Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF SEAGEN INC.

Protocol Number:	MK-7119-001
Version:	Amendment 09/28-Feb-2024
Protocol Title:	A phase 2 open-label, single arm study of tucatinib (ONT-380, MK-7119) in combination with trastuzumab and capecitabine in participants with previously treated locally advanced unresectable or metastatic HER2+ breast carcinoma
Investigational Product:	Tucatinib
Phase:	2
Sponsor:	Seagen Inc.* 21823 30th Drive SE Bothell, WA 98021, USA
SAE Email or Fax:	See email or fax number specified on the SAE report form.

*Please note that as of 14 December 2023, Seagen Inc. became part of Pfizer Inc.

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 9	28-Feb-2024	To change the Sponsor entity name and update title of amendment to include tucatinib and ONT-380.
Amendment 8	29-Aug-2022	To change the Sponsor entity name and address, and to update that newly-obtained tumor biopsy during the prescreening period is not allowed.
Amendment 7	18-Apr-2022	Number of Planned Participants enrolled in this study is changed.
Amendment 6	30-SEP-2021	Contraceptive period, pregnancy reporting period and duration of pregnancy test after receiving last dose of trastuzumab for female participants is updated from 80 days to 7 months.
Amendment 5	2-JUL-2021	South Korea and Taiwan were included to participate in this study.
Amendment 4	16-MAR-2021	Amended Inclusion criteria and Data Analysis method section based on the PMDA's advice.
Amendment 3	6-JAN-2021	Sponsor change

Amendment: 09

Overall Rationale for the Amendments:

To change the Sponsor entity name, update title of amendment to include tucatinib and ONT-380, and provide to updated text regarding overall status of ongoing and completed tucatinib clinical trials.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title page, Protocol Synopsis, and footers	Sponsor entity name change. Updated amendment version. Update title to include the Seagen nomenclature of Tucatinib and ONT-380 (Note: MK-7119 is retained parenthetically).	Effective as of Amendment 9, the sponsor has been updated, amendment version is updated, and the code name for tucatinib was updated.
Investigator Signatory page	Remove sponsor signatory	A standalone sponsor signatory page will be done.
Section 1.3.3	Removed summary statement of tucatinib clinical studies; existing text refers to the IB as the source for additional information on tucatinib clinical trials.	Update

PROTOCOL SYNOPSIS

Protocol Number 001 Version Amendment 09 / 28-Feb-2024 Phase 2	Product Name Tucatinib (ONT-380 or MK-7119) Sponsor Seagen Inc. (hereafter called the Sponsor)

Protocol Title

A phase 2 open-label, single arm study of tucatinib (ONT-380, MK-7119) in combination with trastuzumab and capecitabine in participants with previously treated locally advanced unresectable or metastatic HER2+ breast carcinoma

Study Objectives

Primary

- Assess the objective response rate (ORR) of tucatinib in combination with trastuzumab and capecitabine by independent central review (ICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in Japanese population.

Secondary

- Assess ORR of tucatinib in combination with trastuzumab and capecitabine by ICR per RECIST v1.1 in all participants population.
- Assess ORR of tucatinib in combination with trastuzumab and capecitabine by investigator assessment (INV) per RECIST v1.1 in Japanese population and all participants population.
- Assess the duration of response (DOR) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in Japanese population and all participants population .
- Assess the progression free survival (PFS) of tucatinib in combination with trastuzumab and capecitabine by ICR and INV per RECIST v1.1 in Japanese population and all participants population.
- Assess the overall survival (OS) of tucatinib in combination with trastuzumab and capecitabine in Japanese population and all participants population.
- Assess the safety of tucatinib in combination with trastuzumab and capecitabine in Japanese population and all participants population.

Exploratory

- Evaluate the pharmacokinetics (PK) of tucatinib administered in combination with trastuzumab and capecitabine in Japanese population, South Korean population and all participants population.

Study Population

Inclusion Criteria

1. Participants must have histologically confirmed human epidermal growth factor receptor (HER)2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH) or

immunohistochemistry (IHC) methodology according to the American Society of Clinical Oncology/College of American Pathologists.

a. Tissue blocks or slides must be submitted to confirm HER2 positivity (using IHC, ISH or fluorescence in situ hybridization [FISH]) by a Sponsor-designated central laboratory

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. Received previous treatment with taxane anti-cancer agent, trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1) with the exception is when the use of taxanes is contraindicated or judged not to be the best treatment at the discretion of the investigator.
3. Radiographically and/or histologically confirmed disease progression on last systemic anticancer treatment for unresectable locally advanced or metastatic HER2+ breast carcinoma.

   Note: Clinical exam, rising tumor markers and/or photography are not acceptable as methods for documentation of progressive disease
4. Measurable disease as assessed by RECIST v1.1
5. Age of majority at time of consent
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
7. Life expectancy ≥6 months, in the opinion of the investigator
8. Has adequate organ function (refer to Table 2 in detail). Specimens must be collected within 10 days prior to the start-of-study interventions.
9. 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
10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies

    - Is not a WOCBP

    OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in APPENDIX D during the intervention period and for at least 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
    - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study treatment

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 7.4.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after receiving the last dose of tucatinib or 90 days after receiving the last dose of Capecitabine whichever occurs last for male partner (no contraception requirement for trastuzumab for male).:
    - Refrain from donating sperm

    PLUS either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

    OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [APPENDIX D]) as detailed below:
        - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
12. Participant must provide written informed consent
13. Participant must be willing and able to comply with study procedures

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

14. No evidence of brain metastases
15. Untreated brain metastases not needing immediate local therapy. For participants with untreated CNS lesions >2.0 cm on screening contrast brain MRI, discussion with and approval from the Sponsor is required prior to enrollment.
16. 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. Participants treated with CNS local therapy for newly identified lesions or previously treated progressing 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 ≥14 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 v1.1 are present

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

Exclusion Criteria

1. Prior treatment with:
   a. Lapatinib within 12 months of starting study treatment.

      Note:In cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity, the participant is eligible.

      Note:In cases where lapatinib was given as a part of the last systemic anticancer treatment for unresectable locally advanced or metastatic HER2+ breast carcinoma, the participant is not eligible according to Inclusion Criteria 3.

   b. Neratinib, afatinib, or other investigational HER2/epidermal growth factor receptor (EGFR) or HER2 tyrosine kinase inhibitor (TKI) at any previous time

   c. Tucatinib or enrolled on a tucatinib clinical trial and received Tucatinib.

2. Previous treatment with capecitabine (or other fluoropyrimidine [eg, 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: participants 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, and/or 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. 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. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
   - Alopecia and neuropathy, which must have resolved to ≤ Grade 2
   - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
   - Anemia, which must have resolved to ≤ Grade 2
7. Clinically significant cardiopulmonary disease such as:
   - Ventricular arrhythmia requiring therapy
   - Symptomatic hypertension or uncontrolled hypertension as determined by investigator
   - Any history of symptomatic CHF or symptomatic decreases in ejection fraction
   - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE v4.03] Grade 3 or above) due to complications of advanced malignancy
   - Any history of interstitial lung disease or pneumonitis that is grade 2 or greater.
   - Hypoxia requiring supplementary oxygen therapy
8. Known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
9. Any uncontrolled Grade 3 or higher (per the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.
10. Positive for Hepatitis B by surface antigen expression, or positive for Hepatitis C infection, or the presence of known chronic liver disease. Participants who have been treated for Hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks. As reactivation of these viruses has not been studied with the combination of tucatinib, trastuzumab, and capecitabine, there is a possible risk of reactivation.
    - Participants who are positive for either antibodies to Hepatitis B surface antigen (HBsAb) or antibodies to Hepatitis B core antigen (HBcAb) should be screened using polymerase chain reaction (PCR) measurement of Hepatitis B DNA levels. Participants with Hepatitis B DNA levels by PCR that require nucleoside analogue therapy are not eligible for the trial. The latest local guidelines should be followed regarding the monitoring of Hepatitis B DNA levels by PCR for participants on study treatment.
11. Known to be positive for human immunodeficiency virus (HIV)
12. Participants who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last
13. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)
14. Unable to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications

15. Use of a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or a moderate or strong CYP2C8 inducer within 5 days prior to first dose of study treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks prior to the start of study treatment and requires Sponsor consultation.
16. Known dihydropyrimidine dehydrogenase deficiency
17. Unable for any reason to undergo contrast MRI of the brain
18. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
19. Evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment

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

20. Any untreated brain lesions >2.0 cm in size, unless discussed with the Sponsor and approval for enrollment is given
21. 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, participants on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the Sponsor.
22. 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 participant (e.g. brain stem lesions). Participants 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 16b.
23. Known or suspected leptomeningeal disease (LMD) as documented by the investigator
24. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

Number of Planned Participants

Approximately 55 participants will enroll in this study (Japanese population: approximately 42 participants, South Korean population:approximately 10 participants, Taiwanese population:approximately 3 participants).

Study Design

This is a single-arm, multicenter, phase 2 study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in participants with unresectable locally advanced or metastatic HER2+ BC who have had prior treatment with taxane anti-cancner agent, trastuzumab, pertuzumab, and TDM1. This study consists of Japanese population, South Korean population and Taiwanese population.

In Japanese population, prior to enrollment on the main portion of the trial, a safety run-in will be conducted in approximately 3 to 6 participants to assess the safety and tolerability of the standard doses and schedule for the combination of tucatinib, trastuzumab, and capecitabine. The inclusion and exclusion criteria, treatment doses and schedule, study assessments, and safety reporting rules will be identical to the main portion of the trial, with the exception of additional study visits and laboratory

assessments performed during the first 2 cycles of study treatment. Participants in the safety run-in will be carefully monitored through the first cycle of treatment and evaluated for adverse events (AEs) that are unexpected based on the known safety profile of each individual agent and of the combination of tucatinib, trastuzumab, and capecitabine. Investigators must ensure that participants enrolled in the safety run-in portion of the trial do not have other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures required per the protocol (such as compliance with additional study visits, laboratory assessments, oral medications and close out-patient monitoring). During the first cycle, the participant may be hospitalized for a minimum of 24 hours with discharge permitted if a participant has no ongoing ≥ Grade 3 AEs and is otherwise considered appropriate for discharge by the investigator based on history, physical exam (including vital signs), and laboratory evaluations (including complete blood count, serum chemistry, and liver function tests). History includes assessment of any new or ongoing AEs and concomitant medication use. For participants undergoing outpatient follow-up, the investigator must ensure that the participant will be followed closely in the outpatient setting by methods they determine to be appropriate to assure the participant's safety, and participants should be instructed to contact the investigator immediately in the event they experience an adverse event. In case of emergency, adequate means of communication between the site and the participant should be ensured by the investigator regardless of time of day or in the event of a holiday. The pace of enrollment will be monitored by the Sponsor, where there will be at least 7 days between the start of study treatment for each participant enrolled in the safety run-in.

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

A safety monitoring committee (SMC) consisting of the study clinical director, medical expert, investigators, study statistician, and other study team members will monitor the safety of participants on an ongoing basis throughout the study. For the safety run-in, the SMC will conduct an evaluation of overall safety after 3 participants have enrolled and completed one cycle of study treatment. If the overall safety is deemed acceptable by the SMC in the first 3 participants enrolled, the SMC may recommend opening the efficacy-evaluable portion of the trial. Additionally, based on the observed data, the SMC may also determine that an additional 3 participants should be enrolled in the safety run-in and may consider further safety measures. In this case, after evaluation of the totality of safety data in all participants enrolled, the SMC may recommend proceeding with the trial, enrolling additional participants to evaluate an alternative dosing regimen, or not to proceed with the trial. In the event a significant safety concern was to occur in the interim between scheduled SMC meetings, enrollment will be paused and an ad hoc meeting of the SMC will be called.

Investigational Product, Dose, and Mode of Administration

Treatment will be administered in 21-day cycles.

Tucatinib 300 mg (150 mg tablet× 2 tablets) will be given orally twice a day (total 600mg per day). Depending on the outcome of the safety run-in, the tucatinib starting dose may be adjusted.

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.

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression, death, withdrawal of consent, or study closure. In the absence of clear evidence of radiographic disease progression (per RECIST v1.1), development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the participant, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST v1.1.

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 computed tomography (CT), positron emission tomography (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 at baseline, every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter, irrespective of dose holds or interruptions. Efficacy assessments for each participant will continue until investigator-assessed disease progression (per RECIST v1.1), the start of subsequent anti-cancer therapy, death, withdrawal of consent, or study closure. Contrast MRI of the brain will be required on this same schedule only in those participants with prior history of brain metastases or with brain metastases or equivocal brain lesions at screening. Contrast brain MRI may also be performed in participants 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. Follow-up for survival will continue until death, study closure, or withdrawal of consent.

Pharmacokinetic Assessments

PK assessments of trough levels of tucatinib and ONT-993 (which is the predominant circulating metabolite) will be performed on Day 1 of Cycles 2-6 prior to administration of tucatinib. On Day 1 of Cycle 3, PK assessments of peak levels of tucatinib and ONT-993 will be performed 1–4 hours after administration of tucatinib. For the safety run-in only, additional PK assessments may be performed on Cycle 1 days 1, 8 and 15, and Cycle 2 days 8 and 15.

Safety Assessments

Participants will be assessed throughout the study for safety. Safety assessments including physical exam and collection of adverse events (AEs) and laboratory abnormalities will be performed at a minimum of once every 3 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).

Statistical Methods

Data collected in this study will be presented using summary tables, participant 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. For time-to-event endpoints, the median survival time will be estimated using the Kaplan Meier method; the associated 90% confidence interval (CI) will be calculated based on the complementary log-log transformation.

The primary efficacy analysis will be performed in Japanese population by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall 1-sided 5% level of significance, i.e., H0: $P \leq 0.20$ vs Ha: $P > 0.20$. The point estimate and the 2-sided 90% exact Clopper Pearson CI for the confirmed ORR, as assessed by ICR will be provided. The study will be considered positive if the lower bound of the 2-sided 90% exact Clopper-Pearson CI for confirmed objective response rate (cORR) is greater than 20%, so that the null hypothesis that the cORR is less than or equal to 20% can be rejected. cORR will be also estimated in all participants population including participants enrolled in Japan, South Korea and Taiwan as a secondary endpoint.

Approximately 42 participants will be enrolled in Japan including 4 participants in the safety run-in. With 38 participants, the study will have approximately 80% power to detect a 20% increase in ORR from 20% to 40% and approximately 90% power to detect a 25% increase in ORR from 20% to 45%, at one-sided significance level of 0.05.

On 02-Aug-2021 the SMC conducted an evaluation of overall safety after 4 Japanese participants were enrolled in the safety run-in and the safety and tolerability was deemed acceptable by the SMC; hence the enrollment of the safety run-in was completed and that of the main study was initiated on the following day.

A total of approximately 13 participants from South Korea and Taiwan are planned to be enrolled at this time.

The primary analysis will be conducted when all of the treated participants in Japanese population have been followed for at least 8 months (or all responders have been followed for a minimum of 6 months after their initial response, whichever comes first), have discontinued from the study, or had 30 days safety follow-up after disease progression, whichever comes first. In addition, for the purpose of regulatory submission in South Korea and Taiwan, the additional analyses may be conducted subsequently to the initial analysis.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	AE of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BC	breast cancer
β-hCG	beta human chorionic gonadotropin
BID	twice a day
CBC	complete blood count
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
cORR	confirmed objective response rate
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EGFR	epidermal growth factor receptor
EOT	end of treatment
ESMO	European Society for Medical Oncology
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate

GnRH	gonadotropin releasing hormone
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IAR	infusion-associated reactions
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	independent central review
IEC	independent ethics committee
INR	international normalized ratio
INV	investigator assessment
IRB	institutional review board
ISH	in situ hybridization
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
JBCS	Japanese Breast Cancer Society
LAM	lactational amenorrhea method
LFT	liver function tests
LMD	leptomeningeal disease
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease [study]
MUGA	multiple-gated acquisition scan
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
P-gp	P-glycoprotein
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally

PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMC	Safety Monitoring Committee
SRS	stereotactic radiosurgery
SRT	stereotactic radiation therapy
T-DM1	trastuzumab emtansine
TKI	tyrosine kinase inhibitors
ULN	upper limit of normal
WBRT	whole brain radiation therapy

1 INTRODUCTION

1.1 Background Information on the Target Disease

1.1.1 HER2+ Breast Cancer

Breast cancer (BC) is the most common form of cancer and the second leading cause of cancer-related death in women worldwide (Ferlay 2019). In Japan, BC is the fourth most common cancer, with an incidence of 92,266 cases in 2019 (Kantar Health 2019), and accounts for 9% of all cancer-related deaths (JBCS. Review 1 Changes in breast cancer morbidity and breast cancer mortality among Japanese women. 2018. http://jbcs.gr.jp/guidline/2018/index/ekigakuyobo/s1/ Accessed: Feb 11, 2020). Over the past several years, the incidence of BC in Japan has been increasing (annual percent change of 6.4% between 2003 and 2011 (Sauvaget 2016), with BC accounting for nearly half of the increase in all cancer diagnoses in Japanese women. The BC mortality rate had been steadily increasing from the 1960s, but plateaued starting in 2008. By age group, recent mortality rates for BC have decreased in Japanese women 30–54 years old, but have remained steady among older age groups (Katanoda 2015).

Human epidermal growth factor receptor (HER)-2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. HER2 overexpression or amplification is a critical driver of HER2+ (positive) malignancies (Lee-Hoeflich 2008). BC that is HER2+ accounts for 15%–20% of primary BC cases worldwide and is often associated with a higher initial disease stage and a more aggressive phenotype that is more likely to recur when compared to HER2-negative BC (Musolino 2011). Although, there have been significant advances in HER2-targeted therapy, HER2+ metastatic breast cancer (mBC) almost invariably progresses (Swain 2013). Up to 50% of patients with HER2+ BC develop brain metastases during the course of their disease, which have been associated with faster disease progression, shorter overall survival (OS), and lower quality of life when compared with non-central nervous system (CNS) metastases (Bendell 2003; Olson 2013; Pestalozzi 2013; Freedman 2019; Hurvitz 2019).

1.2 Current Treatment Options for HER2+ Metastatic or Recurrent Breast Cancer

In Japan, the introduction of HER2-targeted therapy using either antibody-based therapies or small molecule tyrosine kinase inhibitors (TKI) has led to significant and ongoing improvements in disease-free survival, progression-free survival (PFS), and OS in the neoadjuvant, adjuvant, and metastatic settings (Slamon 2001; Geyer 2006; Baselga 2012; Verma 2012). Trastuzumab, a humanized antibody that binds to the extracellular domain of HER2, was the first anti-HER2 agent approved by the Ministry of Health, Labour and Welfare (MHLW) for use in HER2+ BC, and remains the backbone of treatment in the neoadjuvant, adjuvant, and metastatic settings (Slamon 2001; Vogel 2002). Additionally, upon improvements in both PFS and OS, the addition of pertuzumab and taxane anti-cancer

agent to trastuzumab-based therapy in the first-line setting, and the use of single-agent trastuzumab emtansine (T-DM1) as second-line treatment, have become important standards of care for patients with metastatic disease. There are no effective treatments for the patients who have been difficult to treat with these standar-of-care therapy, and anti HER2 antibodies and chemotherapy combination or lapatinib and chemotherapy combination have been used for these patients. However, the response rate is approximately 22-23%, and the prognosis has not been imporved (Murthy 2020b; Yokoe 2021; Masuda 2020; Charles 2006). In recent years, the anti HER2 Antibody-Drug Conjugate (ADC), Trastuzumab deruxtecan, was approved in March 2020 for new therapeutic options after second-line treatment. The response rate of Trastuzumab deruxtecan was 60.9% (95%CI : 53.4-68.0) and the median PFS was 16.4 months (95% CI: 12.7-Not reached). However, as some patients are resistant to trastuzumab derxtecan or difficult to administer, the development of effective therapeutic agents with novel mechanisms of action continues to be essential for further prognostic improvement in this patient population.

BC practice guidelines from the JBCS (23 Oc 2019 update; JBCS. CQ22. What is the recommended treatment for first-line treatment of HER2-positive inoperable or metastatic or recurrent breast cancer? 2018 http://jbcs.gr.jp/guidline/2018/index/yakubutu/y2-cq-22 Accessed: Feb 12, 2020) strongly recommend a combination of trastuzumab + pertuzumab + docetaxel as first-line treatment for HER2+ metastatic or recurrent BC. This recommendation is based on results from the phase 3 CLEOPATRA study, in which 808 patients were randomized to receive pertuzumab + trastuzumab + docetaxel or placebo + trastuzumab + docetaxel. PFS in the experimental arm was superior to the control arm (median 18.7 months vs. 12.4 months; hazard ratio [HR] 0.69; 95% confidence interval [CI]: 0.58, 0.81) (Swain 2013). Median OS was also significantly longer in those patients who received pertuzumab (median 56.5 months vs. 40.8 months; HR 0.68; 95% CI: 0.56, 0.84; P<0.001) (Swain 2019). The combination of pertuzumab + trastuzumab + paclitaxel is also an option for first-line treatment for HER2+ mBC in Japan, as data from a phase 2 study showed this combination to be active and tolerable (Dang 2015).

The JBCS strongly recommends T-DM1 for use in patients with HER2+ metastatic or recurrent BC that has progressed during or after trastuzumab administration. This recommendation is primarily based on results from the phase 3 EMILIA study, in which 991 patients with HER2+ locally advanced, metastatic, or recurrent BC who had previously been treated with trastuzumab and a taxane were randomized to receive T-DM1 or capecitabine + lapatinib (Verma 2012). Those randomized to T-DM1 had statistically significant improvements in PFS (median 9.6 months vs. 6.4 months; HR 0.65; 95% CI: 0.55, 0.77; P<0.001), OS (median 30.9 months vs. 25.1 months; HR 0.68; 95% CI: 0.55, 0.85; P<0.001) and objective response rate (ORR) (43.6% vs. 30.8%; P<0.001) as compared to the control group. In addition, T-DM1 is weakly recommended in later lines of therapy based on results from the phase 3 TH3RESA study of T-DM1 vs. physician's choice in patients with previously treated HER2+ mBC and the EMILIA study where 39% of patients (n=500) were

treated in the third-line or later. Currently, no randomized clinical trial has evaluated T-DM1 as second-line treatment in patients with disease progression after trastuzumab + pertuzumab + chemotherapy.

Continuation of anti-HER2 therapy past progression is recommended in the third-line setting by the JBCS. An exploratory analysis from the GBG 26/BIG 03-05 study showed an improved post-progression survival (PPS) for patients who received anti-HER2 treatment as part of third-line treatment (n=52) vs. those who did not (n=88) (PPS: 18.8 months [95% CI: 12.9, 24.8] vs. 13.3 months [95% CI: 10.2, 14.7]; HR 0.63; P=0.02). However, no OS benefit was observed in those who received anti-HER2 treatment (von Minckwitz 2011).

Globally, the current standard of care for HER2+ metastatic or recurrent breast cancer also consists of treatment with trastuzumab + pertuzumab and a taxane as first-line treatment, followed by T-DM1 in second line (Cardoso 2020, NCCN Guidelines® 2021). Trastuzumab deruxtecan is recommended as third line treatment in the ESMO and NCCN guidelines. However, Trastuzumab deruxtecan has not been approved in South Korea and Taiwan.

1.2.1 Treatment Options for HER2+ Breast Cancer with Brain Metastases

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

Treatment of brain metastases often includes surgical resection, radiosurgery, and/or whole brain radiotherapy, combined with continuation of systemic anti-cancer therapy. Unfortunately, CNS-directed therapy often result in significant neurologic toxicities, which may impair quality of life. Stereotactic radiosurgery (SRS) has been increasingly used to avoid the neurologic toxicities of whole brain radiotherapy, but has been associated with inferior control of distant brain relapse outside the local radiation fields (Chang 2009; Brown 2016; Kaidar-Person 2016). Patients with brain metastases have historically been excluded from clinical trials and, as a result, no systemic agents are approved for treatment of HER2+ brain metastases (Lin 2015). Development of treatments for this patient population remains an important unmet medical need, which will require including these patients in clinical trials.

1.2.2 Tucatinib

On 17 April 2020, tucatinib was approved by the US Food and Drug Administration (FDA) under the trade name Tukysa, based on results from the HER2CLIMB trial. Tucatinib was approved for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received

one or more prior anti-HER2-based regimens in the metastatic setting in combination with trastuzumab and capecitabine.

Tucatinib is an orally-available (PO), reversible HER2 small molecule TKI. Two key features of tucatinib are its potency and selectivity for HER2 compared to the closely-related tyrosine kinase epidermal growth factor receptor (EGFR). In comparison to other approved HER2 TKIs for patients with mBC, tucatinib is approximately 6-fold more potent in its inhibition of HER2 compared to lapatinib. In addition, tucatinib is highly selective for HER2 compared to EGFR. With >1000-fold more selectivity for HER2 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 toxicity). This unique feature also differentiates tucatinib from other HER2 inhibitors, including both neratinib and lapatinib, which inhibit HER2 and EGFR with similar potency and are associated with side effects related to EGFR inhibition.

Clinical trials are ongoing to examine the safety and efficacy of tucatinib when combined with other HER2-directed therapies. A complete summary of the clinical and nonclinical data for tucatinib and its trials in human patients is provided in the Investigator's Brochure.

1.3 Data Overview

A complete summary of the clinical and nonclinical data relevant to the evaluation of tucatinib in human participants is provided in the Investigator's Brochure.

1.3.1 Nonclinical

The pharmacological and toxicological properties of tucatinib were evaluated in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidance. The tucatinib Investigator's Brochure provides a complete summary of nonclinical pharmacology, pharmacokinetic (PK), and toxicology study data.

1.3.2 Clinical

1.3.3 Tucatinib Clinical Development in Breast Cancer

A complete summary of the current tucatinib clinical development program is provided in the tucatinib Investigator's Brochure.

The efficacy and safety of the combination of tucatinib + trastuzumab + capecitabine has been evaluated in a phase 1b dose finding trial (ONT-380-005) and a pivotal, randomized, double-blind, placebo-controlled, active comparator study (HER2CLIMB; ONT-380-206).

The phase 1b dose-escalation trial (ONT-380-005) evaluated tucatinib in combination with trastuzumab and/or capecitabine in participants with HER2+ mBC (Murthy 2018). Sixty participants who received prior treatment with both trastuzumab and T-DM1 for metastatic disease were enrolled, including 27 participants treated with tucatinib 300 mg twice a day

(BID), trastuzumab, and capecitabine (1000 mg/m^2 twice daily for 14 days of each 3 week cycle). This study informed dose selection of 300 mg BID tucatinib for the pivotal trial HER2CLIMB. Median PFS for participants treated with tucatinib 300 mg + trastuzumab + capecitabine was 7.8 months. Among those with measurable disease, the ORR for tucatinib 300 mg + trastuzumab + capecitabine was 61%. Treatment was generally tolerable with a manageable safety profile and is consistent with what was observed in the HER2CLIMB trial.

Results from the pivotal HER2CLIMB trial clearly demonstrated the benefit of adding tucatinib to trastuzumab and capecitabine in HER2+ mBC (Murthy 2020b). HER2CLIMB enrolled 612 participants who had been treated with 3 prior HER2-directed agents (trastuzumab, pertuzumab, and T-DM1). Participants were randomized in a 2:1 ratio to receive tucatinib (300 mg BID) or placebo in combination with trastuzumab (8 mg/kg intravenously [IV] followed by 6 mg/kg every 3 weeks) and capecitabine (1000 mg/m^2 twice daily for 14 days of each 3 week cycle). The primary endpoint of PFS was highly statistically significant in favor of the tucatinib combination, with an HR of 0.54 (95% CI: 0.42, 0.71; P<0.001). Additionally, all multiplicity-adjusted secondary endpoints supported the primary endpoint and demonstrated benefit with tucatinib, including OS (HR 0.66; 95% CI; 0.50, 0.88; P=0.005), PFS in participants with brain metastases (HR 0.48; 95% CI; 0.34, 0.69; P<0.001) and confirmed ORR (40.6% [95% CI; 35.3, 46.0] in the tucatinib arm vs. 22.8% [95% CI; 16.7, 29.8] in the control arm, P<0.001). Tucatinib treatment was generally tolerable with a manageable safety profile and low rate of treatment-emergent adverse events (TEAEs) leading to discontinuation of treatment.

The pivotal HER2CLIMB trial met the primary endpoint of PFS, demonstrating that the addition of tucatinib to trastuzumab and capecitabine reduced the risk of disease progression or death by approximately half in heavily pretreated patients with HER2+ locally advanced unresectable or mBC. Tucatinib treatment reduced the risk of disease progression or death by a greater amount in participants with brain metastases. Most importantly, tucatinib also reduced the risk of death by approximately a third in the overall population. Tucatinib treatment was generally tolerable with a manageable safety profile and low rate of treatment-emergent adverse events (TEAEs) leading to discontinuation of treatment.

Based on the statistically significant and clinically meaningful results for the primary and all alpha-controlled secondary endpoints, the Sponsor made the decision to unblind this trial and allow participants on the control arm to cross over to receive tucatinib.

1.3.4 Tucatinib Safety and Pharmacokinetic Data in Japanese Participants

To support clinical development of tucatinib in Japan, a phase 1 safety, tolerability, and PK trial was conducted in healthy Japanese and Caucasian participants in the US (SGNTUC-015). The results of this trial show there were no meaningful differences in PK or safety profiles between Caucasian and Japanese participants at the clinically relevant dose of 300 mg BID. Therefore, no starting dose adjustment is recommended for tucatinib based on

age, albumin, creatinine clearance, body weight, or race in Japanese participants. Additionally, a population PK analysis was performed on the HER2CLIMB trial where race was not identified as a covariate in the model.

1.4 Risk Benefit Assessment

In the global HER2CLIMB trial, all subgroups analyzed, including race (white vs, non-white), demonstrated a PFS benefit with tucatinib treatment consistent with the overall outcome. Additionally, data from the SGNTUC-015 PK trial demonstrated no marked differences in tucatinib exposure or safety between Japanese and Caucasian healthy volunteers at the clinically relevant 300 mg dose level. Taken together, these data support a positive benefit/risk profile for evaluation of tucatinib in combination with trastuzumab and capecitabine in Japanese participants with HER2+ mBC.

2 OBJECTIVES

Table 1: Objectives and corresponding endpoints

Objective	Corresponding Endpoint
Primary	
• Assess ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in Japanese population.	• Confirmed objective response rate (cORR) per RECIST v1.1, as determined by ICR
Secondary	
• Assess ORR per Response Evaluation Criteria in RECIST v1.1 by ICR in all participants population.	• cORR per RECIST v1.1, as determined by ICR
• Assess ORR per RECIST v1.1 by investigator assessment (INV) in Japanese population and all participants population.	• cORR per RECIST v1.1 as determined by INV
• Assess duration of response (DOR) per RECIST v1.1 in Japanese population and all participants population.	• DOR per RECIST v1.1, as determined by ICR and INV
• Assess PFS per RECIST v1.1 in Japanese population and all participants population.	• PFS per RECIST v1.1, as determined by ICR and INV
• Assess overall survival (OS) in Japanese population and all participants population.	• OS
• Evaluate the safety of tucatinib in combination with trastuzumab and capecitabine in Japanese population and all participants population.	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and lab abnormalities • Frequency of dose modifications and treatment discontinuations • Vital signs and other relevant safety variables
Exploratory	
• Evaluate the pharmacokinetics (PK) of tucatinib administered in combination with trastuzumab and capecitabine in Japanese population, South Korean population and all participants population.	• PK

3 INVESTIGATIONAL PLAN

3.1 Summary of the Safety Run-in (Japanese participants only)

Prior to enrollment of participants into the main portion of the trial, a safety run-in will be conducted in approximately 3 to 6 participants to assess the safety and tolerability of the standard doses and schedule for the combination of tucatinib, trastuzumab, and capecitabine. The inclusion and exclusion criteria (Section 4), treatment doses (Section 5), schedule and study assessments (Sections 6 and APPENDIX A), and safety reporting rules (Section 7.4) will be identical to the main portion of the trial, with the exception of additional study visits and laboratory assessments performed during the first 2 cycles of study treatment (Section 6).

The starting dose for participants in the safety run-in will receive tucatinib 300 mg (150 mg tablet × 2 tablets) orally twice a day (total 600 mg per day), trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days, and capecitabine 1000 mg/m^2 PO BID for Days 1-14 only of a 21-day cycle.

Participants in the safety run-in will be carefully monitored through the first cycle of treatment (21 days) and evaluated for AEs that are unexpected based on the known safety profile of each individual agent and of the combination of tucatinib, trastuzumab, and capecitabine. Participants will be enrolled at a limited number of sites for this safety run-in. Investigators must ensure that participants enrolled in the safety run-in portion of the trial do not have other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures required per the protocol (such as compliance with additional study visits, laboratory assessments, oral medications and close out-patient monitoring) (Section 4.2). During the first cycle, the participant may be hospitalized for a minimum of 24 hours with discharge permitted if a participant has no ongoing ≥ Grade 3 AEs and is otherwise considered appropriate for discharge by the investigator based on history, physical exam (including vital signs), and laboratory evaluations (including complete blood count, serum chemistry, and liver function tests). History includes assessment of any new or ongoing AEs and concomitant medication use. For participants undergoing outpatient follow-up, the investigator must ensure that the participant will be followed closely in the outpatient setting by methods they determine to be appropriate to assure the participant's safety, and participants should be instructed to contact the investigator immediately in the event they experience an AE. In case of emergency, adequate means of communication between the site and the participant should be ensured by the investigator regardless of time of day or in the event of a holiday. The pace of enrollment will be monitored by the Sponsor, where there will be at least 7 days between the start of study treatment for each participant enrolled in the safety run-in.

A safety monitoring committee (SMC) consisting of the study clinical director, medical expert, investigators, study statistician, and other study team members will conduct an evaluation of overall safety after 3 participants have enrolled and completed one cycle of study treatment. If the overall safety is deemed acceptable by the SMC in the first 3

participants enrolled, the SMC may recommend opening the main portion of the trial. Additionally, based on the observed data, the SMC may also determine that additional participants should be enrolled in the safety run-in and may consider further safety measures. In this case, after evaluation of the totality of safety data in all participants enrolled, the SMC may recommend proceeding with the trial, enrolling additional participants to evaluate an alternative dosing regimen, or not to proceed with the trial. In the event a significant safety concern was to occur in the interim between scheduled SMC meetings, enrollment will be paused and an ad hoc meeting of the SMC will be called.

A participant will be considered evaluable for the safety run-in if they receive at least 75% of the intended dose amounts of each study treatment in Cycle 1 or if they experience a toxicity as described in (Section 3.1.1). Participants will be replaced if they are not eligible for evaluation due to circumstances completely unrelated to either study treatment (e.g., receipt of prohibited concomitant medication or the participant does not meet eligibility criteria) or if they do not complete the 21-day evaluation period for reasons other than treatment-related toxicity (e.g., withdrawal of consent). For participants that experience a toxicity as described in Section 3.1.1 during the safety run-in part of the trial, the decision whether to continue treatment at the same or a reduced dose (or to discontinue one or more of the individual drugs) will be made by the treating investigator based on the individual participant's benefit-risk assessment. Dose modifications due to AEs will be permitted and guidelines regarding the resumption or discontinuation of study treatment will be followed per Section 5.5. Data from participants who are not DLT-evaluable will be included in safety evaluation for SMC awareness.

3.1.1 Dose Limiting Toxicity

The SMC will base their decision on an evaluation of the totality of data in the safety run-in participants to assess the overall safety and tolerability of the combination, in the context of the expected safety profile for the individual drugs.

The SMC will adjudicate determinations of DLT in participants from initiation of treatment through the end of the DLT period. Among the first 3 DLT evaluable participants,

- If 0 of 3 participants experience a DLT, and the overall safety is deemed acceptable by the SMC, the SMC may recommend that the combination is safe and tolerable in participants, and participants may participate in the main portion of the trial.
- If 1 of 3 participants experiences a DLT, the SMC may recommend enrollment of 3 additional participants.
- If ≥2 of 3 participants experience a DLT, the SMC may recommend a lower dose of tucatinib. In the dose de-escalation stage, tolerability will be evaluated by enrolling 3 participants, such as before the dose de-escalation stage.

In the event the cohort is expanded to a total of 6 DLT-evaluable participants (including the 3 participants enrolled before expansion),

- If ≤1 of 6 participants experiences a DLT, and the overall safety is deemed acceptable by the SMC, the SMC may recommend that the combination is safe and tolerable in participants and participants may participate in the main portion of the trial at the current dose.

- If ≥2 of 6 participants experience a DLT, the SMC may recommend a lower dose of tucatinib. In the dose de-escalation stage, tolerability will be evaluated by enrolling 3 participants, such as before the dose de-escalation stage.

If a second dose de-escalation of tucatinib is required, the SMC may recommend that enrollment of participants not proceed to the main portion of the trial.

The SMC will take into consideration the occurrence of the following toxicities during Cycle 1 if assessed by the investigator to be clinically significant, unexpected, and related to tucatinib or the combination of tucatinib, trastuzumab, and capecitabine. The events unrelated to tucatinib or the combination such as disease progression, medical illness, environmental factors, unrelated trauma etc. will be excluded. Grading will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. These events should be taken into consideration in the evaluation performed by the SMC.

Non-hematologic

- Any treatment-related AE ≥Grade 3 except:
    - Grade 3 fatigue lasting ≤3 days
    - Grade 3 diarrhea, nausea, or vomiting without optimal use of anti-emetics or anti-diarrheals that had recovered to ≤ Grade 1 or pretreatment level within 10 days of initiating appropriate supportive therapy
    - Grade 3 rash without optimal use of corticosteroids or anti-infectives that had recovered to ≤ Grade 1 or pretreatment level within 10 days of initiating appropriate supportive therapy
- >14-day delay in start of Cycle 2 due to AEs related to tucatinib or the addition of tucatinib to trastuzumab and capecitabine
- Missing >25% of tucatinib, capecitabine, or trastuzumab doses as a result of treatment-related toxicities during the first cycle
- Any treatment-related toxicity that leads to treatment discontinuation (tucatinib and/or capecitabine and/or trastuzumab) during Cycle 1

Hematologic

- Grade 4 thrombocytopenia (<25 X 10^3/µL) lasting for >7 days or requiring platelet transfusion
- Grade 3 thrombocytopenia (<50 X 10^3/µL) with significant bleeding (≥ Grade 3)
- ≥Grade 3 febrile neutropenia
- Grade 4 neutropenia (<500/mm^3) lasting for >7 days. Prophylactic use of colony stimulating factors (e.g., G-CSF) for primary prevention of neutropenia is prohibited during the DLT evaluation period.
- Grade 4 anemia or anemia requiring blood transfusion

Hepatic

- Grade 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased (>20 x upper limit of normal [ULN])
- Grade 4 blood bilirubin increased (> 10 x ULN)
- Grade 3 ALT or AST or blood bilirubin increased that has not returned to ≤ Grade 1 or baseline by start of Cycle 2
- ALT and/or AST >3xULN AND total bilirubin >2x ULN

Note: Asymptomatic ≥ Grade 3 laboratory abnormalities will not be considered, except for hematologic and hepatic abnormalities outlined above.

3.1.2 Summary of Study Design

This is a single-arm, multicenter, phase 2 study with a safety run-in designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in participants with locally advanced unresectable or metastatic HER2+ BC who have had prior treatment with taxane anti-cancer agent, trastuzumab, pertuzumab, and T-DM1. This study consists of Japanese population, South Korean population and Taiwanese population.

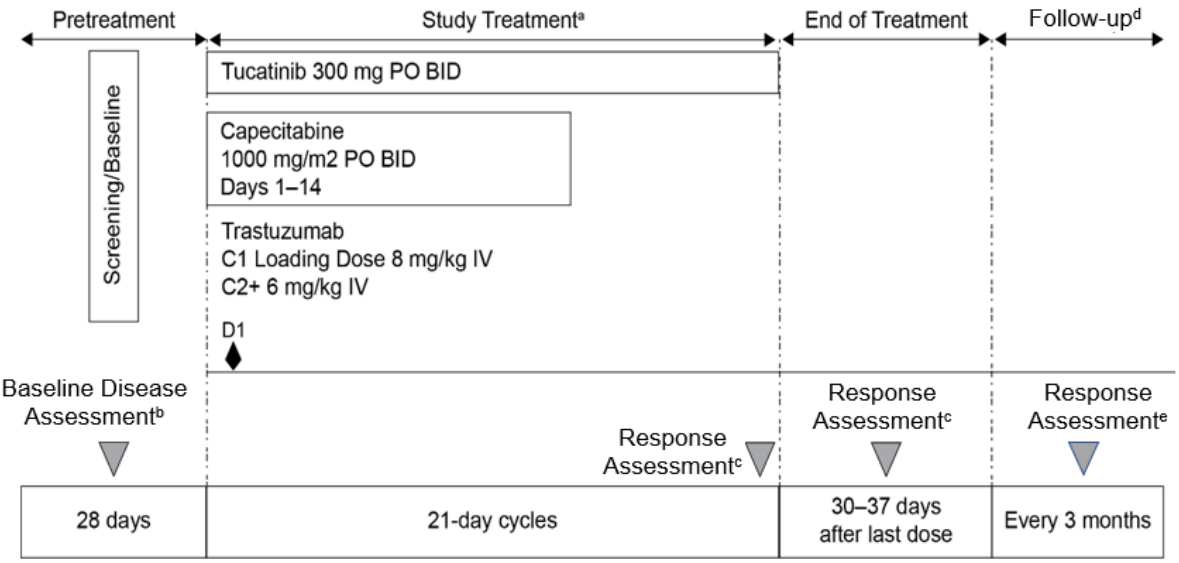
Treatment will be administered in 21-day cycles. Tucatinib 300 mg (150 mg × 2 tablets) will be given orally twice a day (total 600 mg per day). Depending on the outcome of the safety run-in, the tucatinib starting dose may be adjusted. Trastuzumab will be given as a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days. Capecitabine will be given at 1000 mg/m^2 PO BID on Days 1–14 of each cycle. Dose holding of tucatinib, trastuzumab, and capecitabine will be allowed as needed for participant safety. Additionally, dose discontinuation of trastuzumab and/or capecitabine is permitted. Participants who discontinue capecitabine and/or trastuzumab may continue on study treatment. Participants who discontinue tucatinib will be allowed to remain on study treatment.

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

A SMC consisting of the study clinical director, medical expert, investigators, study statistician, and other study team members will monitor the safety of participants on an ongoing basis throughout the study.

Approximately 55 participants（Japanese population: approximately 42 participants including 4 participants in the safety run-in, South Korean population: approximately 10 participants and Taiwanese population: approximately 3 participants) will be enrolled into this study. On 02-Aug-2021 the SMC conducted an evaluation of overall safety after 4 Japanese participants were enrolled in the safety run-in and the safety and tolerability was deemed acceptable by the SMC; hence the enrollment of the safety run-in was completed and that of the main study was initiated on the following day. A study schema is provided in Figure 1. See APPENDIX A for a schedule of events.

Figure 1: Study schema



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

b Includes measurement of all known sites of unresectable locally advanced/metastatic disease via radiographic imaging. Assessment for brain metastases is performed with contrast magnetic resonance imaging (MRI) of the brain for all participants regardless of prior history of brain metastases (Section 7.2).

c Response assessments are performed every 6 weeks for the first 24 weeks, and then every 9 weeks thereafter, irrespective of dose holds or interruptions. Participants without brain metastases

at baseline do not require contrast MRIs while on treatment. Response assessments should be done at the End of Treatment Visit if not done within the previous 30 days only in participants having ended study treatment for reasons other than radiographic disease progression. A contrast brain MRI is required at the End of Treatment Visit for participants with known brain metastases at baseline or a history of brain metastases, unless already done within 30 days of ending study treatment or if progression in the brain has already been documented while on study (Section 6.4).

d Assessment of overall survival and collection of information regarding any additional anti-cancer therapies administered after discontinuation of study treatment.

e For participants who discontinue study treatment prior to disease progression by investigator assessment (per RECIST v1.1), response assessments are performed every 9 weeks (±1 week) until disease progression, death, withdrawal of consent, or study closure. Contrast brain MRI is required on this same schedule only in those participants with known brain metastases at baseline or a history of brain metastases (Section 6.5).

3.1.3 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 participants, either through a safety review by the Sponsor or a safety assessment by the SMC.
- Participant enrollment is unsatisfactory.

3.1.4 End of Study

The study ends when the last participant completes the last visit, last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the Sponsor may terminate the study at any time (Section 10.3.2).

3.1.5 Retreatment

Retreatment with tucatinib is not permitted.

3.2 Discussion and Rationale for Study Design

3.2.1 Rationale for Study Population

The study population is designed to mirror the study population of the pivotal HER2CLIMB study. The key eligibility criteria will be nearly identical to the HER2CLIMB study with the exception that measurable disease by RECIST v1.1 will be required at study entry. Eligible participants for this study are those with progressive, unresectable locally advanced or metastatic HER2+ BC who have had prior treatment with taxane anti-cancer agent, 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+ BC. 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 HER2CLIMB study, the addition of tucatinib to the combination of trastuzumab and capecitabine resulted in statistically significant and clinically meaningful improvements in PFS, OS, PFS in participants with brain metastases, and confirmed ORR, and therefore may be able to meet this need.

Certain participants with brain metastases are also eligible for this trial, including participants 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 whole brain radiation therapy [WBRT], SRS or stereotactic radiation therapy [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 HER2CLIMB have shown clinical activity in participants with either untreated brain metastases or brain metastases progressing after prior radiation therapy. As there are currently no approved systemic therapies for participants 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 participants with brain metastases, as well as allow participants 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.

Participants with asymptomatic brain lesions found during screening not thought to need immediate local therapy are eligible for this study. These participants 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).

To mimic the study population in HER2CLIMB, participants 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 >2 mg 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, 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, 14 or more days after WBRT and 28 or more days after surgical resection) if neurologically stable and on reduced dose of steroids as protocol specified.

The SMC will be monitoring safety data in an ongoing fashion to ensure that participants are not put at excessive risk.

To ensure that participants 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 according to current ASCO/CAP Guidelines (Wolff 2013).

3.2.2 Rationale for Selection of Doses

In participants that have previously been treated with trastuzumab, pertuzumab, and T-DM1, the combination of tucatinib, trastuzumab, and capecitabine has now been evaluated in 431 participants from the Phase 1b (ONT-380-005) and HER2CLIMB studies (Murthy 2018; Murthy 2020b). The selected doses for this study are based upon these data and identical to those used in the HER2CLIMB study.

The addition of tucatinib to trastuzumab and capecitabine provides 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 2012; Blackwell 2012; Gianni 2012). Furthermore, the greater selectivity of tucatinib compared to other oral anti-HER2 agents offers the potential to provide HER2 blockade with fewer toxicities, and allows for the addition of capecitabine, a cytotoxic agent. The Phase 1b ONT-380-005 dose-escalation study of tucatinib in combination with trastuzumab and capecitabine in participants with advanced HER2+ BC established the RP2D of tucatinib at

300 mg BID for the triplet combination. In HER2CLIMB, tucatinib 300 mg BID in combination with trastuzumab and capecitabine demonstrated statistically significant and clinically meaningful efficacy outcomes with a manageable safety profile in participants with metastatic or locally advanced unresectable BC previously treated with trastuzumab, pertuzumab, and T-DM1 (Murthy 2020a). This is the approved tucatinib dosing regimen in the US. Moreover, the established clinical dosing regimen of tucatinib 300 mg BID is supported by data from the SGNTUC-015 PK study, which demonstrated no marked differences in tucatinib exposure or safety between Japanese and Caucasian healthy volunteers at the 300 mg dose level.

The dosing of trastuzumab of 8 mg/kg IV followed by 6 mg/kg once every 21 days is the full dose approved for single-agent use and is the same as the HER2CLIMB trial.

The dosing of capecitabine at 1000 mg/m^2 is the same as was utilized in the ONT-380-005 and HER2CLIMB studies. This dose has 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). 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).

3.2.2.1 Rationale for Regimen in Participants 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. Until tucatinib received US FDA approval in April 2020, there were no systemic therapies are currently approved for the treatment of brain metastases in patients with HER2+ mBC. Effective systemic therapies are needed which could potentially delay the use of radiation or treat lesions which have progressed after radiation. Results from the HER2CLIMB clinical study indicate that the addition of tucatinib to capecitabine and trastuzumab reduced the risk of disease progression or death in participants with brain metastases (Murthy 2020b). Therefore, participants with brain metastases will also be included in this study.

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 CNS 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; Network 2013; Ramakrishna 2014). In this trial, participants 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 7.2.1. For the

analysis of overall PFS, these participants will be considered to have progressed at the time of initial CNS progression as outlined in Section 9.3.

3.2.3 Blinding and Unblinding

This is an open-label study.

4 STUDY POPULATION

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

4.1 Inclusion Criteria

1. Participants must have histologically confirmed HER2+ breast carcinoma, with HER2+ defined by in situ hybridization (ISH) or immunohistochemistry (IHC) methodology according to the American Society of Clinical Oncology/College of American Pathologists.

    a. Tissue blocks or slides must be submitted to confirm HER2 positivity (using IHC, ISH or fluorescence in situ hybridization [FISH]) by a Sponsor-designated central laboratory

    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. Received previous treatment with taxane anti-cancer agent, trastuzumab, pertuzumab, and T-DM1. with the exception is when the use of taxanes is contraindicated or judged not to be the best treatment at the discretion of the investigator.

3. Radiographically and/or histologically confirmed disease progression on last systemic anticancer treatment for unresectable locally advanced or metastatic HER2+ breast carcinoma.

    Note: Clinical exam, rising tumor markers and/or photography are not acceptable as methods for documentation of progressive disease

4. Measurable disease as assessed by RECIST v1.1

5. Age of majority at time of consent

6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1

7. Life expectancy ≥6 months, in the opinion of the investigator

8. Has adequate organ function, as defined in the following table (Table 2). Specimens must be collected within 10 days prior to the start-of-study interventions.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological[1]	
Absolute neutrophil count (ANC)	≥1,500/µL
Platelets	≥100,000/µL (with stable platelet count from 75-100 x 10^3/µL may be included with approval from the Sponsor)
Hemoglobin	≥9.0 g/dL
Renal	
Estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) study equation	≥50 mL/min/1.73m^2
Hepatic	
Total bilirubin	≤1.5 ×ULN, except for participants with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 x ULN.
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) and Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless on medication known to alter INR and aPTT. Note: Warfarin and other coumarin derivatives are prohibited.

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase);
GFR = glomerular filtration rate; ULN = upper limit of normal.
[1]In participants transfused or who receive colony stimulating factors (eg, G-CSF) before study entry, transfusion or colony stimulating factor must be administered ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion or growth factor support
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

9. 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

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies

    - Is not a WOCBP

    OR

    - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in APPENDIX D during the intervention period and for at least 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

        - A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention.

        - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

        - Additional requirements for pregnancy testing during and after study intervention are in Section 7.4.5.

        - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

        - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

11. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after receiving the last dose of tucatinib or 90 days after receiving the last dose of Capecitabine whichever occurs last for male partner (no contraception requirement for trastuzumab for male).:

    - Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [APPENDIX D]) as detailed below:
    - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

12. Participant must provide written informed consent

13. Participant must be willing and able to comply with study procedures

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

14. No evidence of brain metastases

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

16. 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. Participants treated with CNS local therapy for newly identified lesions or previously treated progressing 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 ≥14 days prior to first dose of study treatment, time since 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 v1.1 are present

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

4.2 Exclusion Criteria

1. Prior treatment with:

   a. Lapatinib within 12 months of starting study treatment.

      Note:In cases where lapatinib was given for ≤21 days and was discontinued for reasons other than disease progression or severe toxicity, the participant is eligible.

      Note:In cases where lapatinib was given as a part the last systemic anticancer treatment for unresectable locally advanced or metastatic HER2+ breast carcinoma, the participant is not eligible according to Inclusion Criteria 3.

   b. Neratinib, afatinib, or other investigational HER2/EGFR or HER2 TKI at any previous time

   c. Tucatinib or enrolled on a tucatinib clinical trial and received Tucatinib.

2. Previous treatment with capecitabine (or other fluoropyrimidine [e.g., 5fluorouracil]) 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: participants 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 (eg Doxil, Caelyx, and/or 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. 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. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:

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

7. Clinically significant cardiopulmonary disease such as:

   - Ventricular arrhythmia requiring therapy
   - Symptomatic hypertension or uncontrolled hypertension as determined by investigator
   - Any history of symptomatic CHF or symptomatic decreases in ejection fraction
   - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE] v4.03 Grade 3 or above) due to complications of advanced malignancy
   - Any history of interstitial lung disease or pneumonitis that is grade 2 or greater
   - Hypoxia requiring supplementary oxygen therapy

8. Known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment

9. Any uncontrolled Grade 3 or higher (per the NCI CTCAE, v4.03) viral, bacterial, or fungal infection within 14 days prior to the first dose of study treatment. Antimicrobial prophylaxis or ongoing treatment of resolving/controlled infection is permitted.

10. Positive for Hepatitis B by surface antigen expression, or positive for Hepatitis C infection, or the presence of known chronic liver disease. Participants who have been treated for Hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks. As reactivation of these viruses has not been studied with the combination of tucatinib, trastuzumab, and capecitabine, there is a possible risk of reactivation.

    - Participants who are positive for either antibodies to Hepatitis B surface antigen (HBsAb) or antibodies to Hepatitis B core antigen (HBcAb) should be screened using polymerase chain reaction (PCR) measurement of Hepatitis B DNA levels. Participants with Hepatitis B DNA levels by PCR that require nucleoside analogue

therapy are not eligible for the trial. The latest local guidelines should be followed regarding the monitoring of Hepatitis B DNA levels by PCR for participants on study treatment

11. Known to be positive for human immunodeficiency virus (HIV)

12. Participants who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last.

13. Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)

14. Unable to swallow pills or significant gastrointestinal disease which would preclude the adequate oral absorption of medications

15. Use of a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or a moderate or strong CYP2C8 inducer within 5 days prior to first dose of study treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks prior to the start of study treatment and requires Sponsor consultation.

16. Known dihydropyrimidine dehydrogenase deficiency

17. Unable for any reason to undergo contrast MRI of the brain

18. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

19. Evidence within 2 years of the start of study treatment of another malignancy that required systemic treatment

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

20. Any untreated brain lesions >2.0 cm in size, unless discussed with the Sponsor and approval for enrollment is given

21. 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, participants on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible with discussion and approval by the Sponsor.

22. 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 participant (e.g., brain stem lesions). Participants 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 16b.

23. Known or suspected leptomeningeal disease (LMD) as documented by the investigator

24. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain metastases notwithstanding CNS-directed therapy

4.3 Childbearing Potential

Please refer to APPENDIX D.

4.4 Removal of Participants from Therapy or Assessment

The Sponsor must be notified if a participant is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the participant's medical records and case report form (CRF).

In the absence of radiographic disease progression per RECIST v1.1, development of CNS symptoms, or radiographic changes thought to pose potential immediate risk to the participant, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST v1.1.

4.4.1 Discontinuation of Study Treatment

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

- Progressive disease (PD)
- AE
- Pregnancy
- Investigator decision that the study drug needs to be discontinued including the safety point of view
- Investigator decision due to clinical progression
- Withdrawal of consent
- death
- Participant decision, non-AE
  Note: Ensure that participants who decide to stop treatment **because of an AE** are not included in this rationale.
- Study termination by Sponsor
- Other, non-AE

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

4.4.2 Participant Withdrawal from Study

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

- Participant withdrawal of consent
- Study termination by Sponsor
- Lost to follow-up
- Death
- Other

5 TREATMENTS

5.1 Treatments Administered

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

5.2 Investigational Product (Tucatinib)

5.2.1 Description

Tucatinib is a kinase inhibitor that selectively inhibits HER2, and displays limited activity against the related kinase EGFR.

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

5.2.2 Method of Procurement

The investigational product (tucatinib) will be provided by the Sponsor.

5.2.3 Dose and Administration

Participants will receive tucatinib 300 mg (150 mg×2 tables) orally twice a day (total 600 mg per day). Depending on the outcome of the safety run-in, the tucatinib starting dose may be adjusted. Capecitabine and tucatinib may be taken together or in sequence.

Participants will be instructed to store and take the tucatinib treatment as follows:

- Bottles of tucatinib 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 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 tablets be taken at the same times each day, ± 2 hours.
    - It is recommended that if a participant misses a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be

immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the participant should not take the missed dose but should wait and take the next regularly scheduled dose.

- Tucatinib doses should be ingested with a full 8 oz. glass of water, if possible. Doses may be taken either with or without food.
- Tucatinib bottle and all remaining pills should be brought to the clinic for each study visit.
- It is important for us to know that a participant is receiving the correct amount of drug while participating on the study. If the participant was not able to take the fully prescribed dose or any single tablet of tucatinib as instructed on any day, the participant 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.

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

5.2.4 Storage and Handling

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

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

5.2.5 Packaging and Labeling

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

5.2.6 Study Drug Accountability

Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib is to be tracked and documented from the time of receipt at the site, through participant 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 bottles should be handled according to the Sponsor's instructions.

5.3 Trastuzumab

5.3.1 Description

Trastuzumab is a humanized IgG-1 kappa monoclonal antibody which binds to the extracellular domain of the HER2 protein. It mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which over express HER2 protein.

5.3.2 Method of Procurement

Trastuzumab is provided locally by the study site.

5.3.3 Dose, Preparation, and Administration

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

Approved trastuzumab biosimilars 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.

Trastuzumab should be prepared and administered per instructions in the package insert.

5.3.4 Storage and Handling

Trastuzumab should be stored according to the package insert.

5.3.5 Packaging and Labeling

Each vial of trastuzumab will be labeled in compliance with applicable regulatory requirements.

5.4 Capecitabine

5.4.1 Description

Capecitabine is a PO fluoropyrimidine carbamate with antineoplastic activity. Capecitabine is metabolized to two active metabolites, 5-fluoro-2-deoxyuridine monophosphate and 5-fluorouridine triphosphate, which inhibit DNA synthesis and inhibit RNA and protein synthesis, respectively.

Capecitabine drug product is supplied as a biconvex, oblong film-coated tablet for oral administration. Each white colored tablet contains 300 mg of capecitabine*. Refer to the package insert for information regarding the inactive ingredients and film coating.

*Colour, shape and the unit dose strength of Capecitabine may depend on the market availability for each country.

5.4.2 Method of Procurement

Capecitabine is provided locally by the study site.

5.4.3 Dose, Preparation, and Administration

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

5.4.4 Storage and Handling

Capecitabine should be stored according to the package insert.

5.4.5 Packaging and Labeling

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

5.5 Dose Modifications

Table 3, through Table 5 provide dose modification recommendations for tucatinib, trastuzumab, and capecitabine. Participants who discontinue either capecitabine or trastuzumab may remain on study treatment. In instances where capecitabine and trastuzumab have been discontinued, participants may remain on study treatment with tucatinib alone. Participants who discontinue tucatinib will be allowed to remain on study treatment.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib, trastuzumab, and capecitabine. An AE may be considered related to tucatinib alone, trastuzumab alone, capecitabine 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 Sponsor to discuss which study drug(s) should be held and/or modified. Dosing should be modified 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 Sponsor.

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 participant 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 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, 14-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 Sponsor.

5.5.1 Tucatinib Dose Reductions

Refer to Table 3, Table 4 and Table 6 for the tucatinib 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 are allowed, but dose reductions to below 150 mg BID are not allowed. Participants 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 dose should not be re-escalated after a dose reduction is made.

Table 3: Recommended Tucatinib dose reduction schedule

Starting Dose[a]	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
300 mg orally twice a day (total 600 mg per day)[b]	250 mg orally twice a day (total 500 mg per day)	200 mg orally twice a day (total 400 mg per day)	150 mg orally twice a day (total 300 mg per day)

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 may not be dose reduced below 150 mg BID.
b Depending on the outcome of the safety run-in, the tucatinib starting dose may be adjusted.

5.5.2 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 Sponsor. If trastuzumab cannot be restarted at the same dose after being held for an AE, it must be discontinued. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose of 8 mg/kg should be given per approved dosing instructions. As trastuzumab may be given as an IV infusion, infusion-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 participants 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 participants develop an IAR, participants 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 participants have developed an infusion syndrome. Participants 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 4: Dose modifications of tucatinib and trastuzumab for clinical adverse events other than left ventricular dysfunction related to either tucatinib and/or trastuzumab, or hepatocellular toxicity*

	Tucatinib	**Trastuzumab**
Clinical Adverse Event	Related to Tucatinib	Related to Trastuzumab
≥ Grade 3 AEs other than Grade 3 fatigue lasting ≤3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤ Grade 1 within 7 days.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal use of anti-emetics or anti-diarrheals.	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITH optimal use of anti-emetics or anti-diarrheals.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 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 participant may need to discontinue the drug completely. Participants requiring a hold of tucatinib for > 6 weeks must discontinue study treatment, unless a longer delay is approved by the Sponsor.

5.5.3 Capecitabine Dose Modifications

Capecitabine doses must be modified as described below in Table 5.

Capecitabine must be held for any participant who experiences a Grade 2 or greater AE considered related to capecitabine or to the combination of tucatinib 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 5: Dose modification of capecitabine for clinical adverse events considered related to capecitabine

CTCAE v4.03 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[c]	Interrupt until resolved to Grade ≤1.	75%
3rd appearance[c]	Interrupt until resolved to Grade ≤1.	50%
4th appearance[c]	Discontinue permanently.	NA
Grade 3		
1st appearance	Interrupt until resolved to Grade ≤1.	75%
2nd appearance[c]	Interrupt until resolved to Grade ≤1.	50%
3rd appearance[c]	Discontinue permanently.	NA
Grade 4		
1st appearance	Discontinue permanently.	

NA=not applicable

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 participant from capecitabine dose interruption and/or reduction outweighs the risk to the participant from the adverse event, and when the action is consistent with usual and customary clinical practice.

c For the purpose of this study, 2nd, 3rd, and 4th appearances refers to the appearance of the same event, not any event of the same grade severity.

5.5.4 Dose Modifications for Hepatotoxicity

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

For dose modifications of tucatinib and capecitabine, see Table 6 below. Dose modification of trastuzumab is not required but dosing can be held at investigator discretion. For participants with documented Gilbert's disease, please contact the Sponsor for guidance regarding dose modifications in these participants.

Table 6: Dose modifications of tucatinib and capecitabine for liver function abnormalities

Liver Function Abnormalities	Action for tucatinib 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 5. 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 ≤ Grade 1 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	

5.5.5 Dose Modifications for Left Ventricular Dysfunction

Trastuzumab dose modification guidelines for left ventricular dysfunction are provided in Table 7.

Table 7: Dose modifications for left ventricular dysfunction

Symptomatic CHF	**LVEF < 40%**	**LVEF Below Institutional Limits of Normal and ≥10% Points Below Pretreatment Baseline, or ≥16% Absolute Decrease from Pretreatment Baseline**	**LVEF 40% to ≤45% and decrease is <10% points from baseline**	**LVEF >45%**
Discontinue trastuzumab.	Do not administer trastuzumab. Repeat LVEF assessment within 4 weeks. If LVEF < 40% is confirmed, discontinue trastuzumab.	Do not administer trastuzumab. Repeat LVEF assessment within 4 weeks. If the LVEF has not recovered to within normal limits and within15% points from baseline, discontinue trastuzumab.	Continue treatment with trastuzumab. Repeat LVEF assessment within 4 weeks.	Continue treatment with trastuzumab.

Permanently discontinue trastuzumab for persistent (i.e., > 4 weeks) LVEF decline or for suspension of dosing on >3 occasions for LVEF decline.

5.6 Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered from Cycle 1, Day 1 (predose) through the safety reporting period will be recorded in the electronic CRF (eCRF). Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent through the safety reporting period. 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. Participants 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 the Sponsor as soon as feasible to discuss resumption of study treatment postoperatively.

5.6.1 Required Concomitant Therapy

There are no required concomitant therapies.

5.6.2 Allowed Concomitant Therapy

Participants 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, participants 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 unresectable tumor), these concomitant procedures are permitted for non-target non-CNS lesions only in situations where other disease remains assessable by RECIST v1.1 (APPENDIX H). These interventions should be avoided if clinically feasible until after the second response assessment. The Sponsor 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
- Influenza vaccinations (without live virus) are permitted during the study
- Participants 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 allocated 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 Sponsor.
- Premedication with corticosteroids solely for contrast use in scans or MRI can be used without prior the Sponsor approval. Participants requiring systemic steroids for

control of other comorbidities (e.g., asthma or auto-immune diseases) may be eligible after consultation and approval of Sponsor

- 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)

5.6.3 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 v1.1, which may be given after consultation with the Sponsor, provided that there remain other sites of assessable disease accessible by RECIST v1.1 (follow guidance for holding and resuming study treatment as per CNS radiation in Section 5.5).
- Warfarin or other coumarin derivatives (non-coumarin anti-coagulants are permitted)
- Vaccination with live vaccines
- Strong inhibitors or moderate inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 2 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 halflives of strong inhibitors and inducers, see APPENDIX F.
- 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 inducers may be found in other reference material. For additional information including drug elimination half-lives of strong inducers, see APPENDIX E.

5.6.4 Potential Concomitant Drug Interactions

For sensitive substrates of CYP3A (APPENDIX G); tucatinib exhibits inhibition of human CYP3A enzymes, and therefore has the potential to interact with other medications that are substrates of CYP3A. Therefore, concomitant use of tucatinib with sensitive CYP3A substrates should be avoided. Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.

5.7 Management of Overdose

In the event of an overdose of tucatinib, defined as any dose greater than the prescribed dose, study personnel should:

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

Refer to the package insert for overdose information for trastuzumab and capecitabine, and study personnel should notify the Sponsor as soon as they become aware.

5.8 Treatment Compliance

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

Compliance will be assessed on a participant-by-participant basis. The pharmacist or designee will record the number of tucatinib tablets dispensed to each individual participant, 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.

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 of Cycle 1 (predose) through the safety reporting period (see Section 7.4.1.3). Any study protocol-related AE (defined in Section 7.4.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

All assessments performed on Day 1 of all treatment cycles (as well as on Day 8 and Day 15 during Cycle 1 and 2 for the safety run-in participants only) 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.

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

Study assessments below are applicable to both participants enrolled in the safety run-in and the main study except where noted.

6.2 Screening Visit (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 prescreening consent form (Not applicable to safety run-in participants).

- Informed consent*
- Study eligibility per inclusion/exclusion criteria
- Confirm HER2+ status (confirmatory HER2 testing may be obtained greater than 28 days prior to Cycle 1 Day 1 if prescreening consent form is signed [prescreening not applicable to safety run-in participants])
    - Archival tissue blocks or slides may be submitted to confirm HER2 positivity*
        - A Sponsor-designated central laboratory may use IHC, ISH or FISH to confirm HER2 positivity
        - Centrally confirmed HER2+ results from a previous study using IHC, ISH, or FISH may be used with approval from the Sponsor
    - If archival tissue is unavailable, a fresh tumor biopsy must be obtained and submitted for central assessment for HER2 testing (A newly-obtained biopsy of tumor sample must be performed after obtaining informed consent of this study.)
- Physical examination including height and weight (Section 7.4.4)

- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- Documentation of medical history and disease history (Section 7.1)
- Electrocardiogram (ECG) (Section 7.4.6.2)
- 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* (Section 7.4.6.1).
- ECOG performance status (APPENDIX C)
- Blood samples (Section 7.4.3)
    - Complete blood count (CBC) with differential**
    - Serum chemistry**
    - Liver function tests (LFTs) **
    - Coagulation panel**
    - Hepatitis B and C screening (if positive, contact the Sponsor; see Section 7.4.3)*
- Urine sample for urinalysis**
- For participants of childbearing potential serum or urine pregnancy test within 24 hours for urine or within 72 hours for serum before the first dose of study treatment. (Section 7.4.5)
- Contrast computed tomography (CT), positron emission tomography (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 (Section 7.2).
- Contrast MRI of the brain for all participants for assessment of brain tumor burden; CT of the brain will not be allowed, and participants with known contraindications to undergoing contrast MRI imaging will be excluded from the study (Section 7.2).*
- For participants with brain metastases discovered during screening or a history of brain metastases, confirm relevant MRI brain reports and CNS treatment records can be obtained (Section 7.2).

* For participants 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 Sponsor approval. This includes the following: informed consent, ECHO/MUGA, hepatitis screening, and confirmatory HER2 testing. All other safety labs and assessments will need to be repeated if outside the 28 day window for these participants. 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.

** Test within 10 days prior to the first dose of study treatment.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. However, re-screening is not allowed for those participants whose initial HER2 testing is confirmed negative per central laboratory. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

6.3 Treatment Period

6.3.1 Cycle 1 Day 1

- Physical examination including predose weight* (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (-1 days, results must be reviewed and eligibility confirmed prior to first dose, Section 7.4.3)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - PK samples (safety run-in only; see APPENDIX B for timepoints)
- For participants of childbearing potential serum or urine pregnancy test (within 24 hours for urine or within 72 hours for serum before the first dose of study treatment.; Section 7.4.5)

- Administer study drugs (study drugs may be administered in any order and can be given simultaneously)
    - Dispense tucatinib and administer the first dose
    - Administer the first dose of capecitabine at 1000 mg/m2
    - Administer trastuzumab at 8 mg/kg given IV, unless participant has received trastuzumab within 4 weeks of first dose of trastuzumab on study. In this case, participant will not receive loading dose, and will instead receive trastuzumab 6 mg/kg
- Provide tucatinib day-of dosing instructions for the Cycle 1 Day 8 visit (safety run-in only), so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

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

Safety run-in participants only: for hospitalized participants, an assessment of concomitant medications, AEs, physical exam, vital signs, and laboratory evaluations (including CBC, serum chemistry, and liver function tests) must be performed prior to discharge.

6.3.2 Cycle 1 Day 8 (±2 days, safety run-in participants only)

- Physical examination (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (Section 7.4.3) (Must be performed within 1 day prior to dosing. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - PK samples (APPENDIX B)
- Provide tucatinib day-of dosing instructions for the Cycle 1 Day 15 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.3 Cycle 1 Day 12 (± 3 days, not applicable for safety run-in participants)

- Physical examination (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (Section 7.4.3)
    - CBC with differential
    - Serum chemistry
    - LFTs
- Provide tucatinib day-of dosing instructions for the Cycle 2 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.4 Cycle 1 Day 15 (±2 days, safety run-in participants only)

- Physical examination (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (Section 7.4.3) (Must be performed within 1 day prior to dosing. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - PK samples (APPENDIX B)
- Provide tucatinib day-of dosing instructions for the Cycle 2 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.5 Cycle 2 Day 1 and Day 1 of All Subsequent Cycles (-1 to + 3 Days, - 1 day allowance is not applicable for Cycle 2 Day 1 of safety run-in participants)

- Physical examination including predose weight (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (Must be performed within 1 day prior to dosing. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - Samples for PK (Cycles 2-6 only, pre-dose sample; Cycle 3 only, 1-4 hours post dose, Section 7.3)
- For participants of childbearing potential serum or urine pregnancy test within 24 hours for urine or within 72 hours for serum before the study treatment. on Cycle 2 Day 1 (Section 7.4.5)
- Administer study drugs (study drugs may be administered in any order and can be given simultaneously)
    - Dispense tucatinib and administer the first dose of the cycle
    - Administer first dose of capecitabine of the cycle
    - Administer trastuzumab
- Provide tucatinib day-of dosing instructions for the Cycle 2 Day 8 visit (safety run-in participants only), so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.6 Cycle 2 Day 8 (±2 days, safety run-in participants only)

- Physical examination (Section 7.4.4)
- Vital signs (Section 7.4.2)

- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (APPENDIX C)
- Blood samples (Section 7.4.3) (Must be performed within 1 day prior to dosing. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - PK samples (APPENDIX B)
- Provide tucatinib day-of dosing instructions for the Cycle 2 Day 15 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.7 Cycle 2 Day 12 (± 3 days, not applicable for safety run-in participants)

- Blood samples (Section 7.4.3)
    - LFTs

6.3.8 Cycle 2 Day 15 (±2 days, safety run-in participants only)

- Physical examination (Section 7.4.4)
- Vital signs (Section 7.4.2)
- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECOG performance status (-3 days, APPENDIX C)
- Blood samples (Section 7.4.3) (Must be performed within 1 day prior to dosing. Review results prior to the administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - PK samples (APPENDIX B)

- Provide tucatinib day-of dosing instructions for the Cycle 3 Day 1 visit, so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

6.3.9 Response Assessments: Every Six Weeks (- 7 days) as Determined by Cycle 1 Day 1, through Week 24, then Every 9 Weeks (- 7 days) through End of Treatment

- 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 (Section 7.2).

- Contrast MRI of the brain (only in participants with presence or history of brain metastases) and assessment of CNS lesions (brain or dura) (Section 7.2).

- 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 Sponsor 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 Sponsor.

6.3.10 Every 12 Weeks as Determined by Screening Exam (-7 days)

- ECHO or MUGA, using the same cardiac testing modality performed in screening/baseline (Section 7.4.6.1).

- If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment

6.4 End of Treatment Visit (30 to 37 Days After Last Dose of Study Drug)

End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the participant will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Physical examination including weight (Section 7.4.4)

- Vital signs (Section 7.4.2)

- Documentation of AEs and concomitant medications (Section 7.4.1.1)
- ECHO or MUGA, using the same cardiac testing modality performed in screening/baseline. Not required if done within previous 12 weeks (excluding the Screening/Baseline assessment)
- ECOG performance status (APPENDIX C)
- ECG (Section 7.4.6.2)
- Blood samples for laboratory testing (Section 7.4.3)
    - CBC with differential
    - Serum chemistry
    - LFTs
    - Coagulation
- For participants of childbearing potential serum or urine pregnancy test (if not done within the last 60 days) (Section 7.4.5)
- Contrast CT, PET/CT (if high quality CT scan included) and/or non-brain MRI scan if not done within the previous 30 days only in participants 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 (Section 7.2).
- Contrast MRI of the brain for participants with brain metastases at baseline and assessment of CNS lesions. Not required if brain MRI was performed within 30 days of discontinuing study treatment, or if progression in the brain has already been documented while on study.

6.5 Long-Term Follow-up

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

- High-quality spiral contrast CT (preferred): PET/CT (if high quality CT scan is included), and/or non-brain MRI scan as appropriate. The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.

- Contrast MRI of the brain (only in participants with brain metastases at baseline, as defined in Section 7.2) and assessment of CNS lesions (brain and/or dura)

Once a participant experiences PD (per RECIST v1.1) or clinical progression as assessed by the investigator, participants will continue in long-term survival follow-up. The following information must be collected starting 90 days (±7 days) from the date of the last imaging scan and continuing every 90 days (±7 days) until death, withdrawal of consent, or study closure.

- Participant contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anti-cancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to contact the participant are unsuccessful.

6.6 End of Study/End of Follow-up

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

7 STUDY ASSESSMENTS

Study assessments below are applicable to both participants enrolled in the safety run-in and the main study except where noted.

7.1 Screening/Baseline Assessments

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

Tumor tissue must be submitted to the Sponsor-designated central laboratory for confirmatory HER2 testing to determine participant eligibility; confirmatory HER2 testing may be performed on archival tissue or a newly-obtained biopsy of an accessible tumor lesion that has not been previously irradiated (see Section 7.1.1). A newly-obtained biopsy of tumor sample must be performed after obtaining informed consent of this study.

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

All measurable and evaluable lesions will be assessed and documented at Screening/Baseline (Section 7.2). A contrast MRI of the brain is performed to evaluate for the presence of brain metastases (Section 7.2). Participants with brain metastases at study entry may be eligible for study participation if they meet the inclusion/exclusion criteria and the conditions described in Section 7.2. All sites of disease identified at screening/baseline must be chosen as either target lesions or non-target lesions.

A physical examination including height and weight (Section 7.4.4), vital signs (Section 7.4.2), ECOG performance status (APPENDIX C), clinical laboratory testing, urinalysis (Section 7.4.3), ECG, ECHO/MUGA assessment, and pregnancy testing (Section 7.4.5) will be done at Screening/Baseline.

7.1.1 Confirmation of HER2 Expression for Study Eligibility

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

A central laboratory will be used for confirmatory HER2 testing. HER2 expression will be analyzed using IHC or ISH, and positivity will be assessed according to current ASCO/CAP guidelines.

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

See the Central Laboratory Manual for more details.

7.1.2 Treatment for Brain Metastases Prior to Study Entry

Participants with brain metastases at study entry may be eligible for study participation if they meet the eligibility criteria described in Sections 4.1 and 4.2. In order to minimize the risk of symptomatic cerebral edema in participants with brain metastases in this study, participants 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 participants 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 participants 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 Sponsor.

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

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

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

7.2 Response/Efficacy Assessments

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 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 holds or 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 will be collected for retrospective ICR. All treatment decisions will be made on the basis of the local investigator. Results of centralized review will not be available to investigators for clinical decision making.

All brain contrast MRI images will be performed locally and collected for centralized independent review. However, all treatment decisions will be made on the basis of local review of radiologic imaging. Participants 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 participants with baseline brain lesions, all brain lesions should be included in the baseline RECIST lesion selection as either a target or non-target lesions. Participants without brain metastases at baseline will not require follow-up brain contrast MRIs while on treatment unless clinically indicated.

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

All scans will be assessed per RECIST v1.1. Refer to APPENDIX H for further details.

7.2.1 Isolated Progression in the Brain

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

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

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

Additionally, treatment changes which may mimic progression will be taken into account, and participants with possible "pseudo-progression" should continue on study until unequivocal evidence of radiographic or clinical progression is present. In the absence of clear evidence of PD (per RECIST v1.1), development of CNS symptoms or radiographic changes thought to pose potential immediate risk to participant, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs, as defined in RECIST v1.1.

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

7.3 Pharmacokinetic Assessments

PK assessments of trough levels of tucatinib and ONT-993 (which is the predominant circulating metabolite) will be performed on Day 1 of Cycles 2-6 prior to administration of tucatinib. On Day 1 of Cycle 3, PK assessments of peak levels of tucatinib and ONT-993 will be performed 1-4 hours after administration of tucatinib.

Participants in the safety run-in, additional PK samples will be collected as specified in APPENDIX B.

7.4 Safety Assessments

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

Safety will be monitored over the course of the study by an SMC as described in Section 3.

7.4.1 Adverse Events

7.4.1.1 Definitions

Adverse Event

According to the ICH E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a participant or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

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

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing predose on study Day 1 that worsen in severity, increase in frequency, become related to study drug, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.4.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the participant at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the participant's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a participant exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the participant and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.4.1.2 for the definition of potential DILI).

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

Overdose, Medication Error, Misuse, and Abuse

Overdose of tucatinib is defined in Section 5.7. Refer to the package inserts for overdose information for trastuzumab and capecitabine.

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 medication error, misuse or abuse of study drug should be recorded on the AE eCRF with the diagnosis of the AE. In addition, any overdose event should be reported to the Sponsor within 24 hours of receipt of the information regardless of whether the event is an adverse event or not.

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.

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

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (tucatinib, trastuzumab, capecitabine) should be evaluated by the investigator using the following criteria:

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

7.4.1.2 Procedures for Eliciting and Recording Adverse Events

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

Eliciting Adverse Events

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

Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

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

Important exceptions for this study are adverse reactions associated with the infusion of study drug. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.

- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of Underlying Malignancy

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

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last for female participants, and at least 7 days after receiving the last dose of tucatinib or 90 days after receiving the last dose of Capecitabine whichever occurs last for male participant's partner. Only report pregnancies that occur in a participant's partner if the estimated date of conception is after the participant's first study drug dose. Report to the Sponsor's Drug Safety Department via eCRF, Email or fax within 24 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of Data on the CRF

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

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.4.1.1) should be reported as SAEs.

Potential Drug-induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential DILI in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (i.e., elevated serum alkaline phosphatase),

   AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as a SAE and reported to the Sponsor within 24 hours.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

For potential Hy's Law case, appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug. The study site refers to the guidance of "Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials" for assessment and follow up.

7.4.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

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

period and are considered study treatment-related in the opinion of the investigator should also be reported to the Sponsor.

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

7.4.1.4 Serious Adverse Events Require Immediate Reporting

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

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

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

The completed SAE form is to be reported via the EDC system within 24 hours. If the EDC system is not operational, email or fax the completed paper SAE report form to the Sponsor's Drug Safety Department within 24 hours. (see email or fax number specified on the SAE report form)

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

7.4.1.5 Adverse Events of Special Interest

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

The AESIs will need to be reported to the Sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 7.4.1.4).

Hepatotoxicity

- 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 ULN, except in participants 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. The Sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.4.2 Vital Signs

Vital signs measures are to include respiratory rate, pulse rate, systolic and diastolic blood pressure while participant is in a seated position, pulse oximetry, and temperature.

7.4.3 Clinical Laboratory Tests

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

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

- The CBC with differential is to include the following tests: white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, platelet count, hemoglobin, and hematocrit.

- LFTs are to include the following: AST/SGOT, ALT/SGPT, total bilirubin, and alkaline phosphatase.

- The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL.

  GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American or 0.808 if Japanese (Matsuo 2009))

  If any of the above is not applicable, MDRD equation should be used to calculate estimated GFR in accordance with local regulations or institutional guidelines.

- The coagulation panel is to include the following tests: INR, prothrombin time, and PTT or aPTT

- Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B surface antigen (HBsAb), antibodies to Hepatitis B core antigen (HBcAb), Hepatitis B DNA levels by PCR (as applicable; refer to latest local guidelines for the

management of Hepatitis B virus infection), and antibodies to Hepatitis C (anti-HCV). If positive, contact the Sponsor.

- Routine Urinalysis is color, appearance, specific gravity, pH, leukocyte esterase, nitrites, protein, glucose, ketones, urobilinogen, bilirubin, and blood.
- A serum or urine β-hCG/hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) for participants of childbearing potential (Section 7.4.5)

7.4.4 Physical Examination

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

7.4.5 Pregnancy Testing

For participants of childbearing potential, a serum or urine β-hCG/hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) will be performed at baseline, within 24 hours for urine or within 72 hours for serum prior to Day 1 of each treatment cycle, and at the EOT Visit if not done within the last 60 days. A negative pregnancy result is required before the participant may receive study treatment.

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

After the last dose of study treatment, pregnancy tests will be performed at 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last. Pregnancy tests may also be repeated as requested per institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations.

7.4.6 Cardiac Function

7.4.6.1 MUGA or ECHO

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

7.4.6.2 Electrocardiogram

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

7.5 Appropriateness of Measurements

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

Response will be assessed according to RECIST v1.1 which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

Prior to the enrollment of participants at the site, the Sponsor or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

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

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

comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2 Data Management Procedures

The Sponsor will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry of all required protocol assessments and procedures. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3 Access to Source Data

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

8.4 Accuracy and Reliability of Data

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

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

8.5 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

8.6 Data Handling and Record Keeping

8.6.1 Data Handling

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

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

8.6.2 Investigator Record Retention

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

9 DATA ANALYSIS METHODS

The primary objective of this study is to assess the primary endpoint, ORR of tucatinib in combination with trastuzumab and capecitabine by ICR per RECIST v1.1 in Japanese population, hence, the primary analysis population of the endpoint is the response evaluable set as defined in the section 9.3.1.7 but only includes Japanese participants. Analysis of ORR in all participants population including participants enrolled in Japan, South Korea and Taiwan is included in the secondary endpoints.

9.1 Determination of Sample Size

The study is designed to estimate the confirmed ORR in Japanese population and to detect an improvement in the ORR compared with a historical 20% response rate. The rationale for the historical response rate is based on the observed response rate from the control arm of HER2CLIMB trial and responses of patients treated with drug therapy after multiple treatment lines of anthracyclines, taxanes, trastuzumab, pertuzumab or T-DM1 (Murthy 2020b; Yokoe 2021; Masuda 2020; Charles 2006).

Approximately 42 participants will be enrolled in Japan including 4 participants in safety run-in. The primary efficacy analysis will be performed based on the participants enrolled on the main portion of the trial. With 38 participants, the study will have approximately 80% power to detect a 20% increase in ORR from 20% to 40% and approximately 90% power to detect a 25% increase in ORR from 20% to 45%, at one-sided significance level of 0.05, based on exact methods using EAST®, Version 6.0, by Cytel Inc.

On 02-Aug-2021 the SMC conducted an evaluation of overall safety after 4 Japanese participants were enrolled in the safety run-in and the safety and tolerability was deemed acceptable by the SMC; hence the enrollment of the safety run-in was completed and that of the main study was initiated on the following day.

A total of approximately 13 participants from South Korea and Taiwan are planned to be enrolled.

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

The primary endpoint in this study is the confirmed ORR by ICR. The ORR is defined as the proportion of participants with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Only response assessments before first documented PD or new anti-cancer therapies will be considered. Participants with missing data are considered non-responders.

9.2.2 Duration of Response

DOR is defined as the time from the first objective response (CR or PR that is subsequently confirmed) to documented PD per RECIST v1.1 or death from any cause, whichever occurs first. Only those who achieve a confirmed response will be included in the analysis.

9.2.3 Progression Free Survival

PFS time is defined as the time from the first date of study treatment to the date of documented disease progression using RECIST v1.1 or death from any cause, whichever occurs first. Participants who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment documenting absence of PD. Participants lacking an evaluation of tumor response after their start of study treatment will have their event time censored at 1 day.

9.2.4 Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the participant is known to be alive. Participants lacking data beyond their start of study treatment will have their survival time censored at 1 day.

9.3 Statistical and Analytical Plans

The statistical and analytical plans are presented below.

Since the primary objective of this study is to assess ORR in Japanese population, all the analyses, i.e., efficacy endpoints, safety endpoints as well as demographics and other baseline characteristics, will be performed in Japanese population. All of the analyses will also be conducted in all participants population, i.e., population which include participants enrolled in Japan, South Korea and Taiwan. The details will be provided in a supplemental statistical analysis plan (sSAP).

9.3.1 General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

The 2-sided 90% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates.

For time-to-event end points, the median survival time will be estimated using the Kaplan-Meier method; the associated 90%CI will be calculated based on the complementary log-log transformation (Collett 1994).

9.3.1.1 Randomization and Blinding

Blinding will not be performed.

9.3.1.2 Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

9.3.1.3 Handling of Dropouts and Missing Data

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

9.3.1.4 Multicenter Studies

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

9.3.1.5 Multiple Comparisons and Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only 1 primary endpoint will be estimated in this single arm study.

9.3.1.6 Data Transformations and Derivations

Time variables based on 2 dates, e.g., start date and end date, will be calculated as (end date – start date + 1 [in days]) unless otherwise specified in the sSAP. Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

9.3.1.7 Analysis Sets

The all treated participants set, response evaluable set, safety run-in set and PK analysis set are defined below.

The all treated participants set will include all participants who receive any amount of study drug. Safety, PFS, and OS will be analyzed using this analysis set.

Response evaluable set will include all participants who meet all following criteria: (1) had measurable disease at baseline, (2) received any amount of study treatment, and (3) had at least one post baseline disease assessment or discontinued due to clinical progression, toxicity, or death. ORR will be analyzed using the response evaluable analysis set.

Safety run-in set will include all participants who were treated during the safety run-in period and meet the safety evaluable criteria as defined in section 3.1. Dose limiting toxicity (DLT) information will be summarized for this analysis set.

The PK analysis set will include all participants in the safety set from whom at least one post-baseline PK assessment was reported. The PK analysis set will be used for PK analysis.

Japanese population is defined as Japanese participants enrolled in Japanese sites in the respective data sets. All participants population include all participants enrolled in Japan, South Korea and Taiwan.

Additional analysis sets of participants may be defined in the sSAP.

9.3.1.8 Examination of Subgroups

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

9.3.1.9 Timing of Analyses

The primary analysis will be conducted when all of the treated participants in Japanese population have been followed for at least 8 months (or all responders have been followed for a minimum of 6 months after their initial response, whichever comes first), have discontinued from the study, or had 30 days safety follow-up after disease progression, whichever comes first. In addition, for the purpose of regulatory submission in South Korea and Taiwan, the additional analyses may be conducted subsequently to the initial analysis.

9.3.2 Participant Disposition

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

9.3.3 Participant Characteristics

Demographics and other baseline characteristics will be summarized. Details will be provided in the sSAP.

9.3.4 Treatment Compliance

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of treatment (weeks or months) and the number of cycles per participant will be presented. Details will be provided in the sSAP.

9.3.5 Efficacy Analyses

Efficacy analyses will be performed in Japanese population and all participants population of the respective analysis sets.

9.3.5.1 Primary Efficacy Analyses

Since the primary objective of this study is to assess ORR in Japanese population, the primary analysis will be conducted in Japanese population of the response evaluable set. Analyses of ORR in all participants population are conducted as a secondary endpoint.

The cORR by ICR and its exact 2-sided 90% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

The primary efficacy analysis will be performed by testing the null hypothesis of ORR being less than or equal to 20% against the alternative hypothesis that ORR is greater than 20% at overall 1-sided 5% level of significance, i.e., H0: $P \leq 0.20$ vs. Ha: $P > 0.20$.

The study will be considered positive if the lower bound of the 2-sided 90% exact Clopper-Pearson CI for cORR is greater than 20%, so that the null hypothesis that the cORR is less than or equal to 20% can be rejected.

The participants in response evaluable set who are enrolled after safety run-in period will be used for the primary efficacy analysis. In addition, all participants in response evaluable set which includes participants in safety run-in period may be used as supportive analysis.

9.3.5.2 Secondary Efficacy Analyses

cORR by ICR in all participants population will be analyzed using the same method as for the primary endpoint.

ORR by INV will be analyzed using the same method as for the primary endpoint.

Secondary time-to-event analyses for DOR by ICR and investigator, PFS by ICR and investigator and OS, will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided.

9.3.6 Pharmacokinetic Analyses

Individual (participant) plasma tucatinib concentrations at each sampling time will be listed and summarized with descriptive statistics. Additional exploratory PK analyses may be conducted, including exploratory analyses investigating the relationship between tucatinib exposure and efficacy and safety endpoints. Summaries by ethnicity (Japanese and Korean) may be provided as appropriate. These analyses will be described in a separate PK analysis plan.

9.3.7 Safety Analyses

Safety analysis will be performed in Japanese population as well as all participants population of the all treated participants set.

9.3.7.1 Extent of Exposure

Duration of treatment and number of cycles will be summarized. Details will be provided in the sSAP.

9.3.7.2 Adverse Events

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

AEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 participant, the AE will be counted once as the occurrence.

DLTs will be listed and summarized for the participants in the safety run-in period.

9.3.7.3 Deaths and Serious Adverse Events

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

9.3.7.4 Clinical Laboratory Results

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

9.3.7.5 Other Safety Analyses

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

Cardiac ejection fraction data and change from baseline will be summarized.

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), good clinical practice guideline in Japan (J-GCP), and all applicable regulatory requirements.

10.1 Informed Consent

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

10.2 Ethical Review

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

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

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

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

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

10.3 Regulatory Considerations

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

10.3.1 Investigator Information

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

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study participant) must be approved by the Sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling participants who have met protocol eligibility criteria. Protocol deviations must be reported to the Sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

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

10.4 Study Documentation, Privacy and Records Retention

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

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

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

10.5 Clinical Trial Agreement

Payments by the Sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

11 REFERENCES

Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. Br J Clin Pharmacol. 1998;46(2):101-10.

Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol. 2005;23(10):2155-61.

Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109-19.

Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97(12):2972-7.

Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol. 2010;28(7):1124-30.

Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30(21):2585-92.

Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316(4):401-9.

Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res. 2011;17(14):4834-43.

Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)dagger. Ann Oncol. 2014;25(10):1871-88.

Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009;10(11):1037-44.

Charles E Geyer, John Forster, Deborah Lindquist, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355:2733-43.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

Collett D. Interval-censored survival data. Modelling survival data in medical research. London, Chapman & Hall. 1994:237-51.

Dang C, Iyengar N, Datko F, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015;33(5):442-7.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

F. Cardoso, S.Paluch-Shimon, E.Senkus et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol . 2020 Dec;31:1623-1649.

Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Population Fact Sheets, World. Lyon, France: International Agency for Research on Cancer. https://gco.iarc.fr/today, Accessed: 12 Nov, 2019. 2019.

Freedman RA, Anders CK. Treatment of breast cancer brain metastases. Curr Breast Cancer Rep. 2012;4(1):1-9.

Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol. 2019;37(13):1081-9.

Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355(26):2733-43.

Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32.

Giordano SH, Temin S, Kirshner JJ, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(19):2078-99.

Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010;5(1):61-72.

Hurvitz SA, O'Shaughnessy J, Mason G, et al. Central nervous system metastasis in patients with HER2-positive metastatic breast cancer: patient characteristics, treatment, and survival from SystHERs. Clin Cancer Res. 2019;25(8):2433-41.

Kaidar-Person O, Anders CK, Zagar TM. Whole brain radiotherapy for brain metastases: is the debate over? JAMA. 2016;316(4):393-5.

Kantar Health. CancerMPact® Treatment Architecture: Japan, Breast cancer. Dec. 2019.

Katanoda K, Hori M, Matsuda T, et al. An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. Jpn J Clin Oncol. 2015;45(4):390-401.

Kerb R, Brockmoller J, Staffeldt B, Ploch M, Roots I. Single-dose and steady-state pharmacokinetics of hypericin and pseudohypericin. Antimicrob Agents Chemother. 1996;40(9):2087-93.

Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(7):689-99.

Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. Cancer Res. 2008;68(14):5878-87.

Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16(6):e270-8.

Masuda N, Yoshinami T, Yasojima H, et al. Real-world effectiveness of post-T-DM1 treatments in HER2-positive metastatic breast cancer: KBCSG-TR1917 observational study. Journal of Clinical Oncology 38, no. 15_suppl. Published online May 25, 2020. Accessed: 18 February, 2021.

Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53(6):982-92.

Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018;19(7):880-8.

Murthy R, Loi S, Okines A, et al. Tucatinib vs placebo, both combined with capecitabine and trastuzumab, for patients with pretreated HER2-positive metastatic breast cancer with and without brain metastases (HER2CLIMB). Cancer Res. 2020a;80(4 Suppl):Abstract GS1-01.

Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020b;382(7):597-609.

Musolino A, Ciccolallo L, Panebianco M, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. Cancer. 2011;117(9):1837-46.

Natioinal Comprehensive Cancer Network®. NCCN Cllinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer Version Apr, 2021.

Network NCC. NCCN Guidelines®& Clinical Resources. 2013. Accessed: August 15. http://www.nccn.org/.

Olson EM, Abdel-Rasoul M, Maly J, et al. Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab. Ann Oncol. 2013;24(6):1526-33.

Park IH, Ro J, Lee KS, et al. Trastuzumab treatment beyond brain progression in HER2-positive metastatic breast cancer. Ann Oncol. 2009;20(1):56-62.

Yokoe T, Kurozumi S, Nozawa K, et al. Clinical benefit of treatment after trastuzumab emtansine for HER2-positive metastatic breast cancer: a real-world multi-centre cohort study in Japan (WJOG12519B). Breast Cancer. 2021 Jan 2. doi: 10.1007/s12282-020-01192-y. Epub ahead of print. Accessed: 18 February, 2021.

Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol. 2013;14(3):244-8.

Pivot X, Manikhas A, Zurawski B, et al. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2015;33(14):1564-73.

Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(19):2100-8.

Rossi D, Alessandroni P, Catalano V, et al. Safety profile and activity of lower capecitabine dose in patients with metastatic breast cancer. Clin Breast Cancer. 2007;7(11):857-60.

Sauvaget C, Nishino Y, Konno R, et al. Challenges in breast and cervical cancer control in Japan. Lancet Oncol. 2016;17(7):e305-12.

Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-92.

Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a

randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2013;14(6):461-71.

Swain SM, Miles D, Kim SB, et al. End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)-controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC). J Clin Oncol. 2019;37(15 Suppl):Abstract 1020.

Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.

Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719-26.

von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011;47(15):2273-81.

Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013.

Yokoe T, Kurozumi S, Nozawa K, et al. Clinical benefit of treatment after trastuzumab emtansine for HER2-positive metastatic breast cancer: a real-world multi-centre cohort study in Japan (WJOG12519B). Breast Cancer. 2021 Jan 2. doi: 10.1007/s12282-020-01192-y. Epub ahead of print. Accessed: 18 February, 2021.

APPENDIX A: SCHEDULE OF EVENTS

Safety Run-in Only

		Screening	Cycles 1-2			Subsequent 21-Day Cycles	Response Assessments		EOT	LTFU
			D1[cc]	D8	D15[z]	D1	Every 6 wks, through Wk 24	Every 9 wks, beginning Wk 24	30–37 Days Post Last Dose of Study Drug	Every 90 Days Post EOT Visit[a]
	Visit Window	D -28 to 1		(±2D)	(±2D)	(-1D to +3D)	-7D	-7D		
Baseline and Safety Assessments	Informed consent	X								
	Inclusion/exclusion	X								
	Confirmatory HER2+ testing	X[b]								
	Medical history, disease history	X								
	Physical examination	X	X[c, aa]	X	X	X			X	
	Vital signs[d]	X	X[aa]	X	X	X			X	
	Weight	X	X[e]			X[e]			X	
	Height	X								
	ECG	X							X	
	ECHO/MUGA[g]	X					X[h]	X[h]	X[i]	
	ECOG performance status	X	X[c]	X	X	X			X	
	Labs[j]	X[bb]	X[x, aa]	X[x]	X[x]	X[x]			X	
	Urinalysis	X[bb]								
	Coagulation	X[bb]							X	
	Hepatitis B and C screening[l]	X								
	Pregnancy test (participants of childbearing potential)[m]	X[n]	X[n]			X[n]			X[o]	X[f]
	Participant contact/clinic visit	X	X	X[z]	X[z]	X[z]	X	X	X	X[p]

			Cycles 1-2			Subsequent 21-Day Cycles	Response Assessments		EOT	LTFU
	Visit Window	**Screening** **D -28 to 1**	**D1[cc]**	**D8** **(±2D)**	**D15[z]** **(±2D)**	**D1** **(-1D to +3D)**	**Every 6 wks, through Wk 24** **-7D**	**Every 9 wks, beginning Wk 24** **-7D**	**30–37 Days Post Last Dose of Study Drug**	**Every 90 Days Post EOT Visit[a]**
	Con meds and AEs[q]	Collect if related to study procedures from time of informed consent	Collect Day 1 predose through EOT visit or 30 days after last dose of study treatment, whichever is later							
Response Assessments	CT, PET/CT, or MRI[r]	X					X[r]	X[r]	X[r]	X[r,y]
	Contrast MRI brain	X					X[s]	X[s]	X[s]	X[s,y]
Treatments	Tucatinib [u]		X			X				
	Capecitabine[v]		X			X				
	Trastuzumab[w]		X			X				
PK	Blood samples[t]		X	X	X	X[k]				

a 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

b Archival tissue specimen may be submitted. If archival tissue is unavailable, a fresh tumor biopsy must be obtained. HER2 positive results must be obtained prior to C1D1.

c Does not need to be repeated if performed within 1 day of Cycle 1 Day 1.

d Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure while participant is in a seated position, pulse oximetry, and temperature

e Weight taken pre-dose

f Only required at 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last

g Use the same modality performed at screening visit

h Every 12 weeks determined by the date of screening exam

i If not done within the previous 12 weeks

j Blood samples for CBC with differential, serum chemistry, and liver function tests

k Through Cycle 6 only: Pre-dose at Cycles 3-6 and 1-4 hour post-dose on Day 1 at Cycle 3 only

l Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B surface antigen (HBsAb), antibodies to Hepatitis B core antigen (HBcAb), Hepatitis B DNA levels by PCR (as applicable; refer to latest local guidelines for the management of Hepatitis B virus infection), and antibodies to Hepatitis C (anti-HCV). If positive, contact the Sponsor

m Urine or serum pregnancy test; a positive urine test must be confirmed with a serum pregnancy test

n Serum or urine pregnancy test within 24 hours for urine or within 72 hours for serum prior to Day 1 of each treatment cycle

o If not done within the last 60 days

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 concomitant procedures and hospitalization

r 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. 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. Use the same modality performed at screening/baseline. If bone imaging is collected, any RECIST appropriate imaging modality may be used. Not required at EOT if imaging was performed within 30 days of discontinuing study treatment.

s Contrast MRI of the brain and assessment of brain lesions per RECIST; only in participants with known brain metastases at baseline or a history of brain metastases. At EOT, MRI of the brain required unless already done within 30 days of ending study treatment or progression in the brain has already been documented while on study.

t See APPENDIX B for additional PK assessment

u 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

v 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.

w Trastuzumab is administered intravenously, once every 21 days

x All lab results must be reviewed prior to administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments.

y Scans should be performed every 9 weeks (±1 week) for participants who discontinued treatment prior to disease progression. A contrast MRI of the brain should only be performed in participants with brain metastases at baseline or a history of brain metastases.

z Provide tucatinib day-of dosing instructions for the next visit (Cycles 1-6), so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

aa For hospitalized participants, an assessment of concomitant medications, AEs, physical exam, vital signs, and laboratory evaluations (including CBC, serum chemistry, and liver function tests) must be performed prior to discharge.

bb Test within 10 days prior to the first dose of study treatment.

cc The visit window of Cycle 2 Day 1 is +3.

Main Study

	Visit Window	Screening	Cycles 1-2		Subsequent 21-Day Cycles	Response Assessments		EOT	LTFU
			D1	D12	D1	Every 6 wks, through Wk 24	Every 9 wks, beginning Wk 24	30–37 Days Post Last Dose of Study Drug	Every 90 Days Post EOT Visit[a]
		D -28 to 1	(-1D to +3D)[bb]	(±3D)	(-1D to +3D)	-7D	-7D		
Baseline and Safety Assessments	Informed consent	X							
	Inclusion/exclusion	X							
	Confirmatory HER2+ testing	X[b]							
	Medical history, disease history	X							
	Physical examination	X	X[c]	X[z]	X			X	
	Vital signs[d]	X	X	X[z]	X			X	
	Weight	X	X[e]		X[e]			X	
	Height	X							
	ECG	X						X	
	ECHO/MUGA[g]	X				X[h]	X[h]	X[i]	
	ECOG performance status	X	X[c]	X[z]	X			X	
	Labs[j]	X[cc]	X[x]	X[t]	X[x]			X	
	Urinalysis	X[cc]							
	Coagulation	X[cc]						X	
	Hepatitis B and C screening[l]	X							
	Pregnancy test (participants of childbearing potential)[m]	X[n]	X[n]		X[n]			X[o]	X[f]
	Participant contact/clinic visit	X	X	X[aa]	X	X	X	X	X[p]
	Con meds and AEs[q]	Collect if related to study procedures from time of informed consent	Collect Day 1 predose through EOT visit or 30 days after last dose of study treatment, whichever is later						
	CT, PET/CT, or MRI[r]	X				X[r]	X[r]	X[r]	X[r,y]

			Cycles 1-2		Subsequent 21-Day Cycles	Response Assessments		EOT	LTFU
		Screening	D1	D12	D1	Every 6 wks, through Wk 24	Every 9 wks, beginning Wk 24	30–37 Days Post Last Dose of Study Drug	Every 90 Days Post EOT Visit[a]
	Visit Window	D -28 to 1	(-1D to +3D)[bb]	(±3D)	(-1D to +3D)	-7D	-7D		
Response Assessments	Contrast MRI brain	X				X[s]	X[s]	X[s]	X[s,y]
Treatments	Tucatinib[u]		X		X				
	Capecitabine[v]		X		X				
	Trastuzumab[w]		X		X				
PK	Blood samples[dd]		X[bb]		X[k]				

a 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
b Archival tissue specimen may be submitted. If archival tissue is unavailable, a fresh tumor biopsy must be obtained
c Does not need to be repeated if performed within 1 day of Cycle 1 Day 1.
d Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure while participant is in a seated position, pulse oximetry, and temperature
e Weight taken pre-dose
f Only required at 30 days after receiving the last dose of tucatinib, 7 months after receiving the last dose of trastuzumab, or 180 days after receiving the last dose of Capecitabine whichever occurs last
g Use the same modality performed at screening visit
h Every 12 weeks determined by the date of screening exam
i If not done within the previous 12 weeks
j Blood samples for CBC with differential, serum chemistry, and liver function tests
k Through Cycle 6 only: Pre-dose at Cycles 3-6 and 1-4 hour post-dose on Day 1 at Cycle 3 only
l Blood samples for Hepatitis B surface antigen (HBsAg), antibodies to Hepatitis B surface antigen (HBsAb), antibodies to Hepatitis B core antigen (HBcAb), Hepatitis B DNA levels by PCR (as applicable; refer to latest local guidelines for the management of Hepatitis B virus infection), and antibodies to Hepatitis C (anti-HCV). If positive, contact the Sponsor
m Urine or serum pregnancy test; a positive urine test must be confirmed with a serum pregnancy test
n Serum or urine pregnancy test within 24 hours for urine or within 72 hours for serum prior to Day 1 of each treatment cycle
o If not done within the last 60 days
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 concomitant procedures and hospitalization

r 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. 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. Use the same modality performed at screening/baseline. If bone imaging is collected, any RECIST appropriate imaging modality may be used. Not required at EOT if imaging was performed within 30 days of discontinuing study treatment.

s Contrast MRI of the brain and assessment of brain lesions per RECIST; only in participants with known brain metastases at baseline or a history of brain metastases. At EOT, MRI of the brain required unless already done within 30 days of ending study treatment or progression in the brain has already been documented while on study.

t On Cycle 2 only collect labs for LFTs

u 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

v 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.

w Trastuzumab is administered intravenously, once every 21 days

x All lab results must be reviewed prior to administration of study treatment, in order to confirm continued study treatment and allow for potential dose adjustments.

y Scans should be performed every 9 weeks (±1 week) for participants who discontinued treatment prior to disease progression. A contrast MRI of the brain should only be performed in participants with brain metastases at baseline or a history of brain metastases.

z Cycle 1 only

aa Provide tucatinib day-of dosing instructions for the next Day 1 visit (Cycles 2-6), so that the visit's predose blood sample can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing)

bb Cycle 2 only

cc Test within 10 days prior to the first dose of study treatment.

dd Predose blood sample(Cycles 2-6) can be collected within the required time window (i.e., 2 hours prior to tucatinib dosing).

APPENDIX B: ADDITIONAL PK ASSESSMENTS FOR PARTICIPANTS IN SAFETY RUN-IN ONLY

Cycle	Study Days	Time	Window	Relative Time	Blood Sample
1	1	Predose	Within 24 hr	START of first dose of tucatinib in Cycle 1 Day 1	X
		0.5 hr post dose	±5 min	START of first dose of tucatinib in Cycle 1	X
		1 hr post dose	±5 min	START of first dose of tucatinib in Cycle 1	X
		2 hr post dose	±15 min	START of first dose of tucatinib in Cycle 1	X
		3 hr post dose	±15 min	START of first dose of tucatinib in Cycle 1	X
		4 hr post dose	±15 min	START of first dose of tucatinib in Cycle 1	X
		6 hr post dose	±15 min	START of first dose of tucatinib in Cycle 1	X
		8 hr post dose	±15 min	START of first dose of tucatinib in Cycle 1	X
		10 hr post dose	±30 min	START of first dose of tucatinib in Cycle 1	X
		12 hr post dose	±30 min	START of first dose of tucatinib in Cycle 1; prior to second dose on Cycle 1 Day 1	X
	8	Predose	±48 hours	START of first dose of tucatinib in Cycle 1; prior to dose on Cycle 1 Day 8	X
	15	Predose	±48 hours	START of first dose of tucatinib in Cycle 1; prior to dose on Cycle 1 Day 15	X
2	8	Predose	±48 hours	START of first dose of tucatinib in Cycle 2; prior to dose on Cycle 2 Day 8	X
	15	Predose	±48 hours	START of first dose of tucatinib in Cycle 2; prior to dose on Cycle 2 Day 15	X

APPENDIX C: PERFORMANCE STATUS SCALES CONVERSION

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

APPENDIX D: GUIDANCE ON CONTRACEPTION

Definition

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below Premenopausal female with 1 of the following):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Contraceptives allowed during the study include[a]:

Highly Effective Contraceptive Methods That Have Low User Dependency

Failure rate of <1% per year when used consistently and correctly.

- Progestogen-only subdermal contraceptive implant[b,c]
- IUS[c,d]
- Non-hormonal IUD

- Bilateral tubal occlusion

- Azoospermic partner (vasectomized or secondary to medical cause)

  This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.

  Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Sexual Abstinence

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

b. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.

c. IUS is a progestin releasing IUD.

Note: The following are not acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.

- Male condom with cap, diaphragm, or sponge with spermicide.

- Male and female condom should not be used together (due to risk of failure with friction).

APPENDIX E: CYP3A4 INDUCERS AND THEIR ELIMINATION HALF-LIVES

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

Drug[a, b]	Elimination Half-life[c] (hours)
Strong Inducers	
Barbiturates	Variable
Carbamazepine	25–65 hours (single dose), 12–17 hours (repeat dose)
Phenytoin	7–42 hours
Rifampin	3–4 hours (single dose), 2–3 hours (repeat dose)
St. John's Wort	9–43 hours[d]

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

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

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

c Drug package insert

d (Kerb 1996)

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

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

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

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

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

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

c Drug package insert

APPENDIX G: CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

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

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

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

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

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

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

APPENDIX H: RECIST VERSION 1.1

Response Evaluation Criteria in Solid Tumors

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

From RECIST v1.1 (Eisenhauer 2009)