receive treatment will also be followed for PFS and OS.

For patients who undergo local therapy to brain metastases incidentally found on screening contrast brain MRI, and then continue onto study treatment, the performance of a repeat contrast MRI after completion of local therapy is as follows: For patients 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 patients who undergo surgical resection of brain metastases during the screening period, a post-operative contrast brain MRI will serve as the baseline. Contrast brain MRIs should then be done per the protocol defined schedule of events even if all lesions in the brain receive local treatment after the screening MRI. However, treated lesions will not be considered as target lesions. Treatment changes which may mimic progression will be taken into account, and patients with possible “pseudo-progression” should continue on study until unequivocal evidence of radiographic or clinical progression is present.

Safety Assessments

Safety monitoring will be performed by the sponsor throughout the study on a blinded basis. Safety assessments including physical exam, collection of AEs, and laboratory assessments will be performed at a minimum of once every three weeks throughout study

treatment and 30 days after the last dose of study drugs. Laboratory assessments will be performed locally at sites. Cardiac ejection fraction will be assessed by MUGA scan or ECHO at screening and at least once every 12 weeks thereafter.

During the Double-blind phase, an independent Data Monitoring Committee (DMC) will regularly review all relevant safety data including (but not limited to) deaths, discontinuations, dose reductions, AEs, serious adverse events (SAEs), and cases of progressive disease within 6 weeks of study entry (blinded and unblinded) as outlined in a separate DMC charter. Ad hoc meetings of the DMC may be held upon the request of the sponsor or DMC. During the Unblinded Phase, the monitoring responsibility of the independent DMC will be considered completed and no more DMC reviews will occur.

Pharmacokinetics and Biomarker Assessments

Pharmacokinetic assessments of tucatinib will be performed. Blood samples will also be taken for possible evaluation of potential biomarkers of response, including circulating tumor DNA (ctDNA).

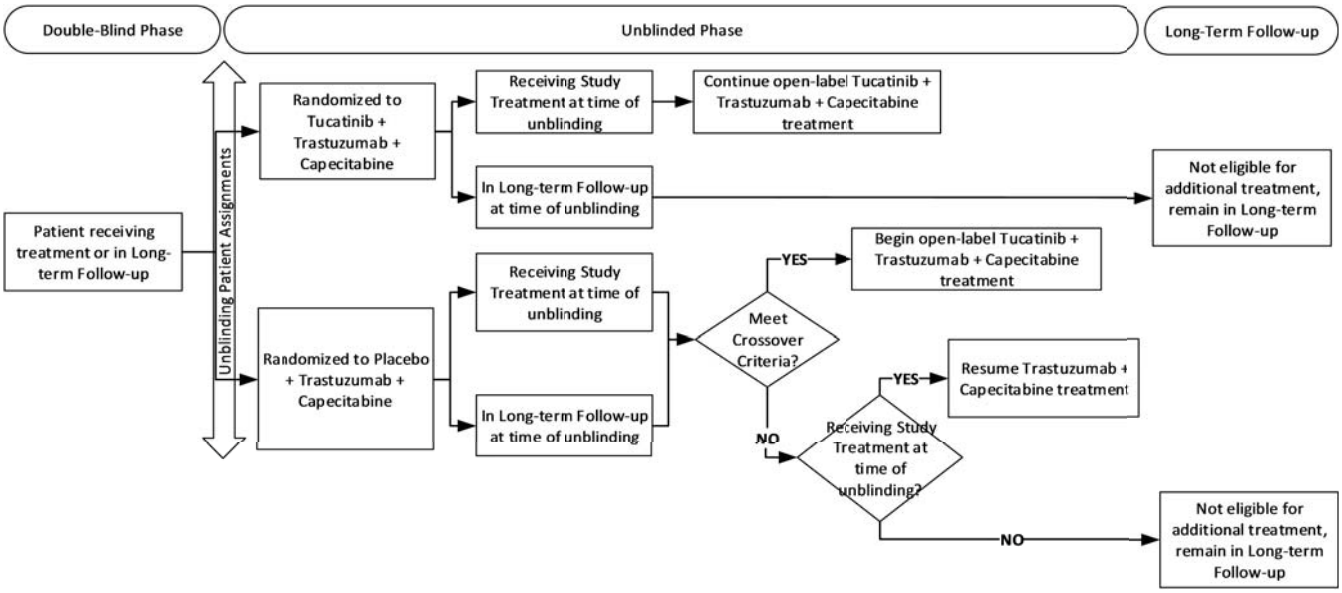
HEOR and QoL

Health-related quality of life and health care economics will be assessed by use of the EQ-5D-5L quality of life instrument and collection of health care resource utilization data.

5.1.2 Unblinded Phase

Based on the positive results of the per-protocol primary analysis of this trial, the Sponsor decided to unblind this trial and offer tucatinib to patients on the control arm. Protocol Version 11 established a new Unblinded Phase of the study, and presented study procedures for these 2 distinct phases: the Double-blind Phase and the Unblinded Phase.

Figure 5-2 Unblinded Phase Study Schematic



With the implementation of protocol version 11, the double-blind phase of the study ended, and all patients were unblinded to their treatment assignment.

- Patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine) and are receiving study treatment at the time of unblinding will continue on that treatment arm with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and Appendix A.2). For these patients, the treatment cycle counting will continue from prior to the unblinding, and patients will continue study treatment at the same doses they were given in the double-blind phase of the study.

- Patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine), ended study treatment and are in the long-term follow-up are not eligible for additional treatment on the experimental arm in this study and will remain in long-term follow-up.

- Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are receiving study treatment at the time of unblinding may crossover to the experimental arm if crossover criteria are met.

    - If the patient does not meet crossover criteria, the patient will continue trastuzumab + capecitabine therapy. At the start of the next scheduled cycle, the patient will continue trastuzumab + capecitabine therapy with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and Appendix A.3). These patients will continue trastuzumab + capecitabine therapy at the same doses they were given in the double-blind phase of the study.

- Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are in long-term follow-up at the time of unblinding may crossover to the experimental arm if crossover criteria are met.

    - If the patient does not meet crossover criteria, the patient will remain in long-term follow-up

Treatments Administered in the Unblinded Phase

In the unblinded phase of the study, tucatinib will be given in combination with trastuzumab and capecitabine. Treatment will be administered in repeating 21-day cycles.

- Patients randomized to the experimental arm will continue tucatinib + trastuzumab + capecitabine at the same doses they were given in the double-blind phase of the study, using a modified schedule of events as outlined in Appendix A.2.

- Patients who were randomized to the control arm and meet crossover criteria will be given:

- Tucatinib 300 mg orally twice daily (PO BID) every day (Days 1–21) of each 21-day cycle using a modified schedule of events as outlined in Appendix A.3.
- Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle. For patients who required dose reductions of capecitabine, capecitabine must be given at the same reduced dose most recently given in the double-blind phase of the study.
- The initial dose of trastuzumab will be given as a loading dose of 8 mg/kg intravenously (IV), unless trastuzumab was administered within the prior 4 weeks, then the initial dose of trastuzumab will be administered at a dose of 6 mg/kg. Each trastuzumab dose is given once every 21 days, except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule. Subcutaneous trastuzumab is given only once every three weeks as there is no allowance for weekly dosing. There is no ability to modify the trastuzumab dose when administered subcutaneously.

Dose modifications of tucatinib and capecitabine will be allowed. Dose holding of tucatinib or dose holding and/or discontinuation of capecitabine and trastuzumab will also be allowed as needed for patient safety. Patients who discontinue either capecitabine or trastuzumab may remain on study treatment. In instances where capecitabine and trastuzumab have been discontinued, patients may remain on study treatment with tucatinib alone. Patients who discontinue tucatinib will not be allowed to remain on study treatment. Treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, or study closure.

Screening for Crossover Criteria

Patients who were randomized to the control arm who wish to crossover to receive tucatinib will undergo a crossover screening period of up to 28 days after signing the revised informed consent. During that time patients will also undergo contrast MRI brain scan imaging in addition to CT, PET/CT, or MRI imaging to include, at a minimum, the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging) for an assessment of tumor burden. Based on this crossover screening imaging, new baseline RECIST lesions will be selected by the investigator.

Cardiac ejection fraction will be assessed by MUGA and ECHO. If an MRI of the brain, systemic imaging for assessment of tumor burden (e.g., CT, PET/CT, or MRI), or cardiac imaging for assessment of ejection fraction have been performed while on the double-blind phase of the study or as part of standard of care within the prior 6 weeks, those assessments can be used for crossover screening purposes. Blood samples for

hematology, chemistry, and liver function tests will be drawn. Pregnancy testing (except in men or in women of non-childbearing potential) will be performed within 7 days prior to start of crossover (tucatinib) treatment.

Tumor Response Assessments

The investigator will determine the frequency and method of tumor assessments performed for patient care decisions according to routine clinical practice, with a maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.

Safety Assessments

Patients will be assessed throughout the study for safety. Safety assessments including physical exam and collection of AEs and laboratory abnormalities will be performed at a minimum of once every three weeks throughout study treatment and 30 days after the last dose of study drugs. Cardiac ejection fraction assessments should be continued to be assessed by MUGA scan or ECHO at least once every 12 weeks. Laboratory assessments will be performed locally.

Assessments after Treatment Discontinuation

A final routine, safety assessment including physical examination and laboratory assessments will be required approximately 30 days after discontinuation of study treatment. Patients will continue in long-term follow-up per the schedule of events as outlined in Appendix A.2 and in Appendix A.3, as appropriate.

5.1.3 Continuation on Study Treatment After CNS-Only Progression

For patients in both the Double-blind and Unblinded Phases, patients may continue study treatment for clinical benefit after a PFS event in brain with medical monitor approval.

If a patient is found to have radiographic progressive disease per RECIST 1.1 based on isolated progression in the CNS (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 patient may be eligible to continue on study drugs after completion of local treatment (radiotherapy or surgery) of the brain/dural metastases to allow for clinical benefit. Continuation of study treatment requires discussion with and documented approval from the study medical monitor and may continue until either systemic progression or a second isolated CNS progression. Because this approach approximates common practice off-study in this clinical scenario, the duration of treatment after the CNS-only progression will be analyzed as an exploratory objective. The patient will remain on the same treatment regimen that they were receiving prior to receipt of CNS-directed therapy, and may continue on study provided the following criteria are met and the patient continues to receive clinical benefit:

- The patient is not experiencing any worsening of cancer-related symptoms. Patients who are clinically deteriorating and unlikely to receive further benefit from continued treatment should discontinue study treatment.
- The patient is tolerating study drug
- Approval by the medical monitor
- Patient has no evidence of unequivocal systemic progression
- Patient has not had a previous isolated CNS progression on tucatinib while 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. Oral study drugs (tucatinib/placebo and capecitabine) are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib is unknown. Capecitabine is a known radiation sensitizer and therefore needs to be held prior to CNS-directed radiotherapy. Trastuzumab has been shown not to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study drugs may be re-initiated 7 days or more after completion of SRS/SRT, 21-days or more after WBRT and 28-days or more after surgical resection. Plans for holding and re-initiating study drugs before and after local therapy will require discussion with, and documented approval from, the medical monitor.

Following CNS-directed therapy for isolated CNS disease progression, RECIST 1.1 criteria would continue to measure a CNS target lesion(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.

For patients in the double-blind phase: 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 progressive disease by RECIST 1.1 unless clinically necessary in the opinion of the investigator. The rationale for this is that target lesions, once treated with local CNS therapy, cannot be adequately assessed for subsequent response to systemic therapy. Because of this, if a patient 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 1.1. assessment.

5.2 Rationale for the Study Design

5.2.1 Rationale for the Patient Population

Eligible patients for this study are those with progressive, unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1 (Freedman 2012; Cardoso 2014; Giordano 2014; Ramakrishna 2014).There is currently no single standard of care therapy for these patients. Treatment options that do exist include continued use of a HER2-directed agent either in combination with a cytotoxic agent (e.g., trastuzumab and capecitabine, or vinorelbine, or lapatinib and capecitabine) or with a second HER2-directed agent (i.e., trastuzumab + lapatinib), with no currently available data to recommend one regimen over another. Treatment selection is generally based upon physician and patient preference (Giordano 2014). There are currently limited published data reporting a median PFS or OS for pertuzumab and T-DM1 experienced patients who require further treatment. The most similar reference population from recent clinical studies may be the control arm of the TH3RESA trial, which evaluated T-DM1 vs. physician's choice of therapy in patients receiving third-line treatment or beyond for metastatic HER2+ breast cancer. The median PFS in the physician's choice control group was only 3.3 months. Given that, and the fact that none of these patients had yet been exposed to T-DM1, the actual PFS for patients receiving third-line therapy after current first- and second-line standard of care may be even shorter (Krop 2014). A well-tolerated regimen which could improve upon overall PFS and OS in patients who have failed current standard of care for metastatic disease would therefore help address an important unmet medical need. In the ongoing Phase 1b study ONT-380-005, tucatinib was associated with anti-tumor activity and an acceptable safety profile when combined with capecitabine and trastuzumab in T-DM1 and pertuzumab treated patients, and therefore may be able to meet this need (Wolff 2013).

Certain patients with brain metastases are also eligible for this trial, including patients with untreated brain metastases not requiring immediate radiotherapy and patients with prior radiotherapy with stable to minimally progressive metastases. Treatment options for patients with HER2+ disease and brain metastases are currently limited, and there is no currently recommended systemic therapy (Ramakrishna 2014). Treatment modalities include radiation therapy (either WBRT, SRS or SRT) or surgery for selected patients. Radiation therapy can be associated with significant morbidity due to treatment-related injury. There is therefore a need for alternative treatment options. Systemic treatment options that have demonstrated some activity include single agent cytotoxic agents, including capecitabine, as well as combination treatment with capecitabine and lapatinib. However, the toxicity associated with these regimens can be substantial, particularly for the combination of capecitabine and lapatinib which has been associated with >50% rate of Grade 3 events (Verma 2012), and none of these systemic regimens have been approved for use in the setting of brain metastases. Data from Phase 1b combination

studies with tucatinib have shown clinical activity in patients with either untreated brain metastases or brain metastases progressing after prior radiation therapy. As there are currently no approved systemic therapies for patients with brain metastases from HER2+ MBC, this clinical scenario represents a significant unmet medical need. An effective systemic treatment with CNS activity could potentially improve overall PFS and OS for patients with brain metastases, as well as allow patients to delay exposure to radiation therapy and its associated negative neurologic toxicities. In addition, patients with progression after prior radiotherapy represent a particular unmet need, since additional treatment options are even more limited due to the increased risks of tissue necrosis from additional radiation to previously irradiated brain tissue.

Patients with asymptomatic brain lesions found during screening not thought to need immediate local therapy are eligible for this study. These patients are being included as there are currently no data showing that early initiation of radiation therapy leads to improved OS, or that delay of initiation of radiation therapy until after a trial of systemic therapy has a negative impact on OS (Ramakrishna 2014).

Patients with high-risk brain metastases, including those with lesions identified during screening that are thought to require immediate local therapy, those with rapidly progressing lesions, those requiring > 2mg dexamethasone or equivalent corticosteroid at the start of the study for control of neurologic symptoms, and those with larger untreated lesions, may be excluded from the trial. However, if these patients are amenable to immediate therapy with either surgery or radiation, they may undergo local CNS-directed therapy and then be eligible for the trial.

For patients in the double-blind phase, the study DMC will be monitoring blinded and unblinded safety data in an ongoing fashion throughout the blinded phase of the study to ensure that patients with brain metastases are not put at excessive risk.

To ensure that patients without true HER2 overexpression who are unlikely to benefit from HER2 directed therapy are excluded from this trial, HER2+ status will be confirmed using a centralized laboratory prior to patient randomization according to ASCO/CAP Guidelines (Gianni 2012).

5.2.2 Rationale for the Dose and Regimen

All patients will receive a treatment backbone of capecitabine and trastuzumab, a combination recommended in current treatment guidelines in this patient population for whom no single standard of care therapy exists. In the CEREBEL study, patients treated with the combination of capecitabine plus trastuzumab were shown to have a significantly prolonged PFS when compared to capecitabine plus lapatinib, another common therapeutic option in this setting. The safety profile of capecitabine plus trastuzumab was also similar to capecitabine plus lapatinib, but with a lower incidence of diarrhea, nausea, rash, and hyperbilirubinemia. The use of the combination of

capecitabine and trastuzumab as the control treatment in this study also allows a randomized, double-blinded study design, thus minimizing bias and allowing a more accurate assessment of the contribution of tucatinib itself to clinical outcomes.

The addition of tucatinib to both capecitabine and trastuzumab, which provides not only dual inhibition of HER2 but also combination with a cytotoxic agent, has the potential to further improve efficacy compared to available therapies for patients previously treated with approved first- and second-line regimens for metastatic disease. The addition of tucatinib to this backbone will provide dual HER2 inhibition through 2 different mechanisms of action. Dual blockade of HER2 has been shown in multiple settings to provide benefit over single agent blockade, even in the setting of previous progression on trastuzumab-containing regimens (Blackwell 2010; Baselga 2012b; Blackwell 2012; Gianni 2012). The addition of the small molecule HER2 inhibitor lapatinib to capecitabine has also been shown to be superior to capecitabine alone, even in the setting of previous progression on trastuzumab-containing regimens (Geyer 2006). Furthermore, the greater selectivity of tucatinib compared to other oral anti-HER2 agents offers the potential to provide HER2 blockade with fewer toxicities than currently available agents.

Selection of the tucatinib dosing regimen for the current study was based upon the RP2D from the Phase 1b dose-escalation study of tucatinib in combination with capecitabine and trastuzumab in patients with advanced HER2+ breast carcinoma (ONT-380-005) that included pharmacokinetic analysis. The dose of trastuzumab is the full dose approved for single-agent use when administered on a q 21 day cycle.

The dosing regimen of capecitabine to be used in both arms of this study is based on the dose used in the Phase 1b combination trial, ONT-380-005. That study used a capecitabine dose of 1000 mg/m^2, the approved dose for combination therapy with lapatinib, an oral inhibitor of HER2/EGFR. The dose of capecitabine (1000 mg/m^2) has also been shown to have similar efficacy to the single-agent approved dose of 1250 mg/m^2 BID when used as monotherapy, with less toxicity (Rossi 2007). For patients in the control arm who will be receiving capecitabine plus trastuzumab without tucatinib, this capecitabine dose is within the single agent RD range of 1000–1250 mg/m^2 given in published guidelines (NCCN 2021). When given as a single agent, capecitabine at the lower dose of 1000 mg/m^2 has been shown to have similar efficacy as well as higher overall dose intensity when compared to 1250 mg/m^2 due to the frequent need for dose interruptions and dose reductions in patients started at the higher dose (Bajetta 2005; Pivot 2015).

5.2.2.1 Rationale for Regimen in Patients with Brain Metastases

Patients with brain metastases have frequently been excluded from trials with systemic cancer therapies due to difficulties in imaging assessment in the brain and a lack of flexibility with regard to treatment discordant responses in CNS and non-CNS locations.

Perhaps as a result of this, no systemic therapies are currently approved for the treatment of brain metastases in patients with HER2+ MBC. However, effective systemic therapies are needed which could potentially delay the use of radiation or treat lesions which have progressed after radiation. Selected patients with brain metastases will therefore be eligible for this trial in order to assess the effectiveness of this study treatment on intracranial metastases.

All patients in this study will receive capecitabine, an agent which is known to be active both as a single agent and in combination therapy in the CNS (Wang 2001; Ekenel 2007; Bachelot 2013). Capecitabine as a single agent is recommended as one option for the treatment of HER2+ brain metastases in ASCO Guidelines (Ramakrishna 2014). The addition of capecitabine has been shown to markedly improve the low CNS response rates of lapatinib alone in patients progressing on lapatinib monotherapy (Eisenhauer 2009). In this study, trastuzumab will also be given in both treatment arms, which has been shown to improve control of systemic disease even after progression on prior trastuzumab (Park 2009; von Minckwitz 2009; Giordano 2014). No other approved HER2-directed agents, including lapatinib, have been shown to be superior to trastuzumab in combination with capecitabine in the treatment of or prevention of brain metastases (Larsen 2013; Pivot 2015).

Because of the limited data set that is currently available for the use of tucatinib in the treatment of brain metastases, patients with high-risk brain metastases, such as those requiring high-dose corticosteroids at the time of study entry (> 2 mg/day of dexamethasone or an equivalent dose of corticosteroid) or those with poorly controlled generalized or complex partial seizures or symptomatic neurologic progression in patients with brain metastases notwithstanding CNS-directed therapy will be excluded from the study. However, high-risk patients who could benefit from immediate CNS-directed therapy, such as those who have untreated lesions in anatomically sensitive areas, may undergo surgery or radiation therapy after screening and then enter the study (7 or more days after SRS/SRT, 21 or more days after WBRT and 28 or more days after lesionectomy) if neurologically stable and on reduced dose of steroids as protocol specified.

As noted in Section 3.2.4, there have been early signs of responses in brain and durable control of brain metastases in patients treated with tucatinib with capecitabine, trastuzumab, or capecitabine and trastuzumab in a Phase 1b study (Study ONT-380-005). For patients in the treatment arm of this study, tucatinib will be added to the active regimen of capecitabine and trastuzumab with the objective of evaluating the impact of tucatinib on the time and incidence of progression in brain as well as the rate and duration of response in brain.

As there are often differences in response to systemic therapies in intracranial vs. extracranial locations due to differences in penetration, tumor heterogeneity, and other

factors, patients who have non-CNS disease control but with isolated brain progression are often given local therapy to the CNS with continuation of systemic therapy until non-CNS progression. This allows the continuation of a therapy that is effective systemically while allowing control of brain metastases, and mirrors clinical practice and established guidelines (Park 2009; Ramakrishna 2014; NCCN 2021). In this trial, patients who have isolated CNS-only (brain or dura) progression on trial may be eligible to continue on study drugs for clinical benefit after undergoing local therapy to the CNS, as described in Section 5.1.3. For the analysis of overall PFS, these patients will be considered to have progressed at the time of initial CNS progression as outlined in Section 11.1.1.4.

5.2.3 Rationale for Efficacy Assessments

Efficacy will be assessed looking at all sites of disease using RECIST 1.1 (Eisenhauer 2009). The primary endpoint will be PFS, as assessed per BICR RECIST 1.1. The two key secondary endpoints, PFS in patients with baseline brain metastases assessed centrally using RECIST 1.1 and OS in the entire study population, will determine efficacy in the brain metastases subgroup and OS in all randomized patients. Exploratory endpoints of DOR, ORR, and time to brain progression will be bi-compartmental using RANO-BM as assessed by BICR. These criteria were published to standardize response and progression criteria for patients with brain metastases as well as non-CNS disease. Selected details regarding RECIST 1.1 are provided in Appendix B, and in the radiology study binder. To standardize efficacy assessments using the RECIST 1.1 criteria in this multi-center study, the primary endpoint of this study will be based on independent, blinded, centralized review. However, local response assessments will be used for patient management decisions to ensure that treatment decisions can be made in a timely manner. Results of centralized review will not be available to investigators for clinical decision-making.

For the Double-blind Phase of the study, efficacy assessments will be performed once every 6 weeks for the first 24 weeks on study, and then once every 9 weeks. These intervals are consistent with standard of care practice and schedule used in prior studies in similar populations (Verma 2012; Krop 2014).In addition, given the predicted duration of time on study for patients in both the treatment and control arms, this schedule will be adequate to measure any clinically meaningful treatment effect without increasing radiation exposure above what is anticipated from standard of care assessments.

For the Unblinded Phase of the study, the investigator will determine the frequency and method of tumor assessments performed for patient care decisions according to routine clinical practice, with a maximum interval of 12 weeks between tumor assessments.

5.2.3.1 Rationale for CNS Efficacy Assessments

Contrast MRI of the brain will be performed at baseline for all patients. This is being performed to more thoroughly evaluate the activity of tucatinib in brain by establishing a baseline in all patients, even those with asymptomatic unsuspected brain metastases. Contrast brain MRIs during study treatment will only be performed in patients with documented brain metastases (historically or at screening) and in patients with brain lesions of equivocal significance in order to follow for effects of treatment and for possible progression and will be consistent in schedule with systemic imaging. Patients without a history of brain metastases and without evidence of brain metastases or brain lesions of equivocal significance at baseline will not undergo regular brain MRIs during study treatment, consistent with current recommendations for radiographic follow-up for these patients (Cardoso 2014; Ramakrishna 2014) and due to the low rate of development of brain metastases in patients without brain metastases at baseline during the expected time frame of this study treatment (Pivot 2015).

During the Double-blind Phase of the study, an additional contrast MRI of brain will be performed in all patients once off study treatment to assess for the development of clinically silent brain metastases in both treatment and control groups. These additional MRIs in patients without brain metastases will expose patients to no additional radiation, and will help to more fully evaluate the effect of tucatinib on brain metastases in this patient population.

Response in brain will also be assessed as an exploratory endpoint by BICR per the RANO-BM Criteria, which takes into account not only radiographic changes, but clinical status and the use of corticosteroids. The use of these criteria will allow a more rigorous look at the activity of tucatinib in the brain, where radiographic assessment has historically proven challenging. It will also allow for more accurate assessment of acute changes which can be seen in the brain after local therapy which can mimic progression but which do not constitute true disease progression, such as temporary edema after the use of radiation or surgery.

5.2.4 Rationale for PK Assessment Plan

Pharmacokinetic assessments of trough levels of tucatinib and metabolite drug levels will be performed on Day 1 of Cycles 2-6 prior to administration of tucatinib or placebo, and peak level on Day 1 of Cycle 3 within 1–4 h after administration of tucatinib or placebo. Patients will be asked to take study drug at clinic on days of PK assessments. The sparse sampling of patients during the described study period will allow for the periodic assessment of the drug trough level at steady state on multiple occasions. The pharmacokinetics of the drug can be related to individual patient characteristics and variability in PK can also be assessed. Data from studies ONT-380-004 and

ONT-380-005 indicated that pharmacokinetics evaluation of capecitabine and trastuzumab is not warranted.

PK assessments will not be performed during the Unblinded Portion of this study.

5.2.5 Rationale for Health Economics Assessments

Health-related quality of life is an important outcome from both clinical and economic perspectives. A substantial body of literature supports the validity and reliability of the health questionnaire EQ-5D-5L instrument for assessing quality of life in a health economic assessment and is therefore the rationale for the use of this instrument in the current study. The objective is to compare improvements, deteriorations and stabilization in health-related quality of life in patients treated with the tucatinib vs. the placebo arm of this study.

The quality of life instrument, the EQ-5D-5L, will be administered at Cycle 1 Day 1 prior to the start of treatment and every six weeks for 24 weeks, and then every nine weeks until disease progression, death, toxicity, withdrawal of consent or study closure. Additionally, a post-treatment assessment will occur approximately 30 days following end of treatment.

To enable cost-effectiveness evaluations, detailed health care resource utilization information will be collected within the following categories (but not limited to): length of stay and length of procedures, hospitalizations/ED visits, planned and unplanned provider visits, medication, radiology, and other treatments/procedures. Within these categories, information will include planned and unplanned treatments, procedures, and planned and unplanned provider visits, and treatment of adverse events.

Health economics assessments will not be performed during the Unblinded Portion of this study.

5.2.6 Rationale for Exploratory Endpoints

5.2.6.1 Biomarker Assessments

Biomarker assessments may include the confirmation of HER2 status by ISH or FISH, and an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. HER2 status will be verified by central laboratory analysis using ASCO/CAP guidelines. Next generation DNA sequence analysis may be performed to interrogate the mutation status of a panel of oncogenes and tumor suppressor genes that are associated with tumor growth, survival and resistance to targeted therapeutics. This assessment may enable the correlation of treatment outcome to either preexisting or acquired cancer gene mutations and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor genotype in the future.

5.3 Double-blind Phase Endpoints

5.3.1 Double-blind Phase Primary Endpoint

- PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST 1.1), or death from any cause, whichever occurs first

5.3.2 Double-blind Phase Secondary Endpoints

Efficacy

Key Secondary Endpoints

- PFS in patients with brain metastases at baseline using RECIST 1.1 based on BICR
- OS

Other Secondary Endpoints

- PFS, defined as the time from randomization to investigator-assessed documented disease progression (per RECIST 1.1), or death from any cause, whichever occurs first
- ORR (RECIST 1.1) as determined by BICR as well as the investigator
- DOR (RECIST 1.1) as determined by BICR as well as the investigator
- CBR (RECIST 1.1) as determined by BICR as well as the investigator

Safety

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab

Pharmacokinetics

- Plasma concentrations of tucatinib and metabolite

Heath Economics and Outcomes

- Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and ED visits
- Health-related quality of life / health status using the EQ-5D-5L instrument

5.3.3 Double-blind Phase Exploratory Endpoints

- ORR in brain per RANO-BM as determined by BICR
- Duration of response in brain per RANO-BM as determined by BICR
- Time to brain progression in patients with brain metastases at baseline per RANO-BM as determined by BICR
- Presence of HER2 mutations or other potential biomarkers of response

5.4 Unblinded Phase Endpoints

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab
- PFS per RECIST 1.1 as determined by investigator
- OS

5.5 Study Stopping Rules and Discontinuation Criteria

Reasons for 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 patients, either through a safety review by the sponsor or an independent safety assessment by the DMC.
- Patient enrollment is unsatisfactory.

5.6 End of Study

An analysis of OS and PFS conducted approximately 2 years after the last patient was randomized to the study demonstrated that the OS benefit with tucatinib was maintained, and PFS per investigator assessment was consistent with the primary analysis (Curigliano 2021). Moreover, the number of OS events observed exceeded the number required for the originally planned final analysis. These data will be included in an addendum to the clinical study report and no additional analyses are planned.

Based on these data, the Sponsor will end the study and a last visit/contact will occur for patients who are still in the study.

5.7 Post-study Care

At the time of study closure, patients will revert to physician care. When applicable, the Sponsor will assist with post-trial access to tucatinib.

5.8 Minimization of Bias

5.8.1 Double-blind Phase Randomization

Patients will be randomized in a 2:1 ratio to receive tucatinib or placebo in combination with capecitabine and trastuzumab by a dynamic hierarchical randomization scheme using an Interactive Response Technology (IRT) system.

Randomization will be stratified by the following stratification factors:

- Known history of treated or untreated brain metastases (yes/no);
- ECOG PS (0, 1); and
- Region of world (United States, Canada, Rest of World).

The first stratification factor (i.e., known history of treated or untreated brain metastases) will be based upon investigator assessment of the screening contrast brain MRI as well as documented patient history. Patients with brain lesions of equivocal significance identified on screening MRI will be considered a "Yes" for stratification purposes.

The employed dynamic hierarchical randomization scheme will include specifications for a biased-coin assignment when the imbalance at a given hierarchical level (overall treatment group balance, then treatment group balance within each of the listed stratification factors) has exceeded a specified threshold.

Under no circumstances will patients who are randomized and treated be permitted to re-enroll for a second course of treatment.

5.8.2 Double-blind Phase Blinding

This phase of the study will be double-blinded, and every attempt will be made to maintain the blind throughout the study. The investigator, study center personnel, clinical research organization staff, and sponsor personnel (except for pre-specified Safety personnel) will not have access to the randomization scheme during the study except in the case of an emergency. Safety data will be monitored by an independent DMC. Suspected unexpected serious adverse reactions (SUSARs) will be unblinded in accordance with local regulatory reporting requirements.

5.8.3 Double-blind Phase Unblinding

As per local regulatory reporting requirements, the sponsor Safety Department will unblind the identity of study medication for any unexpected (as per the IB) SAEs that are considered to be related to the blinded study drug (tucatinib/placebo). All other sponsor

personnel will remain blinded. All such cases of safety unblinding require the approval of the medical monitor. Please see study binders for further detail regarding unblinding procedures.

In the case of a concerning drug related safety event, it is recommended that the Investigator contact and consult with the Medical Monitor. In emergency situations the Investigator may break the treatment code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial patient. The investigator has unrestricted and immediate access to break the treatment code through the IRT system. The investigator will not provide the sponsor with the results of the unblinding. In the event of any unblinding, the sponsor must be notified within one working day (if not involved in the unblinding decision). The patient must subsequently be discontinued from study treatment but must continue in the long-term follow-up period of the study.

Unblinding for ongoing safety monitoring and risk/benefit assessment by the DMC, will be performed through an independent Data Coordinating Center (DCC) to ensure integrity of the study.

At the time of the primary analysis for the primary endpoint (PFS), specific sponsor personnel will be unblinded, however sponsor personnel directly involved in the conduct of the study will remain blinded to individual subject treatment assignments (tucatinib/placebo) until the final analysis for the key secondary endpoint of PFS_{BM}.

5.9 Ethical Considerations

Despite the advances that have been made, unresectable locally advanced or metastatic HER2+ breast cancer is incurable. The primary goals of treatment remain to extend life and palliate symptoms while preserving quality of life. At present, no single treatment regimen can be considered the global standard of care for treatment of locally advanced or metastatic HER2+ breast cancer after treatment with trastuzumab, pertuzumab, and T-DM1.

As demonstrated in Phase 1 and 1b trials, tucatinib has shown activity in heavily pretreated patients with unresectable locally advanced or metastatic HER2+ breast cancer including those with brain metastases with a manageable safety profile and few EGFR-like toxicities. All patients enrolled in this study will receive either tucatinib or placebo in combination with capecitabine and trastuzumab, a recommended regimen for treatment of patients who have progressed after prior treatment with pertuzumab and T-DM1 combinations [(4)]. Patients in the control arm, including patients with brain metastases, will receive an active recommended regimen for this clinical scenario.

Previously, the study sponsor, Seagen, performed the per-protocol primary analysis of this trial. Based on the positive results of this analysis, the Sponsor decided to unblind this trial and offer tucatinib to patients on the control arm.

6 SELECTION AND WITHDRAWAL OF PATIENTS

6.1 Double-blind Phase Inclusion Criteria

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

1. Have histologically confirmed HER2+ breast carcinoma, with HER2+ defined by ISH or FISH or IHC methodology
    a. Tissue blocks or slides must be submitted to confirm HER2 positivity (using ISH or FISH) by a sponsor-designated central laboratory prior to randomization
    b. Centrally confirmed HER2 results (either IHC, ISH, or FISH) from a previous study can be used to determine eligibility for this study with approval from the sponsor
2. Have received previous treatment with trastuzumab, pertuzumab, and T-DM1
3. Have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
4. Have measurable or non-measurable disease assessable by RECIST 1.1
5. Be at least 18 years of age at time of consent
6. Have ECOG PS 0 or 1
7. Have a life expectancy of at least 6 months, in the opinion of the investigator
8. Have adequate hepatic function as defined by the following:
    a. Total bilirubin ≤1.5 X ULN, except for patients with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 X ULN
    b. Transaminases AST/SGOT and ALT/SGPT ≤ 2.5 X ULN (≤ 5 X ULN if liver metastases are present)
9. Have adequate baseline hematologic parameters as defined by:
    a. ANC ≥ 1.5 x 10^3/µL
    b. Platelet count ≥ 100 x 10^3/µL; patients with stable platelet count from 75-100 x 10^3/µL may be included with approval from medical monitor
    c. Hemoglobin ≥ 9 g/dL

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

10. Have creatinine clearance ≥ 50 mL/min as calculated per institutional guidelines or, in patients ≤ 45 kg in weight, serum creatinine within institutional normal limits
11. INR and aPTT ≤ 1.5 X ULN unless on medication known to alter INR and aPTT. (Note: Warfarin and other coumarin derivatives are prohibited.)
12. Have LVEF ≥ 50% as assessed by ECHO or MUGA scan documented within 4 weeks prior to first dose of study treatment
13. If female of childbearing potential, must have a negative result of serum or urine pregnancy test performed within 7 days prior to first dose of study treatment. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Postmenopausal patients with known β-HCG secreting tumors may be eligible when β HCG-based urine or serum pregnancy tests yield false positive if they meet the definition of postmenopausal state and have a negative uterine ultrasound.
14. Women of childbearing potential (as defined above) and men with partners of childbearing potential must agree to use a highly effective birth control method, i.e. methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Such methods 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; intrauterine hormone-releasing system; bilateral tubal occlusion/ligation; vasectomized partner; or sexual abstinence. Male patients with partners of childbearing potential must use barrier contraception. All study patients should practice effective contraception, as described above, starting from the signing of informed consent until 7 months after the last dose of study medication or investigational medicinal product
15. Patient must provide signed informed consent per a consent document that has been approved by an IRB/IEC prior to initiation of any study-related

tests or procedures that are not part of standard-of-care for the patient's disease

16. Patients must be willing and able to comply with study procedures

CNS Inclusion – Based on screening contrast brain MRI, patients must have **one** of the following:

17. No evidence of brain metastases
18. Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions > 2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment
19. Previously treated brain metastases
    a. 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
    b. Patients 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:
        i. Time since WBRT is ≥ 21 days prior to first dose of treatment, time since SRS is ≥ 7 days prior to first dose of treatment, or time since surgical resection is ≥ 28 days
        ii. Other sites of disease assessable by RECIST 1.1 are present
    c. Relevant records of any CNS treatment must be available to allow for classification of target and non-target lesions

6.2 Double-blind Phase Exclusion Criteria

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

1. Have previously been treated with:
    a. 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)
    b. neratinib, afatinib, or other investigational HER2/ EGFR or HER2 TKI at any time previously
2. Have previously been treated with capecitabine (or other fluoropyrimidine [e.g., 5-fluorouracil]) for metastatic disease (except in cases where

capecitabine was given for ≤ 21 days and was discontinued for reasons other than disease progression or severe toxicity)
Note: Patients who have received capecitabine for adjuvant or neoadjuvant treatment at least 12 months prior to starting study treatment are eligible

3. History of exposure to the following cumulative doses of anthracyclines:
    a. Doxorubicin > 360 mg/m^2
    b. Epirubicin > 720 mg/m^2
    c. Mitoxantrone > 120 mg/m^2
    d. Idarubicin > 90 mg/m^2
    e. Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) > 550 mg/m^2
4. History of allergic reactions to trastuzumab, capecitabine, 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 one of the excipients in the study drugs
5. Have received treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤ 3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial. An exception for the washout of hormonal therapies is GnRH agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
6. 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; and
    - 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
7. Have clinically significant cardiopulmonary disease such as:
    - ventricular arrhythmia requiring therapy,
    - uncontrolled hypertension (defined as persistent systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg on antihypertensive medications), or
    - any history of symptomatic CHF
    - severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy

- hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea
- presence of ≥ Grade 2 QTc prolongation on screening ECG
- conditions potentially resulting in drug-induced prolongation of the QT interval or torsade de pointes
    a. Congenital or acquired long QT syndrome
    b. Family history of sudden death
    c. History of previous drug induced QT prolongation
    d. Current use of medications with known and accepted associated risk of QT prolongation (see row "Accepted Association" in Appendix H)

8. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
9. Are known carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease
10. Are known to be positive for HIV
11. Are pregnant, breastfeeding, or planning a pregnancy
12. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)
13. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
14. Have used a strong CYP3A4 or CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 days prior to first dose of study treatment (see Appendix C and Appendix D)
15. Have known dihydropyrimidine dehydrogenase deficiency
16. Unable for any reason to undergo contrast MRI of the brain
17. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
18. Have evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment.

CNS Exclusion – Based on screening brain MRI, patients must not have any of the following:

19. Any untreated brain lesions > 2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given
20. 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, patients on a chronic stable dose of ≤ 2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor
21. 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 patient (e.g. brain stem lesions). Patients 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 criteria 19b
22. Known or suspected LMD as documented by the investigator
23. Have poorly controlled (> 1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

6.3 Unblinded Phase Crossover Criteria

6.3.1 Crossover Inclusion Criteria

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) must meet the inclusion criteria below at the time of crossover screening to be eligible to crossover to the experimental arm. Prior scans and imaging may be used for crossover inclusion/exclusion criteria and tumor burden if these were collected within 6 weeks prior to the time of the patients signing the crossover consent for this Unblinded Phase of the study.

1. Have measurable or non-measurable disease assessable by RECIST 1.1
2. For patients who were randomized to the control arm and on the long-term follow-up period at the time of the crossover screening: have progression of unresectable locally advanced or metastatic breast cancer after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
3. Have ECOG PS 0 or 1
4. Have a life expectancy of at least 6 months, in the opinion of the investigator
5. Have adequate hepatic function as defined by:

a. Total bilirubin ≤1.5 X ULN, except for patients with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 X ULN

b. Transaminases AST/SGOT and ALT/SGPT ≤ 2.5 X ULN (≤ 5 X ULN if liver metastases are present)

6. Have adequate hematologic parameters as defined by:

   a. ANC ≥ 1.5 x 10^3/μL

   b. Platelet count ≥ 100 x 10^3/μL; patients with stable platelet count from 75-100 x 10^3/μL may be included with approval from medical monitor

   c. Hemoglobin ≥ 9 g/dL

   d. In patients transfused before crossover screening, transfusion must be ≥ 14 days prior to start of crossover treatment to establish adequate hematologic parameters independent from transfusion support

7. Have creatinine clearance ≥ 50 mL/min as calculated per institutional guidelines or, in patients ≤ 45 kg in weight, serum creatinine within institutional normal limits

8. Have LVEF ≥ 50% as assessed by ECHO or MUGA scan documented within 6 weeks prior to the time of crossover consent

9. For patients of childbearing potential, 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 starting crossover study treatment. A subject with a false positive result and documented verification that the patient is not pregnant is eligible for starting crossover study treatment.

   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:

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

10. For patients 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
11. Patient must provide signed informed consent per a consent document that has been approved by an IRB/IEC prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the patient's disease
12. Patients must be willing and able to comply with study procedures

CNS Inclusion – Based on crossover screening contrast brain magnetic resonance imaging (MRI) within 6 weeks prior to the time of crossover consent, patients must have **one** of the following:

13. No evidence of brain metastases
14. Untreated brain metastases not needing immediate local therapy. For patients with untreated CNS lesions > 2.0 cm on screening contrast brain MRI, discussion with and approval from the medical monitor is required prior to enrollment

15. Previously treated brain metastases

    a. 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

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

        i. Time since whole brain radiation therapy (WBRT) is ≥ 21 days prior to start of crossover (tucatinib) treatment, time since stereotactic radiosurgery (SRS) is ≥ 7 days prior to start of crossover (tucatinib) treatment, or time since surgical resection is ≥ 28 days prior to start of crossover (tucatinib) treatment

        ii. Other sites of disease assessable by RECIST 1.1 are present

6.3.2 Crossover Exclusion Criteria

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) will be excluded if they meet any of the exclusion criterion below. Prior scans and imaging may be used for crossover inclusion/exclusion criteria and tumor burden if these were collected within 6 weeks prior to the time of the patients signing the crossover consent for this Unblinded Phase of the study.

1. Discontinuation of study treatment (placebo + trastuzumab + capecitabine) due to an adverse event while on the double-blind phase of the study. If the adverse event leading to discontinuation of study treatment has resolved, the patient may be allowed to crossover with approval from the medical monitor.
2. History of exposure to the following cumulative doses of anthracyclines:
    a. Doxorubicin > 360 mg/m^2
    b. Epirubicin > 720 mg/m^2
    c. Mitoxantrone > 120 mg/m^2
    d. Idarubicin > 90 mg/m^2
    e. Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) > 550 mg/m^2
3. History of allergic reactions to trastuzumab, capecitabine, 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 one of the excipients in the study drugs

4. Have received treatment with any systemic anti-cancer therapy (including hormonal therapy), non-CNS radiation, or experimental agent ≤ 3 weeks prior to start of crossover (tucatinib) treatment or are currently participating in another interventional clinical trial. Ongoing treatment with trastuzumab + capecitabine as part of this trial is not exclusionary. An exception for the washout of hormonal therapies is GnRH agonists used for ovarian suppression in premenopausal women, which are permitted concomitant medications
5. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1 (ongoing treatment with trastuzumab + capecitabine as part of this trial is not exclusionary), with the following exceptions:
    - alopecia and neuropathy, which must have resolved to ≤ Grade 2; and
    - 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
6. Have clinically significant cardiopulmonary disease such as:
    - ventricular arrhythmia requiring therapy,
    - uncontrolled hypertension as determined by investigator,
    - any history of symptomatic CHF
    - severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy, or
    - hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea
7. Have known myocardial infarction or unstable angina within 6 months prior to start of crossover (tucatinib) treatment
8. Are known carriers of Hepatitis B or Hepatitis C or have other known chronic liver disease
9. Are known to be positive for HIV
10. Are pregnant, breastfeeding, or planning a pregnancy
11. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)

12. Have inability to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications
13. Have used strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a CYP2C8 or CYP3A4 inducer within 5 day prior to start of crossover (tucatinib) treatment. Strong CYP2C8 inhibitors and CYP2C8 or CYP3A4 inducers are also prohibited in the 2 weeks following discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks prior to start of crossover (tucatinib) treatment
14. Have known dihydropyrimidine dehydrogenase deficiency
15. Unable for any reason to undergo contrast MRI of the brain
16. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
17. Have evidence within 2 years prior to start of crossover (tucatinib) treatment of another malignancy that required systemic treatment.

CNS Exclusion – Based on crossover screening contrast brain MRI within 6 weeks prior to the time of crossover screening, patients must not have any of the following:

18. Any untreated brain lesions > 2.0 cm in size, unless discussed with medical monitor and approval for enrollment is given
19. 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, patients on a chronic stable dose of ≤ 2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the medical monitor
20. 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 patient (e.g. brain stem lesions). Patients who undergo local treatment for such lesions identified by crossover screening contrast brain MRI may still be eligible for the study based on criteria described under CNS inclusion criteria 15b
21. Known or suspected LMD as documented by the investigator
22. Have poorly controlled (> 1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

6.4 Criteria for Discontinuation of Study Treatment

No randomized patients will be replaced, including patients who have not received study treatment. Reasons for patient withdrawal from study treatment may be due to any of the following:

- AE
- Progressive disease
- Second disease progression after isolated progression in brain
- Death
- Withdrawal of consent
- Lost to follow-up
- Physician decision due to clinical progression
- Physician decision (other)
- Patient decision
- Protocol violation
- Study termination by sponsor
- Pregnancy or begins breastfeeding while on trial
- Other

For both phases, the reason for withdrawal from study treatment must be recorded in the patient's eCRF. Evaluations scheduled for the 30-Day Follow-up Visit and Long-Term Follow-up Visits will be completed, unless the patient withdraws consent from the study in writing. Patients also may choose to withdraw consent for procedures and visits but remain on study for PFS and OS follow-up through medical records, public records, or public platform.

In the double-blinded phase of the study, patients should also be followed for progressive disease (per RECIST 1.1) at least until a PFS event has been observed. If an AE is the cause for withdrawal from study treatment, then "Adverse Event" should be recorded as the reason for treatment discontinuation rather than physician decision or patient decision. Treatment discontinuation due to AE should be noted any time that a patient has an AE such that the patient may not re-start tucatinib, either due to investigator discretion or due the requirements of dose modification described in Section 7.4 (e.g. requiring dose reduction to <150 mg BID tucatinib, holding tucatinib >6 weeks due to toxicity, or lack of resolution of AE to a sufficient grade to re-start tucatinib). Patients who discontinue tucatinib or placebo or both capecitabine and trastuzumab should be recorded as an

"adverse event" for the reason for treatment discontinuation if AE led to discontinuation of study drugs.

In the double-blinded phase of the study, because the primary study endpoint is defined as PFS as determined by central radiologic assessment, every effort should be made to confirm disease progression (per RECIST 1.1) whenever possible. However, in instances where patients appear to have progressive symptoms and signs of metastatic breast cancer for whom it is not possible or feasible to undergo radiologic assessment, investigators may remove the patient from study treatment due to "physician decision due to clinical progression." These patients will be censored in the final analysis of the primary endpoint, so use of this reason for removing such patients from study treatment should be restricted to those cases in which it is not clinically appropriate for the patient to undergo further radiologic assessment and where there is clinical confidence for cancer progression in the absence of radiographic confirmation. Special consideration should be given to ensure that other possible reasons, particularly AEs, are not a more accurate description of the reason for study drug discontinuation in these cases.

For both phases, long-term follow-up after discontinuation of study treatment will continue until the patient completely withdraws from the study. Patients also may choose to withdraw consent for procedures and visits but remain on study for PFS and OS follow-up through medical records, public records, or public platform. Reasons for patient withdrawal from the study may be due to any of the following:

- Death
- Withdrawal of consent for follow-up
- Lost to follow-up
- Physician Decision
- Study termination by sponsor
- Other

7 TREATMENTS ADMINISTERED

Patients in the study will receive a combination treatment of capecitabine, trastuzumab, and either tucatinib or placebo. All treatments will be given on a 21-day cycle.

7.1 Standard of Care Treatment

Treatment with capecitabine and trastuzumab will be administered to all patients as standard of care therapy for their HER2+ locally advanced or metastatic breast cancer.

7.1.1 Capecitabine

Capecitabine will be given at 1000 mg/m^2 PO BID for Days 1-14 only of a 21-day cycle.

As capecitabine is an oral drug available in fixed doses, the dose administered may not exactly match the calculated dose. Determination of the rounding of capecitabine doses for administration should be made according to local institutional practices, with documentation of both the calculated and administered dose.

Capecitabine will be obtained as described in the pharmacy binder.

Capecitabine should be prepared and administered per instructions in the package insert. Capecitabine will be administered orally based on instructions provided by the investigator. Per package insert, it is recommended that capecitabine be administered with food. Capecitabine should be stored according to the package insert.

7.1.1.1 Risks Associated with Capecitabine

Risks associated with capecitabine include diarrhea, coagulopathy, cardiotoxicity, hand-and-foot syndrome (also known as PPE), hyperbilirubinemia, and hematologic toxicity. Please see the capecitabine (Xeloda®) SmPC or Package Insert/national prescribing information for more details.

Management of capecitabine toxicities may require temporary interruption, dose reduction, or treatment discontinuation with capecitabine as per guidelines in Table 7-3.

7.1.2 Trastuzumab

Intravenous

Trastuzumab will be given as a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days. However, a loading dose of trastuzumab will not be given to patients who have received trastuzumab within 4 weeks of Cycle 1 Day 1. These patients will receive trastuzumab at 6 mg/kg each cycle, including Cycle 1. 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.

Subcutaneous

Alternatively trastuzumab may be administered as a subcutaneous dose, given as a fixed dose of 600 mg once every 3 weeks. Subcutaneous trastuzumab does not require a loading dose nor is a weekly schedule available for the subcutaneous formulation. Patients are permitted to crossover from IV trastuzumab to subcutaneous trastuzumab or from subcutaneous to IV trastuzumab.

Biosimilar

Approved trastuzumab biosimilars (intravenous or subcutaneous formulations) may be used in the study as either the initial therapy or at a later time if crossover to a biosimilar is determined appropriate by the investigator. However, a trastuzumab biosimilar may only be used during the study if approved for use by national regulatory authorities.

General

Trastuzumab will be obtained as described in the pharmacy binder.

Trastuzumab should be prepared and administered per instructions in the package insert. Trastuzumab will be administered IV or subcutaneously under the direction of the investigator. Trastuzumab should be stored according to the package insert.

7.1.2.1 Risks 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®) SmPC or Package Insert/national prescribing information for more details.

Management of left ventricular dysfunction, pulmonary toxicity, or infusion reactions may require temporary interruption or treatment discontinuation of trastuzumab as per guidelines provided in the package insert as well as in Table 7-2 and Table 7-5.

7.2 Tucatinib

7.2.1 Double-blind Phase Tucatinib and Placebo

Patients will be randomized as described in Section 5.8.1 to receive either tucatinib 300 mg PO BID or placebo tablets. The placebo tablets do not contain the active ingredient but are identical in appearance to active tablets to maintain blinding. Capecitabine and tucatinib/placebo may be taken together or in sequence.

To minimize risks to patients, blinded safety data will be reviewed on an ongoing basis throughout the study by the sponsor and blinded and unblinded data will be reviewed at regular intervals or ad hoc as needed by an independent DMC.

7.2.2 Unblinded Phase Tucatinib

Patients will receive tucatinib 300 mg PO BID. Capecitabine and tucatinib may be taken together or in sequence. If the patient is currently receiving treatment on the control arm (placebo + trastuzumab + capecitabine), does not crossover and remains on trastuzumab and capecitabine treatment, placebo tablets do not need to be administered.

To minimize risks to patients, safety data will be reviewed on an ongoing basis throughout the study by the sponsor.

7.2.3 Dosing Instructions

Patients will be instructed to store and take the tucatinib/placebo treatment (as appropriate) as follows:

- Bottles of tucatinib/placebo tablets should be stored in the refrigerator and should not be left in hot places (for example, in a car on a hot day).
- Tucatinib/placebo tablets will be taken by mouth twice each day (one dose in the morning, and one dose in the evening).
- Instructions will be given as to how many tablets to take each morning and each evening. All the prescribed number of tablets for morning and evening doses should be taken within a 10-minute timeframe.
- It is recommended that tucatinib/placebo tablets be taken at the same times each day, ± 2 hours.
- Tucatinib/Placebo doses should be ingested with a full 8 oz. glass of water, if possible. Doses may be taken either with or without food.
- Tucatinib/Placebo bottle and all remaining pills should be brought to the clinic for each study visit.
- It is important for us to know that a patient is receiving the correct amount of drug while participating on the study. If the patient was not able to take the fully prescribed dose or any single tablet of tucatinib/placebo as instructed on any day, the patient should contact the study coordinator with the reasons that the correct number of tablets or dose were not taken. Missed doses or tablets, or doses that are vomited, will not be replaced.

7.2.4 Risks Associated with Tucatinib alone and in Combination with Trastuzumab and Capecitabine

Overall, tucatinib has been well tolerated in clinical trials to date (Section 3.2.3). The most frequent AEs seen with tucatinib have been mild to moderate in severity, and toxicities associated with dual EGFR/HER2 inhibitors such as Grade 3 diarrhea and rash have been uncommon.

In the Phase 1 single-agent study of tucatinib (Study ARRAY 380-101), the most common AEs (reported in ≥ 20% of patients) were nausea, diarrhea, fatigue, vomiting,

rash, constipation, cough, and pain in extremity. Of these events, the majority were Grade 1 in severity. Grade 3 TEAEs occurring in > 1 patient included anemia and cellulitis (6% each); and abdominal pain, hypokalemia, increased ALT, increased AST, musculoskeletal chest pain and vomiting (4% each).

The most likely potential overlapping toxicities seen for the combination of tucatinib plus capecitabine and trastuzumab in this study include GI toxicity, such as nausea, constipation, and diarrhea, as well as elevation of liver function tests and fatigue. Refer to the Investigator's Brochure for additional information.

There have been rare reports of mild heart failure in patients taking tucatinib in combination with trastuzumab alone or with capecitabine as well as in combination with other cancer treatments.

While interstitial lung disease (ILD) has not been reported with tucatinib, this event has been seen with other HER2-inhibitors, and therefore represents a potential risk.

Patients will be closely monitored for occurrence of GI, cardiac function and liver toxicity. The specific safety plans for monitoring for cardiac toxicity and hepatotoxicity are outlined in Sections 9.4.3 and 9.4.4, respectively. In addition, patients will be closely monitored throughout the study for the occurrence of any other expected and/or unexpected toxicities. Patients will be allowed to use concomitant medication to manage GI and other symptoms, per treating physician discretion.

Dose modifications and treatment interruptions of any of the study drugs will be allowed as described in Section 7.4.

7.2.5 Description of Active Ingredient

Tucatinib is a potent, selective, adenosine triphosphate (ATP)-competitive small-molecule inhibitor of the receptor tyrosine kinase HER2.

Chemical Name: (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine

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 for PO. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidine-vinyl acetate copolymer (PVP-VA), which is then combined with standard pharmaceutical excipients and compressed into tablets.

7.2.6 Packaging and Labeling

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

7.2.7 Storage and Handling

Bottles of tucatinib drug product (tablets) and placebo tablets are to be stored under refrigeration (2 to 8°C).

7.3 Study Drug Accountability

7.3.1 Accountability of Tucatinib Tablets and Placebo

Tucatinib or placebo used during the course of the study should be handled according to the sponsor's instructions. Tucatinib and placebo are to be tracked and documented from the time of receipt at the site, through patient 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 and will conduct final drug accountability monitoring at site closure. All used and unused tucatinib and placebo bottles should be handled according to the sponsor's instructions.

7.3.2 Accountability of Capecitabine and Trastuzumab

Sites will also be required to provide accountability for administration of trastuzumab and for the use of capecitabine for entry into the eCRF.

7.4 Dose Modifications

Table 7-1 through Table 7-5 provide dose modification guidance for tucatinib or placebo, capecitabine, and trastuzumab.

For the Double-blind Phase of this study, patients who discontinue either capecitabine or trastuzumab (but not both) may remain on study treatment. Patients who discontinue tucatinib or placebo, or both capecitabine and trastuzumab will not be allowed to remain on study treatment but will continue to be followed for efficacy assessments per protocol schedule.

For the Double-blind Phase of this study, patients who continue capecitabine and/or trastuzumab after discontinuation of tucatinib/placebo in the absence of progression per RECIST 1.1 but who do not initiate additional new anti-cancer therapy, data related to administration of trastuzumab and/or capecitabine will continue to be collected. Patients will be considered to be no longer receiving study treatment after discontinuation of tucatinib/placebo.

For the Unblinded Phase of this study, patients who discontinue either capecitabine or trastuzumab may remain on study treatment. In instances where capecitabine and trastuzumab have been discontinued, patients may remain on study treatment with tucatinib alone. Patients who discontinue tucatinib will not be allowed to remain on study treatment.

For both phases of this study, all AEs and laboratory abnormalities should be assessed by the investigator for relationship to tucatinib or placebo, capecitabine, and trastuzumab, as applicable. An AE may be considered related to tucatinib or placebo alone, capecitabine alone, trastuzumab alone, 2 of the 3 drugs, all 3 drugs, or to none. In the event that the relationship is unclear, discussion should be held with the medical monitor to discuss which study drug(s) should be held and/or modified. Dosing should be modified (including holding the dose, dose reduction, or discontinuation of drug) as described below.

Any study drug should be discontinued if a delay of that drug greater than 6 weeks is required due to treatment-related toxicity, unless a longer delay is approved by the medical monitor.

Protocol-defined visits and cycle numbering should continue as planned during a 21-day cycle even during dose holds or delays.

Capecitabine should only be taken on Days 1 to 14 of a cycle. No doses should be given on Day 15 through Day 21 of a cycle.

Dose reductions or treatment interruption/discontinuation for reasons other than those described below may be made by the investigator if it is deemed in the best interest of patient safety.

Doses held for toxicity will not be replaced.

Study treatment may be held up to 6 weeks to allow local CNS therapy. Oral study drugs (tucatinib/placebo and capecitabine) are to be held 1 week prior to planned CNS-directed therapy. The potential for radiosensitization with tucatinib is unknown. Capecitabine is a known radiation sensitizer and therefore needs to be held prior to CNS-directed radiotherapy. Trastuzumab has been shown not to potentiate radiation and therefore may continue as per protocol schedule during radiotherapy. Oral study drugs may be re-initiated 7 days or more after completion of SRS/SRT, 21-days or more after WBRT and 28-days or more after surgical resection. Plans for holding and re-initiating study drugs before and after local therapy will require discussion with, and documented approval from, the medical monitor.

7.4.1 Tucatinib or Placebo Dose Reductions

Refer to Table 7-1 through Table 7-5 for the tucatinib or placebo dose modification requirements. 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 or placebo 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.

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

Table 7-1 Recommended Tucatinib or Placebo Dose Reduction Schedule

Starting Dose[a]	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
300 mg PO BID	250 mg PO BID	200 mg PO BID	150 mg PO BID

a. Dose reductions of greater steps 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 or placebo may not be dose reduced below 150 mg BID.

7.4.2 Trastuzumab Dose Modifications

There are no dose reductions for trastuzumab. 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. The subcutaneous dose of trastuzumab (600 mg) cannot be modified as it is administered only once every 3 weeks. 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 or the 600 mg subcutaneous dose should be re-started. As trastuzumab may be given as an IV infusion, infusion-associated reactions (IARs), may occur.

If a significant IAR occurs, the infusion should be interrupted and appropriate medical therapies should be administered (see below). Permanent discontinuation should be considered in patients with severe IAR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

If patients develop an IAR, patients should be treated according to the following guidelines, or according to institutional guidelines, at discretion of the investigator:

1. Stop infusion and notify physician.
2. Assess vital signs.
3. Administer acetaminophen 650 mg PO.
4. Consider administration of: meperidine 50 mg IM, diphenhydramine 50 mg IV, ranitidine 50 mg IV or cimetidine 300 mg IV, dexamethasone 10 mg IV or famotidine 20 mg IV.
5. If vital signs stable, resume trastuzumab infusion.

No standard premedication is required for future treatments if patients have developed an infusion syndrome. Patients 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 7-2 Dose Modifications of Tucatinib or Placebo and Trastuzumab for Clinical Adverse Events Other Than Left Ventricular Dysfunction Related to Trastuzumab, or Hepatocellular Toxicity*

	Tucatinib or Placebo	Trastuzumab
Clinical Adverse Event	Related to tucatinib or Placebo	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 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. Restart without dose reduction.
Grade 3 rash WITHOUT optimal 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 optimal 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

*Note that if the AE in question does not recover to the Grade required for restarting study medication as outlined in the table, the patient may need to discontinue the drug completely. Patients requiring a hold of tucatinib for > 6 weeks must discontinue study treatment, unless a longer delay is approved by the medical monitor.

7.4.3 Capecitabine Dose Modifications

Capecitabine doses must be modified as described below in Table 7-3.

Capecitabine must be held for any patient who experiences a Grade 2 or greater AE considered related to capecitabine or to the combination of tucatinib or placebo and capecitabine and/or trastuzumab (attribution as determined by the investigator). Held doses of capecitabine should not be made up within each cycle.

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

Table 7-3 Dose Modification of Capecitabine for Clinical Adverse Events Considered Related to Capecitabine

CTCAE Toxicity Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of Starting Dose)[a]
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2[b]		
1st appearance	Interrupt until resolved to Grade ≤ 1.	100%
2nd appearance	Interrupt until resolved to Grade ≤ 1.	75%
3rd appearance	Interrupt until resolved to Grade ≤ 1.	50%
4th appearance	Discontinue permanently.	NA
Grade 3		
1st appearance	Interrupt until resolved to Grade ≤ 1.	75%
2nd appearance	Interrupt until resolved to Grade ≤ 1.	50%
3rd appearance	Discontinue permanently.	NA
Grade 4		
1st appearance	Discontinue permanently.	

Abbreviations: Common Terminology Criteria for Adverse Events (CTCAE); not applicable (NA).

a. Dose modification table is based upon XELODA® package insert; dose rounding should be performed per institutional guidelines

b. In certain instances of asymptomatic or mildly symptomatic Grade 2 laboratory abnormalities (for example, anemia), investigators may choose to maintain capecitabine dose level and/or to resume capecitabine prior to resolution to Grade 1. This should be done only when the risk to patient from capecitabine dose interruption and/or reduction outweighs the risk to the patient from the adverse event, and when the action is consistent with usual and customary clinical practice.

7.4.4 Dose Modifications for Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities.

For dose modifications of tucatinib or placebo and capecitabine, see Table 7-4 below. Dose modification of trastuzumab is not required but dosing can be held at investigator discretion. For patients with documented Gilbert's disease, please contact the medical monitor for guidance regarding dose modifications in these patients.

Table 7-4 Dose Modifications of Tucatinib or Placebo and Capecitabine for Liver Function Abnormalities

Liver Function Abnormalities	Action for tucatinib or placebo, Regardless of Relationship to Drug	Capecitabine
Grade 2 elevation of ALT and/or AST (> 3 – ≤ 5 x ULN)	Dose modification not required	If abnormalities are considered related to capecitabine, please follow guidelines as per Table 7-3. If abnormalities are not considered related to capecitabine, modifications are not mandated but may be made at the discretion of the investigator.
Grade 3 elevation of ALT and/or AST (> 5–20 x ULN)	Hold until severity ≤ Grade1 Restart at next lowest dose level	
Grade 4 elevation of ALT and/or AST (> 20 x ULN)	Discontinue drug	
Elevation of ALT and/or AST (> 3 x ULN) AND Bilirubin (> 2 x ULN)	Discontinue drug	
Grade 2 elevation of bilirubin (> 1.5–3 x ULN)	Hold until severity ≤ Grade 1 Restart at same dose level	
Grade 3 elevation of bilirubin (> 3 – ≤ 10 x ULN)	Hold until severity ≤ Grade 1 Restart at next lowest dose level	
Grade 4 elevation of bilirubin (> 10 x ULN)	Discontinue drug	

Abbreviations: alanine aminotransferase (ALT); aspartate aminotransferase (AST); upper limit of normal (ULN).

7.4.5 Trastuzumab Dose Modifications for Left Ventricular Dysfunction

Trastuzumab dose modification guidelines, regardless of relationship, for left ventricular dysfunction are provided in Table 7-5.

Table 7-5 Trastuzumab Dose Modifications for Left Ventricular Dysfunction

LVEF at assessment	Action
LVEF ≥50%	Continue treatment with trastuzumab
LVEF 45% to <50% with <10% decrease from baseline	Continue treatment with trastuzumab
LVEF <45% or 45% to <50% with ≥10% decrease from baseline	Hold trastuzumab, repeat LVEF in 3 weeks
Repeat LVEF at 3 weeks:	
- LVEF ≥50%	Resume treatment with trastuzumab
- LVEF 45% to 49%	
<10% decrease from baseline	Resume treatment with trastuzumab
≥10% decrease from baseline	Discontinue trastuzumab
- LVEF <45%	Discontinue trastuzumab
Symptomatic CHF	Discontinue trastuzumab

7.5 Concomitant Therapy

All concomitant medications will be recorded in the eCRF. Concomitant medications can be administered at the investigator's discretion to conform to standard practice during the treatment period.

Any planned surgery (major or minor) not directly related to cancer that occurs on study requires consultation with the sponsor medical monitor. Patients are required to suspend study treatment 3 to 7 days prior to surgery and depending upon the nature of the surgery resume study treatment 3 to 21 days postoperatively. For emergency surgeries, contact medical monitor as soon as feasible to discuss resumption of study treatment postoperatively.

7.5.1 Required Concomitant Therapy

There are no required concomitant therapies.

7.5.2 Allowed Concomitant Therapy

Patients 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, patients may receive supportive care to include bisphosphonates, denosumab, hematologic / 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 is not required but may be permitted at the discretion of the investigator
- Use of topical 10% urea cream or other topical emollients are permitted for prophylaxis and treatment of PPE related to capecitabine use
- 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 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 1.1 (Appendix B). 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

- Acetaminophen may be used to manage drug-related AEs such as fever, myalgias or arthralgias and anti-histamines may be used to manage drug-related AEs such as pruritus
- Routine prophylaxis with vaccines is permitted, if vaccines used do not contain live micro-organisms
- Patients requiring systemic corticosteroids for control of brain metastases at a dose > 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. Premedication with corticosteroids solely for contrast use in scans or MRI can be used without prior medical monitor approval. Patients 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. (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)

7.5.3 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 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, provided that there remain other sites of assessable disease accessible by RECIST 1.1
- Warfarin or other coumarin derivatives (non-coumarin anti-coagulants are permitted)
- Vaccination with live vaccines
- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within two weeks of discontinuation of tucatinib treatment – Partial and more complete lists of strong inhibitors and inducers may be found in other reference material. For additional information,

including drug elimination half-lives of strong inhibitors and inducers, see Appendix C

- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within two weeks of discontinuation of study treatment – Partial and more complete lists of strong inhibitors and inducers may be found in other reference material. For additional information including drug elimination half-lives of strong inhibitors and inducers, see Appendix D

7.5.4 Potential Concomitant Drug Interactions

For sensitive substrates of CYP3A (see 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-gp substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions (see Appendix G). 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.

7.6 Treatment Compliance

Compliance will be assessed on a patient-by-patient basis. The pharmacist or designee will record the number of tucatinib or placebo tablets dispensed to each individual patient, and the number of tablets returned to the clinic at the end of each cycle. Data regarding the administration and dose of trastuzumab, as well as the number of tablets of capecitabine taken will also be collected by the site after each cycle. Dose modifications and interruptions of any study drug will be documented in the source documents and the eCRF.

7.7 Duration of Participation

Patients will receive study treatments in repeating 21-day cycles. Patients may continue to receive study treatment until disease progression per RECIST 1.1 (except for patients with CNS-only progression who may continue on study treatment after initial CNS-only progression as described in Section 5.1.3), withdrawal of consent, or study closure.

7.7.1 Follow-up After Discontinuation of Study Treatment

Approximately 30 days after the last study treatment, a 30-Day Follow-up Visit will occur.

In the Double-blind Phase of the study, a brain MRI is required for all patients at the 30-Day Follow-up Visit, regardless of presence or absence of brain metastases on screening MRI, unless progression in the brain was previously documented while on study treatment. Additionally, all patients in the double-blind phase of the study for whom study treatment is discontinued for reasons other than confirmed disease progression (per RECIST 1.1) or death, every effort should be made to collect scans approximately every 9 weeks after the previous scan, until disease progression (per RECIST 1.1), death, study withdrawal, or study closure.

Following the 30-Day Follow-up Visit, patients will be considered in the long-term follow-up portion of the study. Patients will be contacted at 90-day intervals until death, withdrawal of consent, or study closure. Patients will be contacted or have an in-person assessment of OS and/or disease recurrence, and collection of any additional anti-cancer therapies administered after completion of study treatment. Review of medical records, public records, or public platforms may be used to obtain this information if reasonable efforts for contact or in-person assessment are unsuccessful.

8 TRIAL PROCEDURES

8.1 Double-blind Phase

The schedule of events is summarized in Appendix A.1. Study activities are listed by visit in this section and descriptions of study assessments are presented in Section 9. All assessments performed on Day 1 of all treatment cycles should be performed prior to administration of study drugs with the exception of AE documentation, concomitant medication documentation, and post-dose PK in Cycle 3 only. Study assessments will continue regardless of any dose holds or delays.

8.1.1 Screening/Baseline (Days -28 to 1)

Optional prescreening to confirm HER2 positivity by central review is permitted at any time prior to study screening, after signing a separate pre-screening consent form.

The following will be obtained or confirmed:

- Informed consent*
- Study eligibility per inclusion/exclusion criteria
- Confirmatory central HER2+ testing, with biopsy showing HER2+ by ISH or FISH (or centrally confirmed HER2+ by ISH, FISH or 3+ staining by IHC in a previous study as approved by the medical monitor).*
    - Confirmatory HER2 testing may be obtained greater than 28 days prior to randomization if separate prescreening consent for confirmatory HER2 testing is signed.
- Documentation of concomitant medications
- Documentation of baseline medical conditions
- Documentation of disease history
- Physical examination
- Vital signs (height, weight, blood pressure, heart rate, temperature, and respiration rate)
- ECG
- ECHO, or MUGA to include at a minimum LVEF; note that whichever testing modality is chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison*
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function tests including all lab tests listed in Section 9.4.2

- Blood samples for coagulation panel that include all tests listed in Section 9.4.2
- Blood samples for hepatitis screening: Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV). (If positive, additional confirmatory testing may be required after discussion with medical monitor.)*
- Blood sample for assessment of potential biomarkers of response*
- Urine sample for urinalysis
- For females of childbearing potential (have not had a hysterectomy and/or bilateral oophorectomy, or ≥ 12 months of amenorrhea) serum or urine pregnancy test within 7 days of first study treatment
- Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging).
- Contrast MRI of the brain for all patients for assessment of brain tumor burden; CT of the brain will not be allowed, and patients with known contraindications to undergoing contrast MRI imaging will be excluded from the study.*
- For patients with brain metastases discovered during screening or a history of brain metastases, confirm relevant MRI brain reports and CNS treatment records can be obtained.
- Documentation of AEs
- Randomization MUST occur on or before Cycle 1 Day 1, such that dosing should commence within 5 days after randomization

*For patients who have unsuspected brain metastases discovered at screening and go on to receive immediate local therapy to the CNS, 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, ECHO/MUGA, hepatitis screening, biomarker sampling, and confirmatory HER2 testing. All other safety labs and assessments will need to be repeated if outside the 28 day window for these patients. In addition, an additional contrast MRI brain following local therapy will not be required prior to starting study treatment if radiation treatment was given. A postoperative contrast MRI brain scan is required prior to starting study treatment if surgical resection was performed.

8.1.2 Cycle 1 Day 1

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination†
- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS†
- Blood samples for hematology and clinical chemistry (Results must be reviewed and eligibility confirmed prior to first dose)†
- Blood samples for liver function tests (Results must be reviewed and eligibility confirmed prior to first dose)†
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to dose administration)
- Dispense tucatinib or placebo and administer the morning dose of tucatinib or placebo ‡
- Administer morning dose of capecitabine at 1000 mg/m^2‡
- Administer trastuzumab at 8 mg/kg given IV, unless patient has received trastuzumab within 4 weeks of first dose of trastuzumab on study. In this case, patient will not receive loading dose, and will instead receive trastuzumab 6 mg/kg. Alternatively, if subcutaneous trastuzumab is used (in countries where approved), 600 mg given as a fixed dose, once every 3 weeks.‡

†These assessments do not need to be repeated if performed within 96 hours of C1D1.

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

8.1.3 Cycle 1 Day 12 (± 3 days)

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination
- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function tests

8.1.4 Cycle 2 Day 1 and Day 1 of All Subsequent Cycles (- 1 day to +3 days)

- Documentation of AEs

- Documentation of concomitant medications including review of number of day(s) anti-diarrheals were taken from previous cycle
- Physical examination
- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECG (through Cycle 4 only)
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function test
- For females of child-bearing potential only: serum or urine pregnancy test for each cycle; a positive urine test must be confirmed with a serum pregnancy test prior to each cycle of therapy
- Pre-tucatinib/placebo blood samples (up to 2 hours pre-dose) for PK analysis (through Cycle 6 only)
- Post-tucatinib/placebo blood sample (1-4 hours) for PK Analysis (Cycle 3 only)
- Completion of the EQ-5D-5L quality of life questionnaire (to be completed prior to dose administration) every 2 cycles regardless of treatment delays from Cycle 3-9 and every 3 cycles starting at Cycle 12
- Review tucatinib or placebo and capecitabine drug compliance from previous cycle and dispense tucatinib or placebo for next cycle‡
- Administer trastuzumab at 6 mg/kg IV or subcutaneously ‡

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

8.1.5 Cycle 2 Day 12 (± 3 days)

- Blood samples for liver function tests (total bilirubin, AST and ALT) (may be obtained at a laboratory outside the clinical site if normal ranges are made available)

8.1.6 Every Six Weeks as Determined by Cycle 1 Day 1, Through Week 24 (- 7 days)

- Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document site of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging)
- Contrast MRI of the brain (only in patients with presence or history of brain metastases) and assessment of CNS lesions (brain or dura)

- If cycles are delayed for any reason continue with initial scan schedule as determined by the date of Cycle 1 Day 1
- If an interim unscheduled assessment is performed, scans should continue to be done on schedule. In cases of medical contraindication for repeat scans, please 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

8.1.7 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

8.1.8 Beginning Week 24, Every 9 Weeks Through End of Treatment (- 7 Days)

- Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document all known sites of disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging)
- Contrast MRI of the brain (only in patients with presence or history of brain metastases) and assessment of CNS lesions (brain or dura)
- If cycles are delayed for any reason, then perform scans every 9 weeks beginning Week 24 as determined by the date of Cycle 1 Day 1
- If an interim unscheduled assessment is performed, scans should continue to be done on schedule. In cases of medical contraindication for repeat scans, please 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

8.1.9 30-Day Follow-up Visit (30 days, + 7 days, after last dose of study treatment)

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination
- Vital signs

- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function tests
- Blood sample for coagulation panel
- Serum or urine pregnancy test; a positive urine test must be confirmed with a serum pregnancy test. (If not done within the last 60 days; not required for females of non-child-bearing potential)
- Blood sample for biomarker analysis
- Contrast CT, PET/CT (if high quality CT scan included) and/or non-brain MRI scan only in patients having ended study treatment for reasons other than radiographic disease progression. Imaging is to be performed within 30 days of ending study treatment. At minimum, contrast scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging)
- Contrast MRI of the brain for all patients and assessment of CNS lesions (unless brain MRI performed within 30 days of ending study treatment or with prior documentation of progression in brain while on study)
- ECHO or MUGA, as appropriate, if not done within previous 12 weeks
- Completion of the EQ-5D-5L quality of life questionnaire

8.1.10 Long-Term Follow-up

- Starting 90 days (± 7 days) from the 30-Day Follow-Up Visit and continuing every 90 days (± 7 days) until death, withdrawal of consent, or study closure, the following must be performed. If a 30-Day Follow-Up Visit was not done, the long-term follow-up should begin every 90 days (± 7 days) starting from the date of the last dose of study treatment.
    - Patient 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 patient are unsuccessful.
    - More frequent long-term follow-up may be conducted as needed for OS event tracking
- **If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death** – Every 9 weeks (± 1 week) starting from the date of the last study treatment until disease progression (per RECIST 1.1), death,

withdrawal of consent, or study closure, in an effort to document a PFS event date:

- Every effort should be made to collect contrast CT, PET/CT (if high quality CT scan included) and/or MRI scans (e.g., skin lesion photography, bone imaging).

8.2 Unblinded Phase

8.2.1 Experimental Arm Continuing on Treatment

At the time of unblinding, patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine) and are on study treatment will remain on that treatment arm. Starting with the next normally scheduled cycle, the patient will continue treatment with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and Appendix A.2). Treatment cycle counting will continue from prior to the crossover, and patients will continue study treatment at the same doses they were given in the double-blind phase of the study.

Study activities are listed by visit in this section and descriptions of study assessments are presented in Section 9. All assessments performed on Day 1 of all treatment cycles should be performed prior to administration of study drugs except for AE and concomitant medication documentation. Study assessments will continue regardless of any dose holds or delays.

8.2.2 Experimental Arm in the Long-term Follow-up

Patients who were randomized to the experimental arm (tucatinib + trastuzumab + capecitabine), ended study treatment and are in the long-term follow-up are not eligible for additional treatment on the experimental arm in this study and will remain in long-term follow-up.

8.2.3 Control Arm Continuing on Treatment or in Long-term Follow-up

At the time of unblinding, patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) may crossover to the experimental arm if crossover criteria are met (Section 8.2.4). Patients who crossover to the experimental arm will restart their cycle number as Cycle 1 at Cycle 1, Day 1, per Section 8.2.5, and Appendix A.3

The schedule of events is summarized in Appendix A.3. Study activities are listed by visit in this section and descriptions of study assessments are presented in Section 9. All assessments performed on Day 1 of all treatment cycles should be performed prior to administration of study drugs except for AE and concomitant medication documentation. Study assessments will continue regardless of any dose holds or delays.

8.2.3.1 Control Arm Patients who do not meet Crossover Criteria

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and were receiving study treatment at the time of unblinding who do not meet crossover criteria will continue trastuzumab + capecitabine therapy. At the start of the next scheduled cycle, the patient will continue trastuzumab + capecitabine therapy with a modified schedule of events beginning at the Day 1 of All Subsequent Cycles visit (See Section 8.2.9 and Appendix A.3). These patients will continue trastuzumab + capecitabine therapy at the same doses they were given in the double-blind phase of the study.

Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and are in long-term follow-up at the time of unblinding who do not meet crossover criteria will remain in long-term follow-up.

8.2.4 Screening for Crossover Criteria

There will be a crossover screening period of up to 28 days after patients sign revised informed consent. Patients currently receiving treatment on the control arm (placebo + trastuzumab + capecitabine) will continue to receive study treatment during this crossover screening period at the same doses they were given in the double-blind phase of the study.

During crossover screening period, the following will be obtained or confirmed:

- Sign Revised Informed Consent
- Documentation of AEs
- Document crossover eligibility
- Document newly developed baseline medical conditions since discontinuation of control arm treatment (for patients who were in long-term follow-up at the time of unblinding)
- Document recent disease history (for patients who were in long-term follow-up at the time of unblinding), specifically all anti-cancer treatment regimens, radiation/surgery for disease since entering long-term follow-up
- Documentation of concomitant medications
- Physical examination
- Vital signs (height, weight, blood pressure, heart rate, temperature, and respiration rate)
- ECG

- ECHO or MUGA, as appropriate, if not done within 6 weeks prior to the time of crossover consent *
- ECOG PS
- Laboratory assessments for hematology, clinical chemistry, and liver function tests, including all lab tests listed in Section 9.4.2
- For females of childbearing potential (have not had a hysterectomy and/or bilateral oophorectomy, or ≥ 12 months of amenorrhea) serum or urine pregnancy test within 7 days prior to start of crossover (tucatinib) treatment
- Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden, if not done within 6 weeks prior to the time of crossover consent. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging)
    - New baseline RECIST lesions will be selected based on the results of these assessments of tumor burden
- Contrast MRI of the brain for all patients for assessment of brain tumor burden, if not done within previous 6 weeks; CT of the brain will not be allowed, and patients with known contraindications to undergoing contrast MRI imaging will be excluded from the study.*

*For patients who have unsuspected brain metastases discovered at crossover screening and go on to receive immediate local therapy to the CNS, 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 patients. In addition, an additional contrast MRI brain following local therapy will not be required prior to starting study treatment if radiation treatment was given. A postoperative contrast MRI brain scan is required prior to starting study treatment if surgical resection was performed.

8.2.5 Crossover to the Experimental Arm, Cycle 1 Day 1

For patients who were receiving study treatment at the time of unblinding, the Cycle 1, Day 1 crossover visit should be scheduled to synch with the patients' current cycle, occurring at the next Day 1.

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination†

- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS†
- Blood samples for hematology and clinical chemistry (Results must be reviewed and eligibility confirmed prior to start of crossover [tucatinib] treatment)†
- Blood samples for liver function tests (Results must be reviewed and eligibility confirmed prior to start of crossover [tucatinib] treatment)†
- Dispense tucatinib and administer the first dose of tucatinib ‡
- Administer the first dose of capecitabine ‡
    - Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each 21-day cycle. For patients who required dose reductions of capecitabine, capecitabine must be given at the same reduced dose most recently given in the double-blind phase of the study.
- Administer loading dose of trastuzumab at 8 mg/kg given IV, unless patient has received trastuzumab within 4 weeks. In this case, patient will not receive loading dose, and will instead receive trastuzumab 6 mg/kg. Alternatively, if subcutaneous trastuzumab is used (in countries where approved), 600 mg given as a fixed dose, once every 3 weeks‡

†These assessments do not need to be repeated if performed within the previous 96 hours.

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

8.2.6 Crossover to the Experimental Arm, Cycle 1 Day 12 (± 3 days)

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination
- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function tests (samples may be collected up to 2 days prior to this visit)

8.2.7 Crossover to the Experimental Arm, Cycle 2 Day 1 (- 1 day to +3 days)

- Documentation of AEs
- Documentation of concomitant medications including review of number of day(s) anti-diarrheals were taken from previous cycle
- Physical examination

- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function test (samples may be collected up to 2 days prior to this visit)
- For females of child-bearing potential only: serum or urine pregnancy test for each cycle; a positive urine test must be confirmed with a serum pregnancy test prior to each cycle of therapy
- Review tucatinib and capecitabine drug compliance from previous cycle and dispense tucatinib for next cycle‡
- Administer trastuzumab at 6 mg/kg IV or subcutaneously ‡

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

8.2.8 Crossover to the Experimental Arm, Cycle 2 Day 12 (± 3 days)

- Blood samples for liver function tests (total bilirubin, AST and ALT) and serum creatinine (may be obtained at a laboratory outside the clinical site if normal ranges are made available)

8.2.9 Day 1 of All Subsequent Cycles (- 1 day to +3 days)

At the first visit after unblinding, patients who were randomized to the experimental arm [tucatinib + trastuzumab + capecitabine] and are continuing treatment must sign the revised informed consent.

The remainder of this section applies to all patients who are continuing to receive study treatments in the Unblinded Phase.

- Documentation of AEs
- Documentation of concomitant medications including review of number of day(s) anti-diarrheals were taken from previous cycle
- Physical examination
- Vital signs (weight, blood pressure, heart rate, temperature, and respiration rate)
- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function test (samples may be collected up to 2 days prior to this visit)
- For females of child-bearing potential only: serum or urine pregnancy test for each cycle; a positive urine test must be confirmed with a serum pregnancy test prior to each cycle of therapy

- Review tucatinib and capecitabine drug compliance from previous cycle and dispense tucatinib for next cycle‡
- Administer trastuzumab at 6 mg/kg IV or subcutaneously ‡

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

8.2.10 Every 12 Weeks as Determined by Crossover Screening Exam or Most Recent Exam (-7 days)

This section applies to all patients who are continuing to receive study treatments in the Unblinded Phase

- 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

8.2.11 Tumor Assessments after Crossover Screening Through End of Treatment

This section applies to all patients who are continuing to receive study treatments in the Unblinded Phase

The investigator will determine the frequency and method of tumor assessments performed for patient care decisions according to routine clinical practice, with a maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.

- Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document all known sites of disease and assessment of tumor burden at intervals as per standard clinical practice as determined by the investigator
- Contrast MRI of the brain, if appropriate, at intervals as per standard clinical practice as determined by the investigator

8.2.12 After Last Dose of Study Treatment - 30-Day Follow-up Visit (30 days, + 7 days)

- Documentation of AEs
- Documentation of concomitant medications
- Physical examination
- Vital signs
- ECHO or MUGA, as appropriate, if not done within previous 12 weeks

- ECOG PS
- Blood samples for hematology, clinical chemistry, and liver function tests
- Serum or urine pregnancy test; a positive urine test must be confirmed with a serum pregnancy test. (If not done within the last 60 days; not required for females of non-child-bearing potential)

8.2.13 Long-Term Follow-up

- Starting 90 days (± 7 days) from the 30-day Follow-Up Visit and continuing every 90 days (± 7 days) until death, withdrawal of consent, or study closure, the following must be performed. If a 30-day Follow-Up Visit was not done, the long-term follow-up should begin every 90 days (± 7 days) starting from the date of the last dose of study treatment.
    - Patient contact or in-person assessment of survival status 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 patient are unsuccessful.
    - More frequent long-term follow-up may be conducted as needed for OS event tracking

9 STUDY ASSESSMENTS

9.1 Efficacy Assessments

9.1.1 Double-blind Phase

Following initiation of study treatment, measurement of all known sites of metastatic or locally advanced unresectable disease (including at a minimum the chest, abdomen, and pelvis) by high quality spiral contrast CT, PET/CT (if high quality CT scan included) and/or contrast MRI scan as appropriate, as well as appropriate imaging of any other known sites of disease (e.g., skin lesion photography, bone imaging) will be obtained at the end of every 6 weeks for 24 weeks, then every 9 weeks while on study treatment. These scans will remain on this schedule irrespective of dose interruptions. Additional imaging, such as nuclear bone scans, may be done as appropriate at the discretion of the investigator. All body contrast CT or MRI scans, bone imaging, and skin lesion photographs, including baseline scans and scans done during long-term follow-up will be collected for retrospective BICR. All treatment decisions will be made on the basis of local investigator assessment. Results of centralized review will not be available to investigators for clinical decision making. If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death, patients will continue to have long-term follow-up for disease progression and every effort should be made to collect scans and clinical data approximately every 9 weeks until disease progression or other criteria for patient withdrawal from the study are met in an effort to document a PFS event date.

All brain contrast MRI images will be performed locally and collected prospectively for centralized independent review. However, all treatment decisions will be made on the basis of local review of radiologic imaging. Patients with any history of brain metastases, any brain metastases at baseline, or brain lesions of equivocal significance at baseline will continue to have follow-up brain contrast MRIs on the same schedule as non-CNS disease re-staging. In patients 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. Patients without brain metastases at baseline will not require follow-up brain contrast MRIs while on treatment unless clinically indicated, but will be asked to have an additional brain contrast MRI at the 30-Day Follow-up Visit, unless a brain contrast MRI has been performed within 30 days or the reason for going off treatment was progression in the brain. If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death, patients will continue to have long-term follow-up for disease progression and every effort should be made to collect scans and clinical data approximately every 9 weeks until disease progression or other criteria for patient withdrawal from the study are met in an effort to document a PFS event date. Brain contrast MRIs will be used to determine the incidence and time to progression in brain, as well as the brain response rate.

In the event of equivocal progression for example a new lesion ≤ 5 mm in maximum diameter (defined as an equivocal new lesion) and no imminent threat to patient safety, all efforts should be made to continue the patient until unequivocal radiologic progression or clinical progression is documented. An unequivocal new lesion is defined as any new lesion > 5 mm in maximum diameter, as defined in the response assessment manual. Demonstration of an unequivocal new lesion constitutes disease progression.

All scans will be assessed per RECIST 1.1. Refer to Appendix B and study binder for further details.

9.1.2 Unblinded Phase

Patients in the unblinded phase of the study will have the frequency and method of tumor assessments done according to routine clinical practice as determined by the investigator with a maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.

9.2 Health Economic Assessments

9.2.1 Double-blind Phase

A quality of life assessment using the EQ-5D-5L questionnaire is to be completed at Cycle 1 Day 1 prior to the start of treatment then every 2 cycles regardless of treatment delays from Cycle 3-9 and every 3 cycles starting at Cycle 12. Additionally, a post-treatment assessment will occur approximately 30 days post-end of treatment. Detailed medical resource utilization data are captured in the eCRF.

9.2.2 Unblinded Phase

Health economic assessments will not be performed in the unblinded phase of the study.

9.3 Pharmacokinetic Assessments

9.3.1 Double-blind Phase

The steady state PK of tucatinib and its metabolite will be assessed through the sparse sampling of the peak and trough levels from Cycle 2 to Cycle 6. PK assessment of trough levels will be performed on all patients on Day 1 of Cycles 2–6 prior to drug administration and peak level assessment will be on Cycle 3 Day 1 within 1-4 h after drug administration. PK samples should continue to be collected on schedule regardless of dose holds or interruptions.

Table 9-1 Pharmacokinetic Sampling

Cycle	Day	Time point	Tucatinib Sampling
2	1	0 h (-2 h) prior to administration of tucatinib/placebo	1 x 5 mL
3	1	0 h (-2 h) prior to administration of tucatinib/placebo	1 x 5 mL
		1 – 4 h following administration of tucatinib/placebo	1 x 5 mL
4-6	1	0 h (-2 h) prior to administration of tucatinib/placebo	1 x 5 mL

9.3.2 Unblinded Phase

Pharmacokinetic and biomarker assessments of tucatinib will not be performed in the unblinded phase of the study.

9.4 Safety Assessments

Safety assessments will consist of monitoring and recording AEs and SAEs; physical examination and vital signs; and measurement of protocol-specified clinical laboratory tests, and either ECHO or MUGA scans deemed critical to the safety evaluation of the study drug(s). Clinically significant changes in these parameters may be captured as AEs.

The investigator is responsible for the appropriate medical care and the safety of patients who have entered this study. The investigator must document all AEs and notify the sponsor of any SAE experienced by patients who have entered this study. Contact information for the sponsor's medical expert is provided on the protocol cover page.

9.4.1 Data Monitoring Committee

9.4.1.1 Double-blind Phase

The independent DMC will be responsible for monitoring the safety of patients in the study at regular intervals. The DMC will look at blinded and unblinded data including deaths, discontinuations, dose reductions, AEs, and SAEs on a regular basis. The DMC 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 DMC Charter will outline the committee's composition, members' roles and responsibilities, and describe DMC procedures. Sponsor will provide a copy of each DMC recommendation to the investigators.

9.4.1.2 Unblinded Phase

The monitoring responsibility of the independent DMC will be considered completed and no more DMC reviews will occur.

9.4.2 Clinical Laboratory Evaluation

All safety labs will be analyzed by the site's local laboratory(ies). A central laboratory will be used for confirmatory HER2 testing during pre-screening and screening in the double-blind phase. Repeat confirmatory HER2 testing will not be required for the unblinded phase.

The chemistry panel is to include the following tests: calcium, magnesium, inorganic phosphorus, total protein, albumin, blood urea nitrogen (BUN), creatinine, bicarbonate, glucose, potassium, chloride, and sodium.

Liver function tests (LFT) are to include the following: AST/SGOT, ALT/SGPT, total bilirubin, and alkaline phosphatase.

The hematology panel is to include the following tests: complete blood count (CBC) with differential, hemoglobin, hematocrit (Hct), and platelets.

9.4.3 Safety Plan for Cardiotoxicity

Trastuzumab and other HER2-targeted therapies are known to increase the risk of the development of asymptomatic and symptomatic declines in LVEF. There have been rare reports of asymptomatic left ventricular ejection fraction decline in patients taking tucatinib in combination with trastuzumab alone or with capecitabine. Cardiac function will therefore be monitored closely.

Patients will be closely monitored throughout the study for the occurrence of any other expected and/or unexpected toxicities. 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 30 days after the last treatment dose (unless done within 12 weeks prior to 30-day follow-up visit).

9.4.4 Safety Plan for Hepatotoxicity

While not among the most common adverse reactions reported in patients taking tucatinib, Grade 3 and 4 elevation of LFTs have been seen in some patients on tucatinib studies. Monitoring of liver function tests is required for any patient taking tucatinib. Refer to the Investigator's Brochure for additional information on LFT elevations.

Patients will have LFTs (ALT, AST, total bilirubin, alkaline phosphatase) monitored closely. Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. Tucatinib should be held according to protocol if liver functions tests are elevated, and monitored for normalization to the appropriate level per protocol before restarting study drugs. Other contributing factors (e.g., concomitant use of hepatotoxic agents) should also be considered and modified as clinically appropriate.

The identification of liver enzyme abnormalities as potential adverse reactions to tucatinib does not impact upon the anticipated favorable benefit-risk profile of tucatinib, and is thus far in line with the types and severity of AEs that may be seen with other cancer therapies for patients with metastatic breast cancer.

9.4.5 Safety Plan for Patients with Brain Metastases

Patients with brain metastases are at risk for occurrence of AEs due to the presence of CNS lesions, progression of disease and toxicities potentially related to study treatment. On occasion, treatment of brain metastases with systemic or radiation therapy has been associated with localized edema thought to be due to treatment effect and not tumor progression. A patient in study ONT-380-005 with known brain metastases was found to have cerebral edema in an area surrounding a known metastasis in the thalamus shortly after starting treatment with tucatinib, capecitabine and trastuzumab. The patient's

symptoms responded rapidly and completely to systemic corticosteroids. It was not known if this patient's symptoms were due to local progression or treatment-related toxicity. Similarly, a patient treated with tucatinib and trastuzumab alone experienced enlargement of a previously irradiated CNS lesion during study treatment. The patient was taken for surgical resection, and found to have no viable tumor. The resected lesion was thought to represent treatment-related necrosis.

In order to minimize the risk of symptomatic cerebral edema in patients with brain metastases in this study, patients 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 patients 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 patients 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.

9.4.6 Safety Plan for Prevention of Pregnancy

Due to the potential effect on embryo-fetal development, women of childbearing potential (who have not undergone surgical sterilization with a hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy; or, are not postmenopausal, as defined as ≥ 12 months of amenorrhea) must agree to use a highly effective birth control method. Highly effective methods of birth control include intrauterine device, bilateral tubal occlusion/ligation, vasectomized partner, or sexual abstinence when it is the preferred and usual lifestyle choice of the subject.

Male patients with partners of childbearing potential must use barrier contraception. All study patients should practice effective method of contraception, as described above, starting from the signing of informed consent until 7 months after the last dose of study medication or investigational medicinal product.

Patients of child-bearing potential are to have serum or urine pregnancy tests performed on Day 1 of each treatment cycle.

9.4.7 Adverse Events

9.4.7.1 Definitions

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Conference on Harmonisation (ICH) E2A guideline; Definitions and Standards for Expedited Reporting; 21 CFR 312.32 IND Safety Reporting.)

The following should be considered when determining whether or not to record a test result or medical condition as an AE:

- Any new undesirable medical occurrence or unfavorable or unintended change of a pre-existing condition that occurs during or after treatment with study drugs should be recorded as an AE.
- Complications that occur as a result of protocol-mandated interventions (e.g. invasive procedures such as biopsies) should be recorded as an AE.
- Elective procedures or routinely scheduled treatment are not considered AEs. However, an untoward medical event occurring during the pre-scheduled elective procedure should be recorded as an AE.
- Baseline conditions are not considered AEs unless the condition worsens following study drug administration. Any change assessed as clinically significant worsening of the disease from baseline must be documented as an AE. Baseline conditions present prior to consent will be recorded as medical history.
- Clinically significant laboratory abnormalities or vital signs (e.g. requiring intervention, meeting serious criteria, resulting in study termination or interruption of study treatment, or associated with signs and symptoms) should be recorded as AEs. If possible, abnormal laboratory results that meet the definition of an AE should be reported as a clinical diagnosis rather than the abnormal value itself (e.g., “anemia” rather than “decreased blood count”).

Serious Adverse Event

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

Fatal:	The AE resulted in death.
Life Threatening:	The AE placed the patient 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 required 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:	Resulted in a substantial and permanent disruption of the patient's ability to carry out activities of daily living.
Congenital Anomaly or Birth Defect:	An adverse outcome in a child or fetus of a patient exposed to the study drug or study treatment regimen before conception or during pregnancy.
Important medical event:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

Overdose, Medication Error, Misuse and Abuse

Overdose is defined as the administration of a quantity of investigational medicinal product given per administration or cumulatively which is above the maximum dose, according to the protocol.

Medication error refers to an unintentional error in dispensing or administration of the investigational medicinal product not in accordance with the protocol.

Misuse is defined as any situation where the investigational medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse is defined as the persistent or sporadic intentional excessive use of the investigational medicinal product, which is accompanied by harmful physical or psychological effects.

Overdoses, medication errors, abuse or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

Any AE associated with an overdose, medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE.

Adverse Event of Special Interest

An AE of special interest 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 following AEs of special interest will need to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 9.4.7.4).

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 patients 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 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 a serious adverse event, 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 Event of Special Interest.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. These criteria are provided in Appendix F.

AE severity and seriousness are assessed independently. Severity characterizes the intensity of an AE. Seriousness is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting requirements (see definition of SAE).

Relationship of the Adverse Event to Study Treatment

The relationship of an AE to all study drugs (tucatinib/placebo, capecitabine, and trastuzumab) should be assessed using the guidelines presented below. An AE for which there has been no causal relationship reported will require follow-up to determine causality.

Is the AE/SAE suspected to be caused by the investigational product on the basis of facts, evidence, science-based rationales, and clinical judgment?	
Related	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
Not related	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely OR other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the AE/SAE.

9.4.7.2 Procedures for Eliciting and Recording of Adverse Events Eliciting Adverse Events

The investigator will assess patients for the occurrence of AEs at all scheduled and unscheduled visits. The occurrence of AEs should be sought by non-direct questioning of the patient at each visit. AEs may also be detected when they are volunteered by the patient during and between visits or through physical examination, or other assessments.

All AEs reported by the patient will be reviewed by the investigator and must be recorded on the source documents and AE eCRFs provided.

Recording Adverse Events

Regardless of relationship to study drug, all serious and nonserious AEs that occur during the protocol-defined reporting period are to be recorded on the eCRF. SAEs occurring between pre-screening consent and main consent do not need to be documented, unless they are caused by a study procedure (for example, biopsy).

The following information will be assessed and recorded on the eCRF for each AE:

- Description of the AE including onset and resolution dates
- Severity (see Definitions)
- Relationship to each study drug (see Definitions)
- Outcome of each event
- Seriousness (see Definitions)
- Action taken regarding each study drug

Diagnosis vs. Signs or Symptoms

Whenever possible, the investigator should group signs or symptoms that constitute a single diagnosis under a single event term. For example, cough, rhinitis and sneezing might be grouped together as “upper respiratory tract infection”. 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 event.

Progression of Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it will not be reported as 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.

9.4.7.3 Reporting Periods and Follow-up of Adverse Events and Serious Adverse Events

Report all AEs identified during the clinical study from the time the patient signs informed consent through the 30-day follow-up visit (tucatinib/placebo, capecitabine, or trastuzumab). For subjects who previously had a 30-day follow-up visit and are now crossing over to the experimental arm, report all AEs through the Unblinded 30-day follow-up visit (Section 8.2.12), or 30 days after the last dose of protocol administered study drug.

Any SAE that occurs after the patient discontinues study treatment considered by the investigator to be related to any study drug should be reported to the sponsor.

All SAEs and AEs of special interest will be followed until the acute event has resolved or stabilized, even if the patient discontinues study treatment prior to SAE resolution. Non-serious AEs will be followed per the reporting period as noted above.

If a non-serious AE is ongoing at the 30-Day Follow-up Visit, the AE will be recorded as ongoing.

9.4.7.4 Serious Adverse Event and Event of Special Interest Reporting Procedures

All SAEs/EOIs regardless of relationship to study drug that occur after the first administration of study drug must be reported to the sponsor on a SAE/EOI form within 24 hours of discovery of the event. An SAE occurring after informed consent but before administration of study drug and possibly related to a protocol procedure must also be reported to the sponsor within 24 hours of discovery of the event. Any new information

or follow-up information pertaining to previously reported SAEs/EOIs should be reported to the sponsor within 24 hours of becoming aware of the new or follow-up information.

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

- Patient number
- AE term(s), including serious criteria and onset date
- Study treatment
- Causality assessment

The processes for reporting and documenting SAEs and EOIs are provided in the study binder. Investigators are responsible for reporting these events to their IRB and/or IEC in accordance with federal and local institutional laws and regulations.

New or follow-up information should be faxed or emailed to the sponsor's clinical safety department. The fax number and email address can be found on the SAE/EOI form and in the study binder. Medical concerns or questions regarding safety should be directed to the medical monitor.

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/EOI form and the eCRF
- 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

9.4.7.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (Section 9.4.7.4).

The sponsor will conduct safety reporting to regulatory authorities, IRBs, and IECs as required per local regulatory reporting requirements. SAEs assessed as related and unexpected (as per IB) to tucatinib/placebo will be unblinded by the sponsor to identify study treatment and will be reported in accordance with local regulatory reporting requirements. In the double-blind phase, investigators will receive all expedited reports in a blinded manner. In the unblinded phase, investigators will receive all expedited reports in an unblinded manner.

9.4.7.6 Pregnancy Reporting

Cases of pregnancy must be reported through 7 months after the last dose of study drug (tucatinib, capecitabine, or trastuzumab, whichever is latest). If a patient or the female partner of a male patient becomes pregnant during participation in the study, the sponsor

must be notified. If a study participant becomes pregnant during administration of the drug, treatment must be discontinued.

The investigator should report all pregnancies within 24 hours to the sponsor including the partners of male patients. The sponsor will ask for follow up evaluation of the pregnancy, fetus, and child.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as a SAE. Congenital anomaly or birth defects should also be reported as a SAE as described in Section 9.4.7.1.

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.

Pregnancy should be reported to the sponsor's clinical safety department on a Pregnancy Report Form.

10 DATA QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Site Monitoring and Training

The following are required of the sponsor or its representatives to ensure accurate, complete and reliable data:

- Provide instructional material to the study sites, as appropriate
- Conduct an initiation/start-up training session to instruct the investigators and study personnel on the protocol, completion of the eCRFs, study procedures, and GCP
- Make periodic monitoring visits to the study site
- Be available for consultation and stay in contact with the study-site personnel by mail, telephone, and/or fax
- Monitor the patient data recorded in the eCRF against source documents at the study site
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection

10.2 Data Management

Web-based eCRFs will be used to collect patient data in this study. This system, provided by a contract research organization, also includes electronic queries to resolve any questions or data discrepancies. All eCRFs and resulting data will be developed and maintained in a manner consistent with currently available regulations and guidances pertinent to the use of computerized systems in clinical trials. All sponsor, sponsor designees, and study-site users of the eCRF system will be trained prior to the use of the system.

10.3 Quality Assurance Audits

The study site may be audited by the sponsor or its representatives and/or regulatory agencies at any time. The sponsor must be notified immediately if an investigator is contacted by a regulatory agency to schedule an audit in relation to this study.

Sponsor audits may be conducted to verify data, protocol compliance and overall adherence to GCP. The investigator and/or clinical staff must agree to allow the auditor direct access to all trial-related documents (i.e., source medical records), and must allocate time to meet with the auditor when applicable. Contact information for the sponsor is provided in the study binder.

11 STATISTICS

11.1 Double-blind Phase

This randomized, international, multi-center, double-blind study is designed to assess the efficacy and safety of tucatinib vs. placebo (in combination with capecitabine and trastuzumab) in patients with progressive unresectable locally advanced or metastatic HER2+ breast carcinoma who have previously received treatment with trastuzumab, pertuzumab and T-DM1. Tumor efficacy, both in extracranial and intracranial locations, will be evaluated.

11.1.1 Statistical Methods

This section outlines the statistical and analytical methods to be used in the study. Exploratory analyses of the data not described in the following subsections may be conducted as deemed appropriate. Additional details will be provided in the Statistical Analysis Plan (SAP), which will be finalized before study unblinding.

11.1.1.1 General Considerations

Data collected in this study will be presented using summary tables, patient 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.

11.1.1.1.1 Analysis Populations

The intent-to-treat (ITT) population will include all randomized patients and will be used for efficacy analyses. In all efficacy analyses, patients will be allocated to the treatment group to which they were randomized.

Safety analyses will include all randomized patients who received at least one dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab), with patients allocated to the treatment group associated with the regimen actually received.

Pharmacokinetic analyses will include all randomized patients who received at least one dose of tucatinib and who had at least one evaluable PK assessment.

11.1.1.1.2 Adjustments for Covariates

The dynamic hierarchical randomization scheme will include the following stratification factors: known history of treated or untreated brain metastases (yes/no); ECOG PS (0 vs. 1); and region of world (US vs. Canada vs. Rest of World). The primary PFS analysis, brain metastases subgroup PFS analysis and the analysis for OS will use re-randomization to reflect the dynamic randomization. For simplicity, descriptive analyses conducted for all other efficacy endpoints will be conducted without stratification.

11.1.1.1.3 Timing of Analyses

First Analysis:

The primary analysis of PFS will occur when: at least 288 PFS events determined by BICR have occurred in the first 480 randomized patients in the ITT population; and enrollment has been completed for the study. An interim analysis for the key secondary endpoints PFS_{BM} and OS in the ITT population will also be performed at this time if PFS is statistically significant (see Section 11.1.1.8 for details).

Second Analysis:

- If PFS_{BM} is not statistically significant at the time of the primary analysis of PFS, the final analysis of PFS_{BM} will be performed when approximately 220 PFS events based on BICR have occurred in the subgroup of patients with a history of brain metastases and/or brain metastases or brain lesions of equivocal significance at baseline. If OS is not statistically significant at the time of the primary analysis of PFS, a second interim analysis for OS will be performed at this time. Update of PFS will also be provided at the time of final analysis for PFS_{BM}.

  or

- If PFS_{BM} is statistically significant at the time of the primary analysis of PFS, no further formal testing of PFS_{BM} will be conducted. A second interim analysis for OS will be performed when approximately 75% (271) of the total required 361 OS events have occurred in the ITT population, if OS is not statistically significant at the time of the primary analysis of PFS.

Third Analysis:

If OS is not statistically significant at the first or second analysis, the final analysis of OS will be performed after 361 OS events have occurred in the ITT population.

11.1.1.2 Patient Disposition

An accounting of study patients by disposition will be tabulated by treatment group. The number of patients in each analysis population will likewise be tabulated by treatment group. Patients who discontinue study drug will be summarized and listed, with the reason for drug or study discontinuation.

Protocol violations will be summarized by treatment group. All non-protocol specified anti-cancer therapies will be listed and summarized by treatment group.

11.1.1.3 Baseline Characteristics

The following baseline characteristics will be summarized

- Patient 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.

11.1.1.4 Efficacy Analyses

11.1.1.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, defined as the time from randomization to documented disease progression as determined by BICR per RECIST 1.1 or death from any cause, whichever occurs earlier.

The analysis of the primary endpoint will be performed using the first 480 randomized patients in the ITT population. For the primary endpoint of centrally-reviewed PFS, the two treatment groups will be compared using a stratified log-rank test. The p-value for this test will be calculated using a re-randomization procedure (Rosenberger 2015) to reflect the dynamic allocation used in randomization: known history of treated or untreated brain metastases (yes/no); ECOG PS (0 vs. 1); and region of world. Patients who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, non-CR/non-PD or SD. Details of the censoring scheme for the primary analysis of PFS are described in the SAP.

Kaplan-Meier methodology will be used to estimate the PFS time curves. The median PFS and its 95% confidence interval (CI) will be provided for two treatment arms. A Cox proportional-hazards model taking into account the stratification factors, will be used to estimate the hazard ratio (HR) and its 95% CI.

For patients who receive non-protocol specified anti-cancer therapy (NPT) prior to documented PD, details of the censoring scheme and sensitivity analyses to be performed for the primary endpoint will be described in the statistical analysis plan for this study.

11.1.1.4.2 Key Secondary Efficacy Endpoints

11.1.1.4.2.1 Progression-Free Survival in Patients With Brain Metastases

If the overall test of PFS is statistically significant at the 0.05 level (2-sided), PFS for the subgroup of patients with brain metastases at baseline (PFS_{BM}), defined as patients with a history of brain metastases, current brain metastases, or equivocal brain lesions at baseline, will be evaluated using the same statistical methods used for the primary analysis of PFS. The multiplicity adjustment is described in Section 11.1.1.9.

11.1.1.4.2.2 Overall Survival

Duration of OS is defined as the time from randomization to death from any cause. The same statistical methods for the primary analysis of PFS will be used for OS. The multiplicity adjustment is described in Section 11.1.1.9. For a patient who is not known to have died by the data cutoff date, OS will be censored on the date the patient was last known to be alive (i.e., date of last contact).

11.1.1.4.3 Other Secondary Efficacy Endpoints

11.1.1.4.3.1 Investigator-Assessed PFS

PFS will also be assessed based solely on investigator assessments, namely: the time from randomization to investigator-assessed documented disease progression per RECIST 1.1 or death from any cause, whichever occurs earlier.

11.1.1.4.3.2 Response Rates – Objective Response Rate and Clinical Benefit Rate

Data summaries for ORR will be provided for patients with measurable disease at baseline, as well as for all patients in the ITT population. For the First Analysis (the primary analysis of PFS), the first 480 randomized patients in the ITT population will be used for this analysis. The 95% CI will be estimated for each treatment group. Additionally, the difference in incidence between the two treatment groups will be provided with its corresponding 95% CI.

A similar approach will be used for the clinical benefit rate (CBR) analysis, but the analysis for CBR will include all patients in the ITT population.

Duration of Response

Only patients with a response will be included in the analysis of duration of response. Duration of response is defined as the time from first documented response to documented disease progression or death from any cause, whichever occurs earlier. Duration of responses will be graphically described using Kaplan-Meier methodology. The median DOR and its 95% confidence interval (CI) will be provided for two treatment arms.

11.1.1.4.4 Exploratory Efficacy Endpoints

ORR and DOR in brain per RANO-BM will be summarized in patients who had brain metastasis at baseline. Time to progression in brain per RANO-BM, defined as the time from the date of randomization to the date of documented disease progression in brain will be summarized using cumulative incidence curves by treatment group (i.e., competing risk methodology) treating non-brain progression and death as competing events.

HER2 and other mutations will be explored as possible predictive biomarkers though the use of descriptive subgroup analyses of the primary and secondary endpoints.

11.1.1.4.5 Health-Related Quality of Life

Health-related quality of life will be evaluated using the EQ-5D-5L questionnaire. The recall time frame for the descriptive system is the day in which the questionnaire is administered. The instrument is in paper format and is completed by the patient prior to being seen by her care providers in clinic.

Responses to the descriptive system form a 5-digit number describing the respondent's health, with 11111 representing the best possible health state and 55555 representing the worst health state. Each health state will be converted into a single number called an index value or health utility. The index value ranges from less than zero (worse than death) to 1 (perfect health) according to the preferences of the general population. This conversion will occur through mapping the EQ-5D-5L responses to the appropriate value sets recommended by EuroQol (van Reenen 2019).

The EQ-5D-5L questionnaire also includes a 20-cm vertical visual analog scale (VAS) with 100 on the top representing the "best imaginable health state" and 0 at the bottom representing the "worst imaginable health state." The recall time frame for the VAS is the day in which it is administered. The treatment and placebo group will be compared using a t-test if the VAS scores are normally distributed and a Mann-Whitney test if the data are non-parametric. A difference of 7 in VAS score will be considered to be clinically important (Pickard 2007).

The treatment and placebo group index values changes will be summarized. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes.

11.1.1.4.6 Health Care Resource Utilization

Health care resource utilization data collected from the eCRF and will include procedures that occur on study, length of stay and procedure time, hospitalizations, ED visits, planned and unplanned provider visits, medication use, radiology, and other treatments and procedures. Analysis by resource utilization category will rely primarily on descriptive summary statistics and confidence intervals.

11.1.1.5 Pharmacokinetic Analyses

Individual (patient) plasma tucatinib and ONT-993 concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated. Additional exploratory pharmacokinetic analyses may be conducted.

Exploratory analyses investigating the relationship between tucatinib exposure and efficacy and safety endpoints may be conducted.

11.1.1.6 Safety Analyses

Safety is 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 criteria.

11.1.1.6.1 Extent of Exposure

Study drug administration data will be listed by treatment group, study site, patient number, and cycle; any dose modifications or dose holdings will be flagged. For each of the regimen components (tucatinib/placebo, trastuzumab, capecitabine), duration of exposure and number of treated cycles will be summarized by treatment group.

For each of the regimen components (tucatinib/placebo, trastuzumab, capecitabine), tolerability will be assessed by tabulating the frequency of study drug interruption and discontinuations due to AE by treatment group. In addition, for tucatinib/placebo and capecitabine, tolerability will be further assessed by tabulating the frequency of dose reductions by treatment group. Treatment compliance (percent of actual to planned dosing) will likewise be summarized for tucatinib/placebo and capecitabine by treatment group.

The summary of trastuzumab and capecitabine exposure will only include the period when patients are on study treatment, i.e., before tucatinib/placebo is discontinued.

11.1.1.6.2 Adverse Events

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

All TEAEs will be summarized by treatment group, as follows:

- All AEs (regardless of grade)
- All Grade 3/4/5 AEs
- All drug-related AEs (regardless of grade)
- All AEs leading to study drug discontinuations
- All serious AEs, including deaths
- All AEs of special interest (regardless of grade)

In the event of multiple occurrences of the same AE with the same preferred term in one patient, the AE will be counted once as the occurrence.

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

11.1.1.6.3 Clinical Laboratory Results

Laboratory values (hematology, chemistry, and liver function) will be summarized by treatment group. Abnormal laboratory 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.

11.1.1.6.4 Vital Signs and Physical Examination Findings

The frequency and percentage of patients with post-baseline clinically significant vital signs will be summarized. Abnormal physical examination findings may be collected as AEs.

11.1.1.6.5 Cardiac Ejection Fraction

Cardiac ejection fraction data will be summarized by treatment group. Corresponding shift tables will also be provided by treatment group.

11.1.1.7 Handling of Missing Data

For the analysis of PFS, data for patients without disease progression (per RECIST 1.1) or death will be censored at the time of last tumor assessment that was CR, PR, non-CR/non-PD or SD (or, if no tumor assessment was performed after the baseline visit, at the time of randomization). Further details describing the censoring scheme for PFS will be described in the SAP.

For the analysis of ORR and CBR, patients without a post baseline tumor assessment will be considered non-responders/non-clinical benefiters.

For the analysis of OS, patients who are alive at the time of analysis will be censored at the last date they were known to be alive. Patients with no post baseline information will be censored at the date of randomization. Further details describing the censoring scheme for OS will be described in the SAP.

11.1.1.8 Interim Analyses

One formal interim analysis for superiority is planned for PFS_{BM} and two formal interim analyses for superiority are planned for OS if the primary analysis for PFS is statistically significant. The interim analyses will be conducted at the timing described in Section 11.1.1.1.3. The stopping boundaries will be determined using Lan-DeMets spending functions for the O'Brien and Fleming boundaries. See Section 11.1.1.9 for control of multiplicity. Further details will be provided in the SAP.

11.1.1.9 Multiple Comparison and Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05, the PFS will be tested using the first 480 randomized patients in the ITT population at 0.05 level first, and if it is significant, then the key secondary endpoints will be tested using the group sequential Holm variable (GSHv) procedure (Ye 2013).

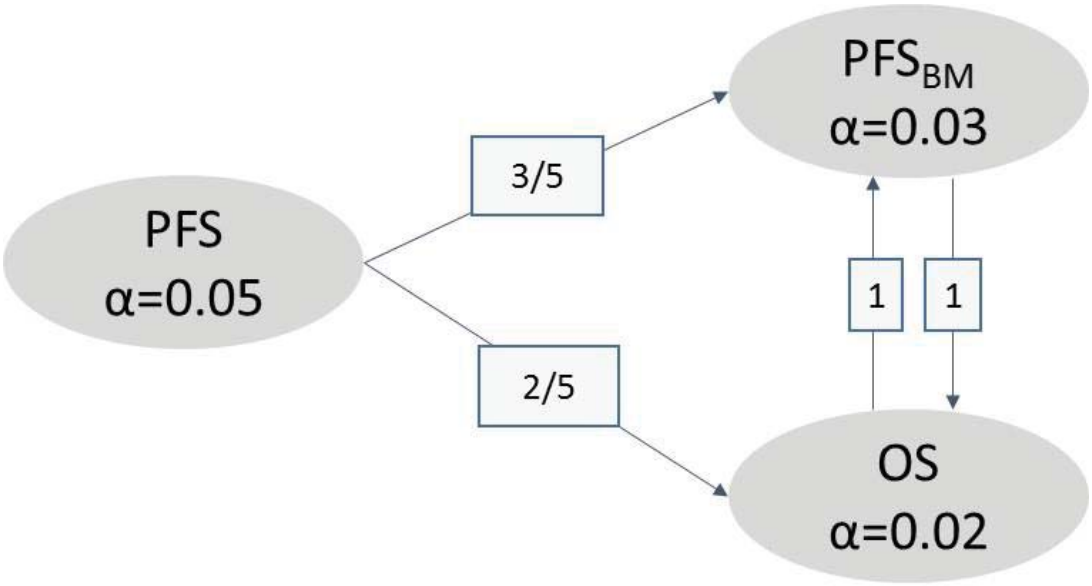


Figure 11-1 Type I Error Reallocation Strategy Following Closed Testing Principle

As illustrated in Figure 11-1, the sequence of testing will begin with the evaluation of PFS. If PFS is statistically significant, then the key secondary endpoints PFS_{BM} and OS will be tested using group sequential boundaries: PFS_{BM} will be tested using a total alpha of 0.03 and OS will be tested using a total alpha of 0.02. If only one of the two key secondary endpoints is statistical significant, the unused alpha can be passed to the other one following the GSHv procedure. A Lan-DeMets O'Brien-Fleming approximation spending function will be used for the calculation of efficacy boundaries for PFS_{BM} and OS.

11.1.2 Determination of Sample Size

The sample size for this study was calculated based on maintaining 90% power for the primary endpoint PFS with an alpha of 0.05 and 80% power for OS with an alpha of 0.02. For PFS, 288 events are required with 90% power to detect a hazard ratio of 0.67 (4.5 months median PFS in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test and alpha of 0.05.

For OS, 361 events are required with 80% power to detect a hazard ratio of 0.70 (15 months median OS in the control arm vs. 21.4 months in the experimental arm) using a 2-

sided log-rank test and alpha of 0.02, taking into account two interim analyses. With 361 OS events, it will provide 88% power using a 2-sided log-rank test with an alpha of 0.05.

For PFS_{BM}, 220 events are required with 80% power to detect a hazard ratio of 0.67 (4.5 months median PFS_{BM} in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test at alpha of 0.05, taking into account one interim analysis. The power will be 74% at 2-sided alpha of 0.03.

Approximately, 600 patients will be randomized in a 2:1 ratio to either the experimental arm or the control arm. Assuming an accrual period of 48 months and a 5% yearly drop-out rate, it is expected that 361 OS events will be observed approximately 59 months after first patient is randomized.

11.2 Unblinded Phase

Safety data will be summarized for the patients who receive study treatment in the unblinded phase. Progression-free survival per RECIST 1.1 by investigator and overall survival will be summarized at approximately 2 years after the last patient was randomized in this study.

12 INFORMED CONSENT, ETHICAL REVIEW, AND ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in the "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations. For studies conducted in the United States or under U.S. IND, the investigator will additionally adhere to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR subchapter D, part 312, "Responsibilities of Sponsors and Investigators," part 50, "Protection of Human Patients," and part 56 "Institutional Review Boards."

In other countries where "Guidelines for Good Clinical Practice" exist, Seagen and the investigators will strictly ensure adherence to the stated provisions.

12.1 Informed Consent

It is the responsibility of the investigator or a person designated by the investigator (if acceptable by local regulations) to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, anticipated benefits, objectives, and potential hazards of the study. Appropriate forms for obtaining written informed consent will be provided by the investigator or by Seagen/designee and must be approved by an IRB/IEC. For patients not qualified to give or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative.

If new safety information results in significant changes in the risk/benefit assessment, the informed consent form (ICF) should be reviewed and updated if necessary. All patients, including those already being treated, should be informed of the new information, given a copy of the revised form, and give their consent to continue in the study.

12.2 Ethical Review

Prior to enrollment of patients into the study, as required by the FDA, applicable European guidelines, and other regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC. By signing the Statement of Investigator Form (FDA Form 1572), the investigator assures that approval of the study protocol will be obtained from the IRB/IEC and that all aspects of the IRB/IEC review will be conducted in accordance with current regulations. Amendments to the protocol will be subject to the same IRB/IEC review requirements as the original

protocol. Only changes necessary to eliminate apparent immediate hazards to the patients may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC and Seagen in writing within 5 working days after implementation. The investigator will also promptly notify the IRB/IEC of any serious, unexpected AEs, or any other information that may affect the safe use of the investigational product. A letter documenting the IRB/IEC approval and a list of the names and titles of the IRB/IEC members or federal wide assurance number must be received by Seagen prior to the initiation of the study. All correspondence with the IRB/IEC should be retained in the investigator's study file. The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to Seagen. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to Seagen. This report should include the dates of initiation and completion of the study, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of patients evaluated, the number of patients who discontinued (and the reasons for discontinuation), the number of patients who completed the study, and the results of the study, including a description of any AEs. Seagen will assist the investigator in the preparation of this report, as needed.

The name and address of the reviewing committee are provided in the investigator file.

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

- The IRB/IEC approvals of the protocol and informed consent document, and any amendments or revisions
- The IRB/IEC periodic re-approval of the protocol where applicable
- Submission to IRB or IEC of safety and SAE reports, as appropriate

12.3 Administrative and Regulatory Considerations

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Seagen and investigators abide by GCP as described in the ICH Harmonised Tripartite Guideline E6 GCP: Consolidated Guideline, and for US Investigators, 21 CFR Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

12.3.1 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and the name and address of the research facilities are included in the trial master files. After reading the protocol, each principal investigator will sign the protocol signature page and return it to the sponsor or the sponsor's designee.

12.3.2 Protocol Amendments and Study Termination

The sponsor may periodically and officially amend the protocol to address safety issues or other developing issues.

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

12.3.3 Payments, Insurance, and Publications

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 described in the Clinical Trial Agreement.

12.4 Study Documentation, Privacy, and Records Retention

As described in the ICH GCP Guidelines, 'essential documents', including eCRFs, source documents, ICFs, laboratory test results and the investigational product inventory records, should be retained by the investigator until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with Seagen.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial be retained by the investigator until notified by the sponsor in writing that retention is no longer necessary. These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA, European Competent Authorities, and Health Canada (HC) in accordance with regulatory requirements.

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 patient medical records in the patient files as original source documents. If requested, the investigator will provide the sponsor, applicable regulatory agencies and applicable IRB/IEC with direct access to original source documents. The investigator will also provide appropriate facilities for periodic monitoring by the sponsor or designee.

Records containing patient medical information must be handled by the investigator in accordance with the required privacy policies and consistent with the terms of the patient authorization contained in the informed consent document for the study. 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, eCRFs and other documents to be transferred to the sponsor or sponsor designee should be completed in strict accordance

with the instructions provided by the sponsor, including the instructions regarding the coding of patient identities.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written approval must be obtained from the sponsor.

The investigator must keep these documents on file according to local regulations after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations. Should the investigator wish to assign the study records to another party or move them to another location, Seagen must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the investigator and Seagen to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator, in case of a regulatory audit. Where source documents are required for the continued care of the patient, appropriate copies should be made before storing outside of the site.

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Appendix A.1 Schedule of Events – Double-blind Phase

		Screening	Cycle 1		Cycle 2		
Study Procedure and Day		**Day -28 to 1**	**Day 1**	**Day 12 (± 3 days)**	**Day 1 (- 1 day to +3 days)**	**Day 12 (± 3 days)**	**CT/MRI Schedule**
Assessments	Informed consent	X					
	Document AEs	X	X	X	X		
	Document study eligibility	X					
	Confirmatory HER2+ testing[l]	X					
	Document concomitant meds[m]	X	X	X	X		
	Document baseline medical conditions	X					
	Document disease history	X					
	Physical exam	X	X[h]	X	X		
	Height	X					
	Vital signs (weight, BP, heart rate, temp, resp rate)	X	X	X	X		
	ECG	X			X		
	ECHO/MUGA	X					
	ECOG PS	X	X[h]	X	X		
	Labs[a]	X	X[h]	X	X	X[j]	
	Coagulation	X					
	Hepatitis B and C screening[b]	X					
	Blood sample for biomarker evaluation	X					
	Urinalysis	X					
	Pregnancy test[o]	X[c]			X		
	CT, PET/CT, or MRI[d]	X					X
	Contrast MRI Brain	X					X[k]
	EQ-5D-5L Questionnaire		X[n]				
Study Drug Treatment	Tucatinib/placebo[e]		X		X		
	Capecitabine[f]		X		X		
	Trastuzumab[g]		X		X		
PK	Blood samples				X[i]		

a. Blood samples for hematology, clinical chemistry and liver function tests.
b. Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV). If positive, contact medical monitor.
c. Serum or urine pregnancy test within 7 days prior to treatment (required only for females of child-bearing potential)
d. Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as skin lesion photography, bone imaging. Scans should

be performed every six weeks (based on Cycle 1 Day 1) through Week 24 then every nine weeks through end of study drug treatment. 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 as described in Section 8.6 and Section 8.8. Use the same modality performed at screening/baseline. If bone imaging is collected, any RECIST appropriate imaging modality may be used.

e. Tucatinib/placebo is administered PO BID, on a 21-day cycle. On day 1 of each cycle, review compliance from previous cycle and dispense tucatinib/placebo for next cycle.
f. Capecitabine is administered PO BID, on Day 1 through Day 14. On day 1 of each cycle, review compliance from previous cycle and dispense capecitabine for next cycle.
g. Trastuzumab is administered intravenously or subcutaneously, once every 21 days.
h. These evaluations do not need to be repeated if obtained within 96 hours of scheduled first dose of study drug on Cycle 1 Day 1. All lab results must be reviewed and eligibility confirmed prior to first dose.
i. Pre-dose
j. Only total bilirubin, AST and ALT are required at this visit.
k. MRI of the brain and assessment of brain lesions; only in patients with known brain metastases.
l. Confirmatory HER2 testing may be obtained greater than 28 days prior to randomization if separate consent for confirmatory HER2 pre-testing is signed.
m. Including concomitant procedures, hospitalization, and review of number of day(s) anti-diarrheals were taken from previous cycle.
n. To be completed prior to administration of any study drug treatment
o. Urine or serum pregnancy test, not required for females of non-child-bearing potential; a positive urine test must be confirmed with a serum pregnancy test.

		Cycle 3 and Beyond		30-Day Follow-Up Visit	Long-Term Follow-Up
Study Procedure and Day		**Day 1 (- 1 day to + 3 days)**	**CT/MRI and ECHO/MUGA Schedule**	**30 days (+ 7 days) after last dose of study treatment**	**90 days following 30-Day Follow-Up Visit and continuing every 90 days[t]**
Assessments	Document AEs	X		X	
	Document concomitant meds[q]	X		X	
	Physical exam	X		X	
	Vital signs (BP, heart rate, temp, and resp rate)	X		X	
	ECG	X[i]			
	ECOG PS	X		X	
	Labs[a]	X		X	
	Coagulation			X	
	Pregnancy test[b]	X[j]		X[m]	
	Blood sample for biomarker evaluation			X	
	ECHO/MUGA[c]		X[l]	X[n]	
	CT, PET/CT, or MRI[d]		X	X[o]	X[s]
	Contrast MRI Brain[e]		X	X[o]	X[s]
	EQ-5D-5L Questionnaire	X[r]		X	
	Patient contact/clinic visit[p]	X		X	X
Study Drug Treatment	Tucatinib/placebo[f]	X			
	Capecitabine[g]	X			
	Trastuzumab[h]	X			
PK	Blood samples	X[k]			

a. Blood samples for hematology, clinical chemistry and liver functions tests.
b. Urine or serum pregnancy test not required for females of non-child-bearing potential; a positive urine test must be confirmed with a serum pregnancy test.
c. Use the same modality performed at screening/baseline.
d. Contrast CT, PET/CT (if high quality CT scan included) or non-brain MRI scan only in patients having ended study treatment for reasons other than radiographic disease progression. At minimum, contrast scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as skin lesion photography, bone imaging. Use the same modality performed at screening/baseline. If bone imaging is collected, any RECIST appropriate imaging modality may be used. Scans should be performed every six weeks through Week 24 then every nine weeks through end of study drug treatment. 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 as described in Section 8.6 and Section 8.8.
e. Contrast MRI of the brain and assessment of brain lesions per RECIST; only in patients with known brain metastases except at the 30-day follow-up visit where all patients should have an MRI of the brain done (unless already done within 30 days of ending study treatment or brain progression has already been documented while on study).
f. Tucatinib/placebo is administered PO BID, on a 21-day cycle. On day 1 of each cycle, review compliance from previous cycle and dispense tucatinib/placebo for next cycle.
g. Capecitabine is administered PO BID, on Day 1 through Day 14. On day 1 of each cycle, review compliance from previous cycle and dispense capecitabine for next cycle.
h. Trastuzumab is administered intravenously or subcutaneously, once every 21 days.
i. ECG should be performed through cycle 4 only.

j. Performed for each cycle.
k. Through Cycle 6 only: Pre-dose at Cycles 3 – 6 and 1-4 hour post-dose at Cycle 3 only.
l. Every 12 weeks as determined by the date of the screening exam.
m. If not done within the last 60 days.
n. If not done within the previous 12 weeks.
o. If not done within the previous 30 ± 7 days. **NOTE:** If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death, patients will continue to have follow-up for disease progression and scan data should be collected approximately every 9 weeks until disease progression, death, withdrawal of consent, or study closure.
p. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful.
q. Including concurrent procedures, hospitalizations, and review of number of day(s) anti-diarrheals were taken from previous cycle.
r. To be completed prior to administration of any study drug treatment every 2 cycles from Cycle 3-9 and every 3 cycles starting at Cycle 12
s. If study treatment is discontinued for reasons other than disease progression (per RECIST 1.1) or death, patients will continue to have follow-up for disease progression and scan data should be collected approximately every 9 weeks until disease progression, death, withdrawal of consent, or study closure.
t. More frequent long-term follow-up may be requested for OS event tracking. If a 30-Day Follow-Up Visit was not done, the long-term follow-up should begin every 90 days (± 7 days) starting from the date of the last dose of study treatment.

Appendix A.2 Schedule of Events – Experimental Arm Continuing on Treatment in the Unblinded Phase

	Subsequent Cycles[g]		30-Day Follow-Up Visit	Long-Term Follow-Up
Assessments	**Day 1 (- 1 day to + 3 days)**	**CT/MRI and ECHO/MUGA Schedule**	**30 days (+ 7 days) after last dose of study treatment**	**90 days (+7 days) following 30-Day Follow-Up Visit and continuing every 90 days [k]**
Sign Revised Informed Consent	X [a]			
Document AEs	X		X	
Document concomitant meds [h]	X		X	
Physical exam	X		X	
Vital signs (weight, BP, heart rate, temp, resp rate)	X		X	
ECOG PS	X		X	
Labs [b]	X		X	
Pregnancy test [i]	X		X	
ECHO/MUGA		X [c]	X [l]	
CT, PET/CT or MRI		X [c]		
Contrast MRI Brain		X [c]		
Patient contact/clinic visit	X		X	X [j]
Study Drug Treatment				
Tucatinib [d]	X			
Capecitabine [e]	X			
Trastuzumab [f]	X			

a. For the first visit after unblinding only.
b. Blood samples for hematology, clinical chemistry and liver function tests. Samples may be collected up to 2 days prior to visits.
c. Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as skin lesion photography, bone imaging. While on treatment, scans should be performed at intervals as per standard clinical practice as determined by investigator with a maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.
d. Tucatinib is administered PO BID, on a 21-day cycle. On day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.
e. Capecitabine is administered PO BID, on Day 1 through Day 14. On day 1 of each cycle, review compliance from previous cycle and dispense capecitabine for next cycle.
f. Trastuzumab is administered intravenously or subcutaneously, once every 21 days.
g. Patients will continue treatment cycle counting from prior to unblinding.
h. Including concomitant procedures, hospitalization, and review of number of day(s) anti-diarrheals were taken from previous cycle.
i. Urine or serum pregnancy test not required for males or females of non-child-bearing potential; a positive urine test must be confirmed with a serum pregnancy test prior to each cycle of therapy.
j. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful.
k. More frequent long-term follow-up may be requested for OS event tracking. If a 30-day Follow-Up Visit was not done, the long-term follow-up should begin every 90 days (± 7 days) starting from the date of the last dose of study treatment.
l. ECHO or MUGA, as appropriate, if not done within previous 12 weeks

Appendix A.3 Schedule of Events – Control Arm Continuing on Treatment in the Unblinded Phase

	Crossover Screening	Crossover to the Experimental Arm, Cycle 1		Crossover to the Experimental Arm, Cycle 2		Cycle 3 and Subsequent Cycles		30-Day Follow-Up Visit	Long-Term Follow-Up
Assessments	**Day -28 to 1**	**Day 1**	**Day 12 (± 3 days)**	**Day 1**	**Day 12 (± 3 days)**	**Day 1 (- 1 day to + 3 days)**	**CT/MRI and ECHO/MUGA Schedule**	**30 days (+ 7 days) after last dose of study treatment**	**90 days (+ 7 days) following 30-Day Follow-Up Visit and continuing every 90 days [l]**
Sign Revised Informed Consent	X								
Document AEs	X	X	X	X		X		X	
Document crossover eligibility	X								
Document concomitant meds [i]	X	X	X	X		X		X	
Document newly developed baseline medical conditions	X								
Document recent disease history	X								
Physical exam	X	X [g]	X	X		X		X	
Height	X								
Vital signs (weight, BP, heart rate, temp, resp rate)	X	X	X	X		X		X	
ECG	X								
ECHO/MUGA	X [c]						X [m]	X [n]	
CT, PET/CT or MRI	X [c]						X [m]		
Contrast MRI Brain	X [c]						X [m]		
ECOG PS	X	X [g]	X	X		X		X	
Labs [a]	X	X [g]	X	X	X [h]	X		X	
Pregnancy test [j]	X [b]	X		X		X		X	
Patient contact/clinic visit	X	X	X	X		X		X	X [k]
Study Drug Treatment									
Tucatinib [d]		X		X		X			
Capecitabine [e]		X		X		X			
Trastuzumab [f]		X		X		X			

a. Blood samples for hematology, clinical chemistry and liver function tests. Samples may be collected up to 2 days prior to visits
b. Serum or urine pregnancy test within 7 days prior to start of crossover (tucatinib) treatment (required for only females of child-bearing potential only)
c. Screening imaging not required if performed in the previous 6 weeks; Contrast CT, PET/CT (if high quality CT scan included) or MRI scan as appropriate to document sites of extracranial disease and assessment of tumor burden. At minimum, scans must include chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as skin lesion photography, bone imaging. While on treatment, scans should be performed at intervals as per standard clinical practice as determined by investigator. Contrast MRI of the brain should also be done at intervals as per standard clinical practice after screening.

d. Tucatinib is administered PO BID, on a 21-day cycle. On day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle. Patients who were randomized to the control arm (placebo + trastuzumab + capecitabine) and were receiving study treatment at the time of unblinding who do not meet crossover criteria will continue trastuzumab + capecitabine therapy without tucatinib.
e. Capecitabine is administered PO BID, on Day 1 through Day 14. On day 1 of each cycle, review compliance from previous cycle and dispense capecitabine for next cycle.
f. Trastuzumab is administered intravenously or subcutaneously, once every 21 days.
g. These evaluations do not need to be repeated if obtained within the prior 96 hours. All lab results must be reviewed, and crossover eligibility confirmed prior to start of crossover (tucatinib) treatment.
h. Only total bilirubin, AST, ALT, and serum creatinine are required at this visit.
i. Including concomitant procedures, hospitalization, and review of number of day(s) anti-diarrheals were taken from previous cycle.
j. Urine or serum pregnancy test not required for males or females of non-child-bearing potential; a positive urine test must be confirmed with a serum pregnancy test.
k. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful.
l. More frequent long-term follow-up may be requested for OS event tracking. If a 30-Day Follow-Up Visit was not done, the long-term follow-up should begin every 90 days (± 7 days) starting from the date of the last dose of study treatment.
m. A maximum interval of 12 weeks between tumor assessments. Investigators should continue to use RECIST 1.1 for tumor assessments and for patient care decisions.
n. ECHO or MUGA, as appropriate, if not done within previous 12 weeks

Appendix B RECIST 1.1 Criteria

RECIST 1.1 is to be used to assess all sites of disease. Selected sections from RECIST 1.1. criteria are provided below. For detailed guidelines, see study binder and/or published guideline (Eisenhauer 2009).

Measurability of Tumor Lesions at Baseline

Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] with a minimum size of 10 mm with spiral contrast CT scan with slice thickness no greater than 5 mm or if CT scan with slice thickness > 5 mm, the minimum lesion size must have a longest diameter twice the actual slice thickness or nonmeasurable (all other lesions, including small lesions [longest diameter < 10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks (approximately 30 days) before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: blastic bone lesions, LMD, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques. Lytic bone lesions and cystic lesions must meet criteria detailed in the study binder and RECIST 1.1.

Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

- Clinical Examination – Clinically detected lesions will be considered measurable only when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is required.

- Contrast CT and MRI – CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional contrast CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral contrast CT should be performed by use of a 5-mm or less contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, whereas head and neck tumors and those of the extremities usually require specific protocols.

Tumor Response Evaluation

Baseline Evaluation

Assessment of Overall Tumor Burden and Measurable Disease – To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Baseline Documentation of "Target" and "Nontarget" Lesions – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Lymph nodes are considered one organ. Only two lymph nodes should be measured as target lesions (Schwartz 2016). Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as the reference by which to characterize the objective tumor response. All other lesions (or sites of disease) should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

New Lesions

If a new lesion is equivocal (for example because of its small size [< 5 mm in diameter] or due to differences in scanning technique) therapy should be continued, and follow-up assessment performed will confirm whether it represents truly new disease.

Lesions identified in anatomic locations not scanned at baseline and > 5mm in diameter are considered new.

New lesions identified on ultrasound should be confirmed on contrast CT/MRI.

Treatment Effect or Pseudoprogression or Equivocal Progression

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or treatment effects in existing lesions) in clinically stable patients, treatment may continue until the next scheduled assessment or until unequivocal progression is confirmed.

Response Criteria

Evaluation of Target Lesions – This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: CR—the disappearance of all target lesions; PR—at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters; PD—at least a 20% increase in the sum of the of diameters of target lesions, taking as reference the smallest sum of diameter recorded since the treatment started or the appearance of one or more new lesions; SD—neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameter since the treatment started.

Evaluation of Non-target Lesions – This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: CR—the disappearance of all non-target lesions and normalization of tumor marker level; incomplete response/SD—the persistence of one or more non-target lesion(s) and/or the maintenance of tumor marker level above the normal limits; and PD—the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response – The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The table below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

Overall Responses for All Possible Combinations of Tumor Responses in Target and Non-Target Lesions With or Without the Appearance of New Lesions[a, b]

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

a. Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).

b. In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the CR status).

Frequency of Tumor Re-Evaluation – Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment.

Appendix C Selected Strong Inhibitors and Inducer of CYP2C8 and Their Elimination Half-Lives

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

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

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

Appendix D Selected Strong Inhibitors or Inducers of CYP3A4 and Their Elimination Half-Lives

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]

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 AUC of oral midazolam or other CYP3A substrates ≥ 5-fold. Ritonavir, indinavir, nelfinavir, atazanivir, and saquinavir are also strong CYP3A3 inhibitors, but would not be used in this study as patients with known HIV are excluded.
d. Drug package insert
e. Bailey et al., *Br J Clin Pharmacol* 1998; 46: 101-110
f. Kerb et al., Antimicrob Agent & Chemother 1996, 40(9): 2087-2093

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

Appendix E Examples of Clinical Substrates for CYP3A-Mediated Metabolism

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.

Abbreviations: AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; 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

This table is prepared to provide examples of clinical substrates and not intended to be an exhaustive list.

DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

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

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

Appendix F Adverse Event Severity Grading Scale (CTCAE Version 4.03)

Severity	Grade	Description
Mild	1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate	2	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Severe	3	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Life-threatening	4	Life-threatening consequences; urgent intervention indicated
Death	5	Death related to adverse event.

Appendix G List of Selected Substrates or Inhibitors of P-gp and Substrates of BCRP Oral Drugs

Drug[a]	Class	Drug[a]	Class
P-gp Substrates or Inhibitors[b, c]		**BCRP Substrates[d, e, f]**	
Captopril	angiotensin-converting enzyme (ACE) inhibitor	Nitrofurantoin	antibiotic
Erythromycin	antibiotic	Ciprofloxacin	antibiotic
Azithromycin	antibiotic	Norfloxacin	antibiotic
Conivaptan	anti-diuretic hormone	Ofloxacin	antibiotic
Itraconazole	anti-fungal	Glyburide	antidiabetic
Ketoconazole	anti-fungal	Methotrexate	anti-metabolite
Ivermectin	anti-parasitic	Prazosin	MT3 receptor antagonist (anti high blood pressure)
Digoxin	atrial fibrillation	Sulfasalazine	RA
Carvedilol	beta-blocker	Cerivastatin	Statin
Cyclosporin A	calcineurin inhibitors	Pitastatin	Statin
Tacrolimus	calcineurin inhibitors	Pravastatin	Statin
Amlodipine	calcium channel blocker	Rosuvastatin	Statin
Diltiazem	calcium channel blocker		
Felodipine	calcium channel blocker		
Verapamil	calcium channel blocker		
Domperidone	dopamine antagonist		
Cimetidine	H2-receptor antagonist		
Ranitidine	H2-receptor antagonist		
Clarithromycin	macrolide antibiotics		
Morphine	pain		
Aldosterone	steroid		
Cortisol	steroid		
Dexamethasone	steroid		
Methylprednisolone	steroid		

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. Marchetti, S., R. Mazzanti, J. H. Beijnen and J. H. Schellens (2007). "Concise review: Clinical relevance of drug drug and herb drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein)." Oncologist 12(8): 927-941.

c. Kim, R. B. (2002). "Drugs as P-glycoprotein substrates, inhibitors, and inducers." Drug Metab Rev 34(1-2): 47-54.

d. Ni, Z., Z. Bikadi, M. F. Rosenberg and Q. Mao (2010). "Structure and function of the human breast cancer resistance protein (BCRP/ABCG2)." Curr Drug Metab 11(7): 603-617.

e. Poirier, A., R. Portmann, A. C. Cascais, U. Bader, I. Walter, M. Ullah and C. Funk (2014). "The need for human breast cancer resistance protein substrate and inhibition evaluation in drug discovery and development: why, when, and how?" Drug Metab Dispos 42(9): 1466-1477.

f. Lee, C. A., M. A. O'Connor, T. K. Ritchie, A. Galetin, J. A. Cook, I. Ragueneau-Majlessi, H. Ellens, B. Feng, M. E. Taub, M. F. Paine, J. W. Polli, J. A. Ware and M. J. Zamek-Gliszczynski (2015). "Breast cancer resistance protein (ABCG2) in clinical pharmacokinetics and drug interactions: practical recommendations for clinical victim and perpetrator drug-drug interaction study design." Drug Metab Dispos 43(4): 490-509.

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

Appendix H Drugs Accepted or Possibly Associated with Risk of QT Prolongation or Torsade de Pointes

	Anti-infectives	Anti-psychotics	Opioid analgesics	Antihistamines	Antidepressants	Anti-emetics/ Gastric motility drugs	Anti-cancer	Anti-arrythmics
Accepted association	Clarithromycin Erythromycin Chloroquine Pentamidine	Haloperidol Chlorpromazine	Methadone	Terfaenadine		Domperidone Cisapride		Amiodarone Sotalol Disopyramide Dofetilide Procainamide Quinidine
Possibly associated	Azithromycin Roxithromycin Telithromycin Moxifloxacin Amantadine	Resperidone Quetiapine Sertinodole Zisprasidone Lithium Clozapine			Escitalopram Venlafaxine	Ondansetron Dolasteron Granisetron	Tamoxifen Nilotinib Lapatinib	

Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) October 2005, ICH. Geoffrey K Isbister and Colin B Page. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2013 Jul; 76(1): 48–57.

Note: This table is prepared to provide examples and is not intended to be an exhaustive list.

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan (SAP)

Data Monitoring Committee (DMC) Charter

DMC Charter version 1

DMC Charter version 2

DMC Charter version 2.1

DMC Charter version 3

DMC Charter version 4

Data Monitoring Committee (DMC) Meeting Report and Minutes

09 Sep 2016

02 May 2017

26 September 2017

27 March 2018

26 September 2018

01 May 2019

STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma **(HER2CLIMB)**
Protocol Number:	ONT-380-206
Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Version:	1.0, 7-Aug-2019

SPONSOR APPROVAL PAGE

Document Title: Statistical Analysis Plan

Protocol Number: ONT-380-206

Version: 1.0; 7-Aug-2019

The individuals signing below have reviewed and approve of this statistical analysis plan.

Approval(s)

[redacted] 8- Aug - 2019
Date

Seattle Genetics, Inc.

[redacted] 8 Aug 2019
Date

Seattle Genetics, Inc.

[redacted] 7- Aug-2019
Date

Seattle Genetics, Inc.

[redacted] 7- Aug - 2019
Date

Seattle Genetics, Inc.

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LIST OF ABBREVIATIONS

AE	Adverse Event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
CBR	Clinical Benefit Rate
CDISC	Clinical Data Interchange Standards Consortium
CDS	Clinical Drug Safety
CMH	Cochran Mantel Haenszel
CNS	Central Nervous System
CR	Complete Response
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DMC	Data Monitoring Committee
DOR	Duration of response
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
ED	Emergency Department
HER2	Human Epidermal Growth Factor Receptor 2
IRT	Interactive Response Technology
ITT	Intent-To-Treat
LFT	liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	multiple-gated acquisition scan
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
T-DM1	ado-trastuzumab emtansine or trastuzumab emtansine
ULN	Upper Limit of Normal
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol ONT-380-206, entitled "Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma (HER2CLIMB)". Results of the proposed analyses will become the basis of the clinical study report for this protocol.

The purpose of this plan is to provide specific guidelines from which the analyses will proceed. All planned analyses specified in this document will be performed. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on progression-free survival (PFS) per RECIST 1.1 based on blinded independent central review (BICR)

2.2 Secondary Objectives

2.2.1 Key Secondary Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS in patients with a history of brain metastases or brain metastases at baseline or equivocal brain lesions at baseline using RECIST 1.1 based on BICR
- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on overall survival (OS)

2.2.2 Other Secondary Objectives

- To assess the effects of tucatinib vs. placebo in combination with capecitabine and trastuzumab on objective response rate (ORR) per RECIST 1.1 based on BICR and investigator
- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on PFS per RECIST 1.1 based on investigator assessment
- To assess the duration of response (DOR) of tucatinib in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR and investigator
- To assess the clinical benefit rate (CBR) [stable disease (SD) or non-CR/non-PD for ≥ 6 months, or best response of complete response (CR) or partial response (PR)] of tucatinib vs. placebo in combination with capecitabine and trastuzumab per RECIST 1.1 based on BICR and investigator

- To assess health-related quality of life and health economics associated with tucatinib vs. placebo in combination with capecitabine and trastuzumab based on patient health status collected using the EQ-5D-5L instrument and health care resources utilized in patient care
- To assess the safety and tolerability of tucatinib in combination with capecitabine and trastuzumab
- To evaluate the pharmacokinetics of tucatinib and metabolite ONT-993 when administered in combination with capecitabine and trastuzumab

2.2.3 Exploratory Objectives

- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab using RANO-BM by BICR in the subgroup of patients with brain metastases at baseline
- To assess the effect of tucatinib vs. placebo in combination with capecitabine and trastuzumab on progression in brain in the subgroup of patients with brain metastases at baseline.
- To identify potential biomarkers of response, including human epidermal growth factor receptor 2 (HER2) mutations and other mutations by DNA sequence analyses of ctDNA isolated from plasma samples

3 STUDY DESIGN

3.1 Description

This is a randomized, international, multi-center, double-blinded study of tucatinib or placebo in combination with capecitabine and trastuzumab in patients with unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab and T-DM1 (ado-trastuzumab emtansine or trastuzumab emtansine). After signing informed consent and meeting all eligibility criteria, patients will be randomized to receive tucatinib or placebo in combination with capecitabine and trastuzumab.

Treatment will be administered in cycles of 21 days each. Tucatinib or placebo will be given PO BID. Capecitabine will be given at 1000 mg/m2 PO BID on Days 1–14 of each 21-day cycle. Trastuzumab will be given as a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days (or as 600 mg of trastuzumab given subcutaneously once every 3 weeks), except in specific circumstances where it may be given weekly to compensate for modifications in treatment schedule.

3.2 Method of Assigning Subjects to Treatment Arms

Subjects will be assigned to the tucatinib or placebo arms (in combination with capecitabine and trastuzumab) in a 2:1 ratio using a dynamic hierarchical randomization scheme. The randomization scheme will control for the stratification factors:

- Presence or history of treated or untreated brain metastases (Yes, No),
- Eastern Cooperative Oncology Group Performance Status (0, 1)
- Region of world (US, Canada, Rest of World)

The presence or history of brain metastases will be determined based upon investigator assessment of screening MRI and clinical history. Patients who have a documented history of prior brain metastases or unequivocal presence of brain lesions on screening MRI will be considered a "Yes" for stratification purposes, and subsequent efficacy assessments. Patients with brain lesions of equivocal significance on screening MRI will also be considered a "Yes" for purposes of stratification and follow-up.

The dynamic hierarchical randomization scheme includes specifications for a biased-coin assignment when the imbalance at a given hierarchical level (overall treatment group balance, then treatment group balance within each of the listed stratification factors) has exceeded a specified threshold.

3.3 Endpoints

3.3.1 Primary Endpoint

The primary endpoint is progression-free survival (PFS) time defined as the time from the date of randomization to the date of documented disease progression (as determined by BICR assessment using RECIST 1.1) or death from any cause, whichever occurs first.

3.3.2 Secondary Endpoints

Key secondary endpoints

- Progression-free survival (PFS_{BM}) time in the subgroup of patients with a history of brain metastases or brain metastases at baseline, or with brain lesions of equivocal significance on screening MRI, defined as the time from the date of randomization to the date of documented disease progression (as determined by BICR assessment using RECIST 1.1) or death from any cause, whichever occurs first.
- Overall survival (OS) time defined as the time from the date of randomization to the date of death from any cause.

Other Secondary Efficacy Endpoints

- Objective response rate (ORR). Objective response is defined as achieving a best overall response of complete (CR) or partial response (PR) as determined by BICR and by investigator using RECIST 1.1.
- Progression-free survival (PFS_{INV}) time defined as the time from the date of randomization to the date of documented disease progression (as determined by the investigator using RECIST 1.1) or death from any cause, whichever occurs first.

- Duration of response (DOR) defined as the time from the first objective response (CR or PR) to documented disease progression (PD) (as determined by BICR and by investigator using RECIST 1.1) or death from any cause, whichever occurs first.
- Clinical benefit rate (CBR). Clinical benefit is defined as achieving stable disease (SD) or non-CR/non-PD for ≥ 6 months or a best overall response of complete (CR) or partial response (PR) as determined by BICR and by investigator using RECIST 1.1.

Safety Endpoints

- Adverse events (AEs)
- Clinical laboratory assessments
- Vital signs and other relevant safety variables
- Frequency of dose holding, dose reductions, and discontinuations of capecitabine
- Frequency of dose holding, dose reductions, and discontinuations of tucatinib
- Frequency of dose holding and discontinuations of trastuzumab

Pharmacokinetic Endpoints

- Plasma concentrations of tucatinib and metabolite ONT-993

Heath Economics and Outcomes

- Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and emergency department (ED) visits.
- Health-related quality of life / health status, assessed using the EQ-5D-5L instrument.

3.3.3 Exploratory Endpoints

- Presence of HER2 mutations or other potential biomarkers of response
- In the subgroup of patients with a history of brain metastases or brain metastases at baseline, the following exploratory endpoints will be evaluated, as assessed by BICR using RANO-BM for brain metastases.
    - Objective response rate (ORR_{BC}) in brain
    - Duration of response (DOR_{BC}) in brain
    - Time to progression in brain (excluding body)

3.4 Data Monitoring Committee

An independent data monitoring committee (DMC) will monitor the safety of subjects and provide an ongoing clinical assessment of the study treatment's evolving safety profile as the

trial progresses. The DMC will review blinded and unblinded data that include deaths, discontinuations, dose reductions, adverse events, events of special interest, and serious adverse events. The DMC will meet on a regular basis and make recommendations to the sponsor regarding the conduct of the trial. Further details regarding the DMC's roles, responsibilities, and operating procedures are described in a separate DMC charter.

3.5 Blinding

This is a double-blinded trial. Patients, site investigators and personnel, the sponsor (except for designated Clinical Drug Safety (CDS) personnel), and all other individuals involved in the monitoring, data management, and/or conduct of the trial will be blinded. Designated CDS personnel may request the treatment assignment of an individual subject in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) but will not have access to the overall randomization scheme.

Unblinded data including deaths, discontinuations, dose reductions, adverse events (serious and non-serious) will be monitored regularly by an independent DMC. The independent data coordinating center preparing this output for the DMC will be unblinded and have access to the overall randomization scheme.

At the time of the primary analysis for the primary endpoint (PFS), specific sponsor personnel will be unblinded, however sponsor personnel directly involved in the conduct of the study will remain blinded to individual subject treatment assignments (tucatinib/placebo) until the final analysis for the key secondary endpoint of PFS_{BM}.

4 GENERAL STATISTICAL CONSIDERATIONS

4.1 Analysis Sets

Intent-to-Treat

The intent-to-treat (ITT) analysis set will include all randomized subjects.

Specifically, the primary analyses for the primary endpoint of PFS per BICR will be conducted using the first 480 randomized subjects in the ITT analysis set (henceforth referred to as ITT-PFS set). The analyses of the key secondary endpoint OS will be conducted on all the randomized subjects in the ITT analysis set (henceforth referred to as ITT-OS set). The analysis of the key secondary endpoint PFS_{BM} will be conducted using all the randomized subjects in the BM subgroup (as defined in section 4.2) in the ITT analysis set (henceforth referred to as ITT-$PFS_{BrainMets}$ set).

Subjects will be evaluated by their randomized treatment assignment.

Safety

The safety analysis set will include all randomized subjects who received at least one dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab). Subjects will be evaluated by the study treatment actually received.

Pharmacokinetics

The pharmacokinetic analysis set will include all randomized subjects who received at least one dose of tucatinib and who have at least one evaluable PK assessment. Subjects will be evaluated by the treatment actually received.

4.2 Subgroups

The following subgroup variables will be evaluated for primary and key secondary efficacy endpoints when applicable, as supportive analyses. If the total number of subjects in a subgroup is less than 10% of the total population, the subgroup analysis will not be performed. Subgroup analyses will be conducted using conventional stratified log rank statistical methods (i.e., rerandomization methods will not be used), as well as stratified Cox proportional hazards regression model. If the subgroup is a stratification factor, then the stratified models will use all the other stratification factors.

- History of parenchymal brain metastases or brain metastases at baseline (Yes, No): Patients with target and/or non-target parenchymal brain lesions (per RECIST 1.1) at baseline or who have a history of brain metastases, or with brain lesions of equivocal significance on screening MRI based on screening data collected in eCRF will be assigned to the 'Yes' subgroup. This group will henceforth be referred to as "BM subgroup" in this document. Patients not meeting the above criteria will be assigned to the 'No' subgroup for this variable. Patients with dural lesions only, i.e. no parenchymal brain lesions, will be assigned to the 'No' subgroup. Patients with incomplete screening data and not meeting the criteria for BM subgroup will be not evaluable (NE) for this subgroup determination.
- Geographic Region: North America, Rest of World
- ECOG: 0 vs. 1 as recorded in eCRF at baseline
- Age : <65 vs. ≥65 years
- Race: White, African-American, others
- Hormone Receptor Status (Negative, Positive): Patients 'positive' for either or both estrogen receptor and progesterone receptor will be assigned to the 'positive' subgroup. Patients not meeting the above criteria will be assigned to the 'negative' subgroup.

4.3 Handling of Missing Data

4.3.1 Efficacy

Partial dates of start of post study treatment anti-cancer therapy and dates of concomitant medication or procedure, will be imputed as follows:

- Missing day only: For partial dates with only the day of the month missing, the day will be imputed as the 15th day of the month, provided that a preceding or succeeding

date of interest does not occur in the same month. If the preceding date does occur in the same month, then the missing day will be imputed as half the distance between the preceding date and the end of the month. If the succeeding date does occur in the same month, then the missing day will be imputed as half the distance between the beginning of the month and the succeeding date.

- Missing month and day: For partial dates with the month and day missing, the month and day will be imputed as July 1st, provided that a preceding or succeeding date of interest does not occur in the same year. If the preceding date occurs in the same year, then the month and day will be imputed as half the distance from the preceding date to the end of the known year. If the succeeding date does occur in the same year, then the missing day will be imputed as half the distance between the beginning of the year and the succeeding date.

The date of death, tumor assessment dates, dates of last contact, hospitalization, date of initial diagnosis and first date of metastases will be imputed if only day is missing, following the "Missing day only" rule as above.

4.3.2 Safety

For AEs where the date of onset is during or after administration of the first dose of study treatment, missing or partial start dates will be imputed as the earliest possible date that is on or after the date of the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and before the AE end date.

- Missing day only: If the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start date month is after the month of first dose, day will be imputed as the 1st (i.e., 01-MMM-YY).
- Missing month and day: If the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start date year is after the year of first dose, the month and day will be imputed as January 1st (i.e., 01-JAN-YY).
- Missing month, day, and year: Missing start dates will be imputed as the date of first dose.

For AEs where the end date is a partial date, the end date will be imputed as:

- Missing day only: AE end date will be imputed as the minimum of (death date, data cutoff date, last day of the end date month/year)
- Missing month and day: AE end date will be imputed as the minimum of (death date, data cutoff date, December 31st of the end date year)
- Missing month, day and year: not imputed.

4.3.3 Pharmacokinetics

Missing values for PK measurements will be listed as missing and excluded from the calculation of summary statistics.

4.4 Multicenter Studies

Approximately 600 subjects will be randomized to the study from approximately 200 sites worldwide.

4.5 Determination of Sample Size

The sample size for this study was calculated based on maintaining 90% power for the primary endpoint PFS and 80% power for OS with an alpha level of 0.02.

For PFS, 288 events are required with 90% power to detect a hazard ratio of 0.67 (4.5 months median PFS in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test and alpha of 0.05.

For OS, 361 events are required with 80% power to detect a hazard ratio of 0.70 (15 months median OS in the control arm vs. 21.4 months in the experimental arm) using a 2-sided log-rank test and alpha of 0.02, taking into account of two interim analyses. With 361 OS events, it will provide 88% power using a 2-sided log-rank test with an alpha of 0.05.

For PFS_{BM}, 220 events are required with 80% power to detect a hazard ratio of 0.67 (4.5 months median PFS_{BM} in the control arm versus 6.75 months in the experimental arm) using a 2-sided log-rank test at alpha of 0.05, taking into account of one interim analysis. The power will be 74% at 2-sided alpha of 0.03.

Approximately 600 subjects will be randomized in a 2:1 ratio to either the experimental arm or the control arm. Assuming an accrual period of 48 months and a 5% yearly drop-out rate, it is expected that 361 OS events will be observed approximately 59 months after first subject randomized.

Sample size and power were calculated using EAST® version 6.4, by Cytel Inc.

4.6 Timing of Analyses

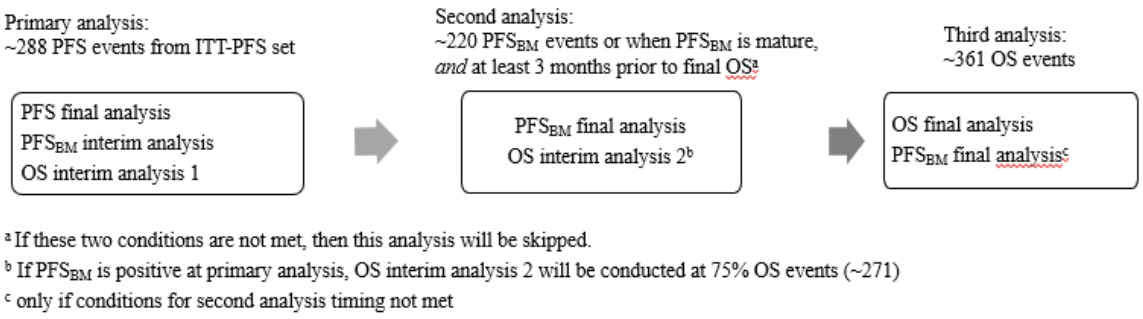
The primary analysis of PFS will occur when approximately 288 PFS events determined by BICR have occurred in the ITT-PFS set and enrollment has been completed for the study. An interim analysis for the key secondary endpoints PFS_{BM} and OS will also be performed at this time if PFS is statistically significant (see Section 5.6 for details).

If PFS_{BM} is statistically significant at the first interim analysis, no further formal testing of PFS_{BM} will be conducted. The second interim analysis for OS will be performed when approximately 75% (271) of total OS events have occurred in the ITT-OS set, and the final OS analysis will be conducted after approximately 361 OS events have occurred in the ITT-OS set.

If PFS_{BM} is not statistically significant at the first interim analysis, a second analysis of the key secondary endpoints will be performed when (a) approximately 220 PFS_{BM} events have occured in the ITT-$PFS_{BrainMets}$ set or the PFS_{BM} events are sufficiently mature (e.g. approximately less than 6 events are expected with 3 months additional follow up) and (b) at least 3 months before the projected OS final analysis. If both of the above conditions (a and b) are not met, this analysis of PFS_{BM} and OS will not be conducted, and the OS final analysis at 361 OS events will also be the timing of the final PFS_{BM} analysis.

The timing of analyses for the primary and key secondary endpoints are illustrated in Figure 1.

Figure 1: Timing of Primary and Key Secondary Endpoints Analyses



[a] If these two conditions are not met, then this analysis will be skipped.
[b] If PFS_{BM} is positive at primary analysis, OS interim analysis 2 will be conducted at 75% OS events (~271)
[c] only if conditions for second analysis timing not met

4.7 Multiple Comparison/Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05, the PFS will be tested at 0.05 level first in the ITT-PFS set, if it is significant, then the key secondary endpoints will be tested using the group sequential Holm variable (GSHv) procedure (Ye et.al. 2013).

The α split between PFS_{BM} and OS is α=0.03 and α=0.02, respectively, and each one will be tested at the interim analysis(s) and again at the final analysis, if not rejected at the interim analysis. The information fraction t is the ratio between number of events at interim analysis and number of events at final analysis. For illustration purpose, we assume t=0.812 for PFS_{BM} and t_1=0.626, t_2=0.779 for the two interim analyses for OS.

The boundary at interim analysis is determined according to the Lan-DeMets O'Brien-Fleming (LD(OF)) approximation spending function LD(OF): $\alpha(t) = 4 - 4\Phi(\frac{z_{\alpha/4}}{\sqrt{t}})$ for two-sided tests, where $z_{\alpha/4}$is the upper $\frac{\alpha}{4}$ critical point of the standard normal distribution.

The GSHv procedure operates as follows.

- Begin with a 0.03-level group sequential boundary for PFS_{BM} and a 0.02-level group sequential boundary for OS. The corresponding boundaries for the two endpoints are given in Table 1.

Table 1: Initial LD (OF) boundaries for PFS_{BM} (2 analyses) and OS (3 analyses)

Analysis	PFS_{BM} (α=0.03, t=0.812)	OS (α=0.02, t1=0.626, t2=0.779)

1	0.0139	0.0023
2	0.0259	0.0069
3		0.0176

If both of the endpoints are found significant at analysis 1 (primary analysis), then no more formal statistical testing for PFS_{BM} and OS will be conducted.

- If only one endpoint is found significant at the analysis 1 (primary analysis) then the α can be recycled to the other endpoint: If PFS_{BM} is significant at interim but OS is not then the α will be recycled from PFS_{BM} to OS and use a 0.05-level LD(OF) boundary for OS. On the other hand, if OS is significant at analysis 1 (primary analysis) but PFS_{BM} is not then the α will be recycled from OS to PFS_{BM} and use a 0.05-level LD(OF) boundary for PFS_{BM}. The corresponding 0.05-level LD(OF) boundaries are given in Table 2. The unrejected hypothesis can be re-tested at the current and future analysis using the modified boundaries.

Table 2: LD (OF) boundaries for PFS_{BM} (2 Io analyses) and OS (3 analyses) at α=0.05 level

Analysis	PFS_{BM} (α=0.05, t=0.812)	OS (α=0.05, t1=0.626, t2=0.779)
1	0.0258	0.0092
2	0.0425	0.0194
3		0.0429

- If neither of the endpoints is found significant at analysis 1 (primary analysis), then both endpoints will be tested again at analysis 2. The initial boundaries for final analysis follow Table 1 (analysis 2). If only one endpoint is found significant by these initial boundaries, then the other one can be tested again using the modified boundary as shown in Table 2 (analysis 2). For example, if PFS_{BM} was found significant at final analysis at α=0.0259 level, but OS was not significant at α=0.0069 level, then OS can be tested again at the α=0.0194 level.
- If PFS_{BM} is significant at analysis 1 or 2, the boundary of OS analysis at analysis 3 is 0.0429; otherwise, the boundary for OS analysis at analysis 3 is 0.0176.
- Note that the boundaries presented in the tables will be adjusted with the actual information fraction.

As detailed in Section 4.6, the second interim analysis for OS may not be conducted, which means both PFS_{BM} and OS will have at most 2 analyses. In that case, LD(OF) boundaries at each analysis will be modified as illustrated in Table 3 and Table 4. Similar to Table 1 and Table 2, the information fraction (*t*) in Table 3 and Table 4 are for illustration purpose only.

Table 3: Initial LD (OF) boundaries for PFS_{BM} (2 analyses) and OS (2 analyses)

Analysis	PFS_{BM} (α=0.03, t=0.812)	OS (α=0.02, t=0.626)
1	0.0139	0.0023
2	0.0259	0.0193

Table 4: LD (OF) boundaries for PFS_{BM} (2 analyses) and OS (2 analyses) at α=0.05 level

Analysis	PFS_{BM} (α=0.05, t=0.812)	OS (α=0.05, t=0.626)
1	0.0258	0.0092
2	0.0425	0.0471

If both PFS_{BM} and OS are statistically significant, the secondary endpoint of ORR by BICR in the ITT-OS set will be formally tested between two treatment arms at the two sided α=0.05 level.

4.8 Data Conventions, Definitions, and Formulas

The following data conventions will be used for the tables, listings, and figures.

- **Study treatment**: tucatinib/placebo, capecitabine or trastuzumab. Subjects who discontinued tucatinib/placebo and only continued with capecitabine and/or trastuzumab are not considered to be receiving study treatment anymore.
- **Baseline:** The last non-missing observation prior to or on the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab), unless otherwise specified. If more than one assessment meet the above criteria and were collected on the same date, the value of the assessment indicating better status will be used as baseline to be conservative, for instance, lower vs. higher lab grade, ECOG 0 vs. 1, ECG normal vs. abnormal. If there are no directional difference (for instance, lab values of the same grade) of observation on the same date, the last record in database (identified by sequence number or visit number) will be marked as baseline. For patients who were randomized but not treated, the observation on screening visit will be marked as baseline.
- **Pre-treatment Period:** Prior to first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab)
- **Study Treatment Period:** Period of time that begins on the date of the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) through 30 days after the date of the final dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) as recorded in the End of Treatment eCRF page.
- **Study Day:**
    - **Safety**: Study day will be calculated for safety endpoints relative to the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab). The first dose of study treatment will be Day 1, and the date preceding Day 1 will be Day –1 which is consistent with the Submission Data Standards (Version 3.1) from Clinical Data Interchange Standards Consortium (CDISC).
    - **Efficacy**: Study day will be calculated for efficacy endpoints relative to the date of randomization. The day of randomization will be Day 1.

- **Duration of Exposure:**
    - For tucatinib/placebo, duration of exposure (days) = date of last dose – date of first dose + 1
    - For capecitabine, duration of exposure (days) = (date of last dose +7) – date of first dose) + 1
    - For trastuzumab, duration of exposure (days) = (date of last dose +20) – date of first dose) + 1

Note that for each study drug, the date of last dose is as recorded in the End of Treatment eCRF page.

- **Total Dose of tucatinib/placebo (mg), capecitabine (mg/m^2), and trastuzumab (mg/kg):**

  Total dose (*units*) = $\sum_{i=1}^{n}(dose_i)$

  where i = dose number, $dose_i$ = i^{th} dose received (*units*), n = total number of doses received

- **Intended dose intensity (IDI):** the intended dose of drug per unit of time (day).

  For example, tucatinib/placebo: IDI = 300mg BID =600 (mg/day);

  capecitabine: IDI = 2000 mg/m^2/day * (14 dosing day/21 days in a cycle) =1333.3 mg/m^2/day

- **Absolute dose intensity (ADI):** the actual dose per unit of time that the subject received over the duration of exposure for that study drug.

  ADI = Total dose / Duration of exposure (days)

- **Relative dose intensity (RDI):** the percent of the intended dose intensity over the entire treatment period:

  RDI = ADI/IDI * 100%

- **Response assessment date**

  For efficacy assessments, the date of response assessment of CR, PR or non-CR/non-PD, SD will be the latest of all radiologic scan dates for the given response assessment. The date of equivocal progression or progression will be the earliest of all radiologic scan dates that showed evidence of PD for the given response assessment.

5 STATISTICAL METHODOLOGY

5.1 Trial Details

5.1.1 Subject Disposition

Patient enrollment and disposition will be summarized by treatment group and total. The table will present the number and percentage of patients who were randomized in each stratum, received study drug, received treatment per randomization assignment, and participated in follow-up visits. The number and percentage of patients who discontinued treatment will be summarized by the reason for treatment discontinuation. The number and percentage of patients who discontinued the study will be summarized by the primary reason for study discontinuation. The summary of disposition will be conducted for ITT-PFS, ITT-OS and ITT-$PFS_{BrainMets}$ sets.

Number of patients who signed informed consent and number of patients in each analysis set will be summarized by treatment group and total.

Number of screen failures and the percentage relative to the total number of subjects screened will be summarized. A listing of subjects who failed screening will also be produced, with reasons for screen failure and available demographic information.

The number of patients enrolled in each country and at each site will be summarized by treatment group and total.

5.1.2 Protocol Deviations

Protocol deviations (as defined in the ONT-380-206 Global Clinical Monitoring Plan) will be identified by site monitors, the medical monitor and by checks of the clinical database. Important deviations will be summarized for each treatment arm by type of deviation. All protocol deviations will be listed.

5.1.3 Baseline Characteristics and Disease History

Baseline characteristics will be summarized for each treatment arm using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables. Characteristics to be summarized include the following:

- Demographic variables: age, sex, race, and ethnicity
- ECOG performance status
- Disease history:
    - Time (months) from diagnosis of breast cancer to randomization
    - Time (months) from metastatic diagnosis to randomization
    - Unresectable locally advanced breast cancer (yes, no)

- Stage at diagnosis
- History of brain metastases or brain metastases at study entry
- Estrogen/progesterone receptor status
- Non-CNS metastatic disease sites
- Brain metastases treatment status at baseline (treated stable, treated progressive and untreated)
- Time (months) from date of first diagnosis of brain metastases to randomization in subject previously diagnosed with brain metastases
- Prior surgery and/or radiotherapy for brain metastases (yes, no)
- Type of prior radiotherapy for brain metastases (whole brain vs. targeted radiation)
- Prior systemic therapies

The summary of demography and baseline disease characteristics will be conducted for ITT-OS, ITT-PFS and ITT-PFS$_{BrainMets}$ sets.

5.1.4 Concomitant Therapy

Concomitant medications will be listed and coded using the World Health Organization Drug Dictionary (WHODRUG) Version 2009Q3 or higher and summarized for each treatment arm by preferred term and treatment arm using counts and percentages. Multiple occurrences of the same medication within a subject will be summarized only once.

Concomitant systemic corticosteroids, antidiarrheals as well as concomitant procedures will be summarized and listed.

5.1.5 Extent of Exposure

Exposure will be summarized by treatment arm using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables.

The following information will be summarized separately for capecitabine, trastuzumab, and tucatinib/placebo:

- Total number of treatment cycles per subject
- Duration of exposure
- Total cumulative dose
- Percentage of subjects with interrupted, missed, reduced and discontinued infusions/doses overall and by reason

- Absolute dose intensity (ADI) and relative dose intensity (RDI).

Dose reduction and ADI/RDI will only be summarized for tucatinib/placebo and capecitabine.

For tucatinib/placebo, the type, reason and time to first dose modification will be summarized. The total number of dose modifications and reasons will also be summarized.

The summary of trastuzumab and capecitabine exposure will only include the period when patients are on study treatment, i.e., before tucatinib/placebo is discontinued.

The extent of exposure will be summarized both for the safety set within first 480 randomized subjects and the safety set in all randomized subjects.

5.1.6 Subsequent anticancer treatment

The type and regimen of subsequent anticancer treatment after discontinuation from study treatment will be summarized by treatment arm.

5.2 Analysis of Efficacy

Table 5 summarizes the analysis population at the time of primary analysis for PFS, as well as whether the re-randomization procedure needs to be used to calculate p-value. Subjects will be analyzed based on their randomized treatment arm (‘intent-to-treat’ analysis).

Table 5: Analysis population and re-randomization procedure for efficacy endpoints

Analysis	Population for primary analyses	Use of re-randomization procedure
Primary endpoint: PFS per BICR[a]	ITT-PFS	Yes
Sensitivity analysis for primary endpoint	ITT-PFS	Yes
Subgroup analysis for primary endpoint	ITT-PFS	No
Key secondary endpoints: PFS_{BM}	ITT-$PFS_{BrainMets}$	Yes
Sensitivity analysis for PFS_{BM}	ITT-$PFS_{BrainMets}$	Yes
Subgroup analysis for PFS_{BM}	ITT-$PFS_{BrainMets}$	No
Key secondary endpoints: OS	ITT-OS	Yes
Sensitivity analysis for OS	ITT-OS	Yes
Subgroup analysis for OS	ITT-OS	No
PFS per INV[a]	ITT-PFS	No
PFS_{BM} per INV	ITT-$PFS_{BrainMets}$	No
ORR, CBR and DOR[b]	ITT-OS	No
Exploratory efficacy endpoints	ITT-OS	No

[a] exploratory analyses will also be conducted using ITT-OS analysis set.
[b] exploratory analyses will also be conducted using ITT-PFS analysis set.

For the primary analysis of PFS and OS, the stratification factors per Interactive Response Technology (IRT) system will be used as strata in stratified analysis. For a stratification factor with two strata, if one of the two strata has a sample size too small (e.g., less than 20%), the statistical analysis will not include this randomization stratification factor in the analysis. For a stratification factor with more than two strata, if one of the strata has a sample size too small (e.g., less than 20%), this stratum will be combined with some other strata of this stratification factor. For example, for the region stratification factor, if the stratum Canada has a small sample size of less than 20% per the pooled blinded data, the stratum Canada will be combined with the stratum US in the statistical analysis.

For the primary analysis of PFS_{BM}, the actual stratification factor (brain metastasis as recorded in eCRF) will be used to define the population; the stratification factors per Interactive Response Technology (IRT) system (ECOG and region) will be used as strata in stratified analysis.

Sensitivity analyses using the eCRF values for the actual stratification factors as strata may be performed for the primary endpoint and the two key secondary endpoints if the percentage of mis-stratification exceeds five percent.

5.2.1 Primary Endpoint

5.2.1.1 Primary Analysis

Progression-free survival (PFS) time is defined as the time from the date of randomization to the date of documented disease progression (as determined by BICR assessment using RECIST 1.1) or death from any cause, whichever occurs first. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor

assessment that was a CR, PR, non-CR/non-PD or SD. Details of the censoring scheme for the primary analysis of PFS are described below in Table 6.

Table 6: Censoring Scheme for Primary Analysis of PFS

Scenario	Progression/Censor Date	Outcome
No post-baseline tumor assessments	Date of randomization	Censored
No documented disease progression or death	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored
New anti-cancer treatment (systemic, radiation, or surgery) started before PD or death observed	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer treatment	Censored
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment	Date of death	Event
Death or progression right after two or more consecutive missed tumor assessments	Date of last tumor assessment of CR, PR, SD, or non-CR/non-PD	Censored

Note: CT, PET/CT scans are performed every 6 weeks starting at Cycle 1 Day1 through Week 24 and every 9 weeks starting at Week 24 until documented PD or death.

Partial or missing dates of death, dates of last contact, and tumor assessment dates will be imputed as described in Section 4.3.

The two treatment arms will be compared for PFS using a stratified, log-rank test controlling for the randomization stratification factors [i.e., history of brain metastases or presence of brain metastases or lesions of equivocal significance on screening MRI (yes, no), ECOG status (0, 1), and region of the world (US, Canada, Rest of world)]. The p-value for this test will be calculated using a re-randomization based procedure (Rosenberger and Lachin, 2002) to reflect the dynamic, hierarchical allocation scheme (Section 3.2) used for the study randomization. The null hypothesis for this comparison is that the assignment of subjects to the two treatment arms had no effect on response for the subjects randomized to treatment. The procedure for performing the comparison and calculating the p-value are described below. Details of the specific significance level to be used for the treatment arm comparison are described in Section 4.7.

Using the randomized treatment assignments for the trial, a stratified, log-rank test chi-square statistic will be computed for the comparison of the two treatment arms for PFS. This test statistic will be referred to as X_0 and will be calculated based on the following sample SAS code:

```
** Pfstime = PFS time;
** Censor = Censor variable (1 = censored);
** Trt = treatment arm;
** BM = presence or history of treated or untreated brain metastases at baseline or
lesions of equivocal significance (Yes, No)
** ECOG (0,1)
** Region (US, Canada, Rest of World)
ODS OUTPUT HomTests=chisq;
```

```
PROC LIFETEST DATA = pfsdata;
    TIME pfstime*censor(1);
    STRATA bm ecog region / GROUP=armcd TEST=logrank;
RUN;

DATA x0(keep=x0);
SET chisq;
    where test = 'Log-Rank';
    X0=ChiSq;
RUN;
```

Utilizing the dynamic randomization algorithm used to create the original randomization scheme for the trial, 10,000 alternative subject randomizations will then be generated. Each subject randomization will then be merged with each subject's observed PFS time, censoring status, and values for each stratification variable to produce an analysis data set with the basic structure shown in Table 7.

Table 7: Analysis Data Set Structure based on Alternative Randomizations

		Baseline Stratification Variables					
Randomization ID Number (i)	Subject ID	Prescence/History of Brain Metatases or lesions of equivocal significance	ECOG	Region	PFS Time	Censor	Treatment Arm
1	1	Y	0	US	T_1	0	A
1	2	N	1	Canada	T_2	1	B
-	-	-	-	-	-	-	-
1	600	Y	1	US	T_{600}	1	A
-	-	-	-	-	-	-	-
10,000	1	Y	0	US	T_1	0	B
10,000	2	N	1	Canada	T_2	1	A
-	-	-	-	-	-	-	-
10,000	600	Y	1	US	T_{600}	1	B

For each alternative randomization, a stratified, log-rank test chi-square statistic will then be computed (using the same SAS code above used to calculate X_0) for the comparison of the two treatment arms for PFS. The test statistic for the i-th randomization and comparison will be referred to as X_i where i = 1 to 10,000.

The two-sided p-value (based on the rerandomization procedure), will then be calculated as the number of times $X_i \geq X_0$ divided by 10,000.

$$p - value = \sum_{i=1}^{10,000} \frac{I(\cdot)}{10,000}, where\ I(\cdot) = \begin{cases} 1\ if\ X_i \geq X_0 \\ 0\ if\ X_i < X_0 \end{cases}$$

The critical value (X_c) for a 0.05 significance level test using the rerandomization reference distribution will correspond to the 5th percentile of the X_i's.

For the purpose of describing the treatment effect, the treatment arm hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors. This analysis will be implemented using the following SAS sample code.

```
PROC PHREG DATA = pfsdata;
    CLASS armcd(ref='B');
     STRATA stratvar1 stratvar2 stratvar3;
     MODEL pfstime*censor(1) = armcd / TIES=BRESLOW RL;
     HAZARDRATIO armcd;
RUN;
```

Kaplan-Meier curve will be generated by treatment arms. Kaplan-Meier estimates of the median and quartiles (corresponding 95% confidence intervals), as well as probability of PFS at different timepoints (for instance, 3, 6, 9 months) will be computed for each treatment arm.

In addition to the primary efficacy analysis (i.e., re-randomization model analysis), an analysis of PFS time will also be performed using a stratified, log-rank test based on the randomized treatment assignments. The analysis will be implemented using the following sample SAS code.

```
PROC LIFETEST DATA = pfsdata;
TIME pfstime*censor(1);
STRATA bm ecog region / GROUP=armcd TEST=logrank;
RUN;
```

5.2.1.2 Sensitivity Analyses

- **Non-proportional hazard:** In the case that the proportional hazard assumption is violated (by plotting the "log-negative-log" of the Kaplan Meier estimator vs time by treatment group, and the Schoenfeld residuals by treatment group), a restricted mean survival time (RMST) analysis up to 18 months will be performed to compare the mean survival time of the two treatment arms. In addition, the Max-Combo test (Losorok and Lin, 1999; Karrision et al., 2016) will be performed to compare the two treatment arms.

If the primary analysis of PFS is significant, the following analyses may be performed for PFS, using the same rerandomization procedure as for the primary analysis.

- **Missing Assessments of Disease Response:** To explore the potential impact of missing assessments of disease response on the primary analysis of PFS, two sensitivity analyses will be performed
    - (1) Ignoring the missing assessments, i.e., subjects who missed two or more consecutive scheduled assessments before death or PD are considered to have had an event on the date of death or progression.

- (2) Imputing the missing assessment, i.e., subjects who missed two or more consecutive scheduled assessments before death or PD are considered to have events at the time of the next scheduled assessment after the last non-missing assessment.

- **Stratification:** In the case of stratification errors >5% between what is recorded in IRT and eCRF, the hazard ratio and its 95% CI will be estimated using a stratified Cox proportional hazards regression model controlling for the eCRF stratification factors.

- **New therapy before PD/death:** For subjects who received new anti-cancer therapy before PD or death, two sensitivity analyses will be conducted:

  - (1) Not to consider any anti-cancer therapies (whether systemic, radiation, or surgery) as a censoring reason,

  - (2) Not to consider radiation therapies as a censoring reason.

5.2.2 Key Secondary Endpoints

5.2.2.1 Progression-Free Survival in BM subgroup

BM subgroup is defined as subjects with target and/or non-target parenchymal brain lesions per RECIST 1.1) at baseline or who have a history of brain metastases, or with brain lesions of equivocal significance on screening MRI based on screening data collected in eCRF. Progression-free survival time (as defined for the primary efficacy endpoint) in the BM subgroup will be tested if the test of the primary endpoint of PFS is statistically significant (Section 4.7). This analysis will be performed using the same statistical methods and set of alternative subject randomizations used to evaluate the primary endpoint overall PFS. This will be accomplished by selecting only subjects in the BM subgroup from the set of 10,000 randomizations and calculating the stratified log-rank statistics (using stratification factors of ECOG and region) and rerandomization procedure p-value as described for primary analysis of PFS in Section 5.2.1.1. Details of the specific significance level to be used for the treatment arm comparison are described in Section 4.7.

The hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors of ECOG and region.

The sensitivity analyses described in Section 5.2.1.2 for the primary endpoint may be performed if appropriate.

As an exploratory analysis, the Kaplan Meier curve and summary for PFS in the non-BM subgroup among all randomized subjects will also be presented.

5.2.2.2 Overall Survival

Overall survival time (OS) is defined as the number of days from the date of randomization until the date of death from any cause. Subjects who did not achieve the event (death) at the time of the analysis or are lost to follow-up will be censored at the date they were last known to be alive (i.e., right censored). Partial or missing dates of death or last contact will be imputed as described in Section 4.3. Details of the censoring scheme for the primary analysis of OS are described below in Table 8.

Table 8: Censoring Scheme for the Primary Analysis of OS

Scenario	Death/Censor Date	Outcome
Not known to have died by data cutoff date	Date last known alive	Censored
Death	Death date	Death

This analysis will be performed using the same statistical methods and set of alternative subject randomizations used to evaluate the primary endpoint PFS. This will be accomplished by merging each subject's observed survival time and censoring status to each subject randomization to produce an analysis data set. The stratified log-rank statistics and rerandomization procedure p-value will then be calculated as described for the primary efficacy analysis of PFS as described in Section 5.2.1.1. Details of the specific significance level to be used for the treatment arm comparison are described in Section 4.7.

The hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors.

The sensitivity analyses for non-proportional hazard and stratification described in Section 5.2.1.2 for the primary endpoint may be performed if appropriate.

5.2.3 Other Secondary Endpoints

Analyses of the following secondary endpoints will not be subject to formal type I error control and will be analyzed using conventional log rank statistical methods (i.e., rerandomization methods will not be used).

5.2.3.1 Objective Response Rate

Objective response is defined as achieving a best overall response of confirmed complete (CR) or confirmed partial response (PR) per RECIST 1.1. Only response assessments before first documented PD or new anti-cancer therapies will be considered. The proportion of subjects with objective response will be calculated by treatment arm. Comparison of the two treatment arms will be performed using a 2-sided Cochran-Mantel-Haenszel (CMH) test controlling for the study stratification factors. ORR determined by BICR will be summarized for subjects who had at least one measurable target lesion at baseline as assessed by BICR among ITT-OS set. If both of the key secondary endpoints (OS and PFS_{BM}) are statistically significant, then the ORR by BICR will be formally tested between two treatment arms (see Section 4.7), the p-value from the stratified CMH test will be reported.

ORR determined by investigator assessment will be summarized for subjects who had at least one measurable target lesion at baseline as assessed by investigator among ITT-OS set. As exploratory analyses, the same analyses for ORR will also be conducted using ITT-PFS set. The nominal p-value from the stratified CMH tests will be reported for ORR determined by investigator in ITT-OS and ITT-PFS sets and ORR determined by BICR in ITT-PFS set.

5.2.3.2 Investigator Assessed Progression-Free Survival

Progression-free survival (PFS_{INV}) time is defined as the time from the date of randomization to the date of documented disease progression (as determined by the investigator using RECIST 1.1) or death from any cause, whichever occurs first. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, non-CR/non-PD, SD or equivocal progression. Details of the censoring scheme for the analysis of PFS_{INV} are described above in Table 6. The primary analysis of PFS_{INV} will be performed based on ITT-PFS set. PFS_{INV} will also be summarized based on ITT-OS set as an exploratory analysis.

In the cases where an equivocal new lesion was later confirmed to be a truly new disease lesion, or a non-target lesion assessed as equivocal progression changed to unequivocal progression in consecutive later assessment, the PD date should be backdated to the visit when the equivocal new lesion or non-target lesion with equivocal progression was first identified. Note: in cases where PD occurs at a date after an equivocal new lesion or equivocal progression of non-target lesion is identified, but the progression is *not* due to a change of the same equivocal new lesion or equivocal non-target lesion progression to an unequivocal lesion or unequivocal non-target lesion progression, but rather from progression of other lesions, the PD date will not be backdated, but will be the date when definitive PD is recorded.

The treatment arm hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the study stratification factors. Comparison of the two treatment arms will be performed using a stratified log-rank test controlling for the study stratification factors. The nominal p-value from the stratified log-rank test will be provided. Kaplan-Meier estimates of the median (corresponding 95% confidence intervals) will also be computed for each treatment arm.

To explore the potential impact of clinical progression on the analysis of PFS, a sensitivity analysis will be performed using the same censoring scheme and methods described for the primary analysis of PFS with the exception that subjects who discontinued any study treatment due to clinical progression will be counted as ‘progressed’ in the analysis.

PFS_{INV} will also be summarized based on ITT-$PFS_{BrainMets}$ set as exploratory analyses.

In addition, the concordance between BICR and investigator assessed PFS event will be summarized.

5.2.3.3 Clinical Benefit Rate

Clinical benefit is defined as achieving stable disease (SD) or non-CR/non-PD for ≥6 months (i.e., subject has been followed for at least 6 months and no documented PD or death within 6 months from date of randomization) or a best overall response of confirmed complete (CR) or confirmed partial response (PR) per RECIST 1.1. A subject will have a best response of SD or non-CR/non-PD if there is at least one SD or non-CR/non-PD assessment ≥5 weeks after the date of randomization and the subject does not qualify for CR or PR. The duration of SD or non-CR/non-PD will be calculated for subjects who had a best response of SD or non-CR/non-PD, and is defined as the duration from the date of randomization to documented PD or death. Only response assessments before first documented PD or new anti cancer therapies will be considered. The same derivation of PD date and censoring rules as for primary PFS analysis will apply for duration of SD or non-CR/non-PD.

The proportion of subjects with clinical benefit determined by BICR will be calculated by treatment arm. Comparison of the two treatment arms will be performed using a 2-sided CMH test controlling for the study stratification factors. The nominal p-value from the stratified CMH test will be reported. Similar analysis will be performed for CBR determined by investigator assessment. For investigator assessed CBR, the same algorithm for backdating equivocal progression will be applied as in Section 5.2.3.1. CBR will be summarized for the ITT-OS set. As exploratory analyses, the same analyses for CBR will also be conducted using ITT-PFS set.

5.2.3.4 Duration of Response

Duration of response (DOR) is defined as the time from the first objective response (CR or PR that is subsequently confirmed) to documented disease progression (PD) per RECIST 1.1 or death from any cause, whichever occurs first. Only those who achieve a confirmed response among the ITT-OS set will be included in the analysis. Kaplan-Meier estimates of the median (corresponding 95% confidence intervals) will be computed for each treatment arm. The nominal p-value from the stratified log-rank test will be reported. The same derivation of PD date and censoring rules as for primary PFS analysis will apply for DOR. The analysis of DOR will be repeated based on BICR assessment and investigator assessment. For DOR per investigator assessment, the same algorithm for backdating equivocal progression will be applied as in Section 5.2.3.1. As exploratory analyses, the same analyses for DOR will also be conducted using ITT-PFS set.

5.2.4 Exploratory Efficacy Endpoints

Analyses of the following exploratory endpoints will not be subject to formal type I error control and will be analyzed using conventional log rank statistical methods (i.e., rerandomization methods will not be used). Analyses for the exploratory endpoints may not be performed at time of primary analysis for PFS, depending on data availability.

5.2.4.1 Incidence of HER2 and Other Mutations

The incidence of HER2 mutations and other tumor-related mutations will be summarized by treatment arm using counts and percentages. Cox proportional hazards regressions will be performed for the primary efficacy endpoint and the two key secondary endpoints. Each model will include treatment arm and type of mutation as independent variables and the time-to-event variable as the dependent variable. Hazard ratios and 95% confidence intervals will be estimated.

5.2.4.2 RANO-BM assessment for BM subgroup

In the BM subgroup (as defined in Section 4.2) from the ITT analysis set, disease status in brain will be assessed by BICR using RANO-BM for brain metastases. The following exploratory endpoints will be evaluated for the BM subgroup.

Objective Response Rate in Brain

Objective response in brain is defined as achieving a best overall response of confirmed complete (CR) or confirmed partial response (PR) in brain. The proportion of subjects with objective response in brain (ORR_{Brain}) will be calculated by treatment arm. ORR_{Brain} will be summarized for subjects who had at least one measurable target lesion in brain at baseline as assessed by BICR.

Duration of response in Brain

Duration of response in brain (DOR_{Brain}) is defined as the time from the first objective response (CR or PR that is subsequently confirmed) in brain to documented disease progression (PD) in brain or death from any cause, whichever occurs first. Only subjects who achieve a confirmed response in brain will be included in the analysis. Kaplan-Meier estimates of the median (corresponding 95% confidence intervals) will be computed for each treatment arm. The same censoring rules as for primary PFS analysis will apply.

Time to Progression in Brain

Time to progression in brain is defined as the time from the date of randomization to the date of documented disease progression in brain. This endpoint will be evaluated using cumulative incidence methodology for competing risks treating non-brain progression and death as competing events. The treatment arm hazard ratio and 95% confidence interval will be estimated using a Cox proportional hazards regression model based on the following SAS sample code.

```
** tte = Time to event;
** Status (0=censored, 1=brain progression, 2=death or non-brain progression);
** Trt = treatment arm;
PROC PHREG DATA = ttedata;
    CLASS armcd(ref='B') param=glm;
    MODEL tte*status(0) = armcd / TIES=BRESLOW EVENTCODE=1;
```

```
    HAZARDRATIO armcd;
RUN;
```

To designate brain progression (Status = 1) in the model, EVENTCODE = 1 is specified in the MODEL statement.

5.3 Analysis of Safety

All analyses of safety will be produced for the safety analysis set.

5.3.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical or investigational product, in this case, tucatinib/placebo, capecitabine or trastuzumab. Per the study protocol all adverse events (AE) occurring during the study, whether or not attributable to study treatment, will be recorded in the subject's source documents and eCRF. AE severity will be assessed and graded by the Investigator using Version 4.03 of the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE). In addition, the Investigator will also assess the relationship (related, not related) of each AE to capecitabine, trastuzumab, and tucatinib/placebo. All AEs will be coded by the Sponsor to standard "preferred terms" (PT) and system organ classifications (SOC) using MedDRA Version 22.0 or higher.

Definitions

Treatment-emergent adverse events (TEAE): Treatment-emergent AEs are defined as events that are new or worsened on or after receiving the first dose of study treatment (tucatinib/placebo, capecitabine or trastuzumab) and up through 30 days after the last dose of study treatment.

Treatment-related adverse events: Adverse events assessed by the Investigator as 'related' to capecitabine, trastuzumab, or tucatinib/placebo.

Summaries

Adverse events will be summarized by PT or by SOC and PT for each treatment arm using counts and percentages. Multiple occurrences of the same adverse event within a subject will be summarized only once at the most severe grade level for the time frame under consideration. For summaries by severity, only the worst grade for an AE will be counted for a particular subject.

Summaries to be produced include:

- Incidence of TEAE by SOC and preferred term
- Incidence of TEAE by decreasing frequency of preferred term
- Incidence of TEAE by toxicity grade, SOC and preferred term
- Incidence of grade 3 or higher of TEAE by decreasing frequency of preferred term

- Incidence of TEAEs which lead to premature discontinuation of study treatment by decreasing frequency of preferred term
- Incidence of TEAEs which lead to dose interruption or dose reduction of study treatment by decreasing frequency of preferred term
- Incidence of treatment related TEAEs by decreasing frequency of preferred term

In addition to summary tables, the following listings will be produced.

- All AEs
- AEs which resulted in Death
- AEs which lead to discontinuation of study treatment
- Grade 3 or higher AEs

5.3.2 Serious Adverse Events

Serious adverse events (SAEs) will be summarized by preferred term and SOC for each treatment arm using counts and percentages. The following summaries of SAEs will be produced.

- Incidence of treatment emergent SAEs (TESAEs) by decreasing frequency of preferred term
- Incidence of TESAEs by decreasing frequency of SOC and preferred term
- Incidence of treatment related TESAEs by decreasing frequency of preferred term

In addition to summary tables, listings of SAEs will be produced.

5.3.3 Adverse Events of Special Interest

The incidence of treatment emergent adverse events of special interest will be summarized by treatment arm and preferred term or lab values and listings also produced. Adverse events of special interest to be summarized are described in the protocol Section 9.4.7.1 and are the following:

AE of Special Interest	Search Strategy
Potential drug-induced liver injury	• Laboratory abnormalities: LFTs meeting the following criteria - AST/ALT >3xULN and Bilirubin >2xULN occurring within 21 days
Cerebral edema not clearly attributable to progression of disease	• Brain oedema (PT) • Cytotoxic oedema (PT) • Vasogenic cerebral oedema (PT)
Left ventricular systolic dysfunction leading to a change in study treatment or discontinuation of study treatment	• Cardiomyopathy SMQ (Narrow) • Cardiac failure SMQ (Narrow) • Left Ventricular Ejection Fraction measurements by ECHO/MUGA

5.3.4 Clinical Laboratory Results

Serum chemistry and hematology samples will be collected per protocol specified schedules.

All laboratory results will be converted into Système International (SI) units for analysis and graded using the laboratory reference ranges and the criteria from NCI CTCAE (Common Terminology Criteria for Adverse Events, Version 4.03) by the Sponsor. For lab parameters ALT, AST, BILI, ALP, APTT and INR, the reference ranges from individual laboratories will be used if available; for other lab parameters, the Sponsor's standard normal range will be used to perform toxicity grading.

Incidence of Laboratory Toxicities

The incidence of laboratory toxicities by grade will be summarized by treatment arm. For each test, only the worst (i.e., highest) toxicity grade will be counted for subjects with multiple toxicities within a time period (including scheduled and unscheduled assessments). The change of toxicity grade from baseline to worst baseline grade (shift table) will also be summarized. In addition to summary tables, listings of laboratory test results will be provided.

Incidence of Liver Abnormalities

The incidence of liver abnormalities will be summarized by treatment arm. A liver abnormality is defined as AST or ALT elevations that are >3 x ULN with concurrent elevation (same day or within 21 days following AST and/or ALT elevations) of total bilirubin >2 x the ULN.

5.3.5 Ejection Fraction

The minimal post baseline ejection fraction and the maximum decrease from baseline will be summarized for each treatment group. Time to minimal post baseline ejection fraction may also be tabulated.

5.3.6 Vital Signs

Vital signs (weight, body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure) will be listed. The frequency and percentage of patients with post baseline clinically significant vital signs will be summarized. The clinically significant vital signs are defined as:; heart rate >100 bpm; Temperature >38.0 degrees C (100.4 F) and respiratory rate >20 breaths per min. Blood pressure will be summarized both for subjects with systolic blood pressure >120 mmHg or diastolic blood pressure >80 mmHg, as well as for subjects with systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

For weight, the maximum decrease from baseline will also be summarized.

5.3.7 Deaths

Death information will be listed by subject.

5.4 Pharmacokinetic Analyses

The analyses described in this section will be produced for the pharmacokinetics analysis set.

Tucatinib and metabolite drug levels will be summarized with descriptive statistics at each PK sampling time point. The primary efficacy endpoint and the adverse events of special interest will be summarized by the quartiles of tucatinib trough concentration. Additional PK and PK/PD analyses may be performed and described in a separate pharmacometric analysis plan.

5.5 Health Economics and Outcomes

5.5.1 Health Care Resource Utilization

Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and ED visits will be summarized by treatment group in safety analysis set.

5.5.2 Health-Related Quality of Life

Health-related quality of life/health status using the EQ-5D-5L instrument will be analyzed for ITT-OS set. Figures may be produced for utility score and compliance with PRO completion (the number of completed surveys at each measure divided by number expected) over time by treatment group for ITT-OS analysis set.

5.6 Interim Analyses

No interim analyses for efficacy are planned for the primary endpoint. One formal interim analysis for superiority is planned for the key secondary endpoint of PFS_{BM} and two formal interim analyses for superiority are planned for the key secondary endpoint of OS if the primary analysis for PFS is statistically significant. The second interim analysis for OS may not be conducted as described in Section 4.6. The interim analyses will be conducted at the timing described in Section 4.6. The stopping boundaries will be determined using Lan-DeMets spending functions for the O'Brien and Fleming boundaries. See Section 4.7 for control of multiplicity.

5.7 Changes in the Planned Analysis

There are no changes from the planned analysis outlined in the protocol for this trial.

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