Protocol Number:	ACCRU-GI-1617, SGNTUC-017
Version:	Amendment 12 [09-Mar-2023]
Protocol Title:	MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer
Investigational Product:	Tucatinib
Brief Title:	Tucatinib plus Trastuzumab in Patients with HER2+ Colorectal Cancer
Phase:	2
IND Number:	134840
EudraCT Number	2020-000540-60
ClinicalTrials.gov Identifier	NCT03043313
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	PPD , MD Tel: PPD Email: PPD
SAE Email or Fax:	See email or fax number specified on the SAE report form.

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SPONSOR PROTOCOL APPROVAL PAGE

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Protocol Title:	MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer
Investigational Product:	Tucatinib
Version:	Amendment 12; 09-Mar-2023

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

The individuals signing below have reviewed and approve this protocol.

PPD , MD
PPD

Date

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PROTOCOL SYNOPSIS

Protocol Number ACCRU-GI-1617, SGNTUC-017 **Version** Amendment 12; 09-Mar-2023 **Phase** 2	**Product Name** Tucatinib **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

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

Study Objectives

This study consists of 3 cohorts:

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

Primary Objectives

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

Secondary Objectives

Efficacy

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

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Safety

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

Exploratory Objectives

- To evaluate the pharmacokinetics (PK) of tucatinib
- To explore any correlations between tissue and blood-based biomarkers and clinical outcomes
- To assess the PFS in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment
- To assess the OS in subjects treated with tucatinib monotherapy, in Cohort C
- To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with trastuzumab
- To explore health resource utilization

Study Endpoints

Primary endpoints

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

Secondary endpoints

Efficacy

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

Safety

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

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

Exploratory endpoints

- PK parameters of tucatinib
- To explore potential biomarkers of response, resistance or toxicity from archived paraffin-embedded tumor samples and circulating tumor DNA (ctDNA) isolated from plasma samples.
- PFS (RECIST 1.1), according to BICR assessment, in Cohort C
- OS, in Cohort C
- Change from baseline in PRO assessments of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L), and European Organization for Research and Treatment of Cancer Quality-of-Life 30-item core questionnaire (EORTC QLQ-C30)
- Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and emergency department (ED) visits

Study Population

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

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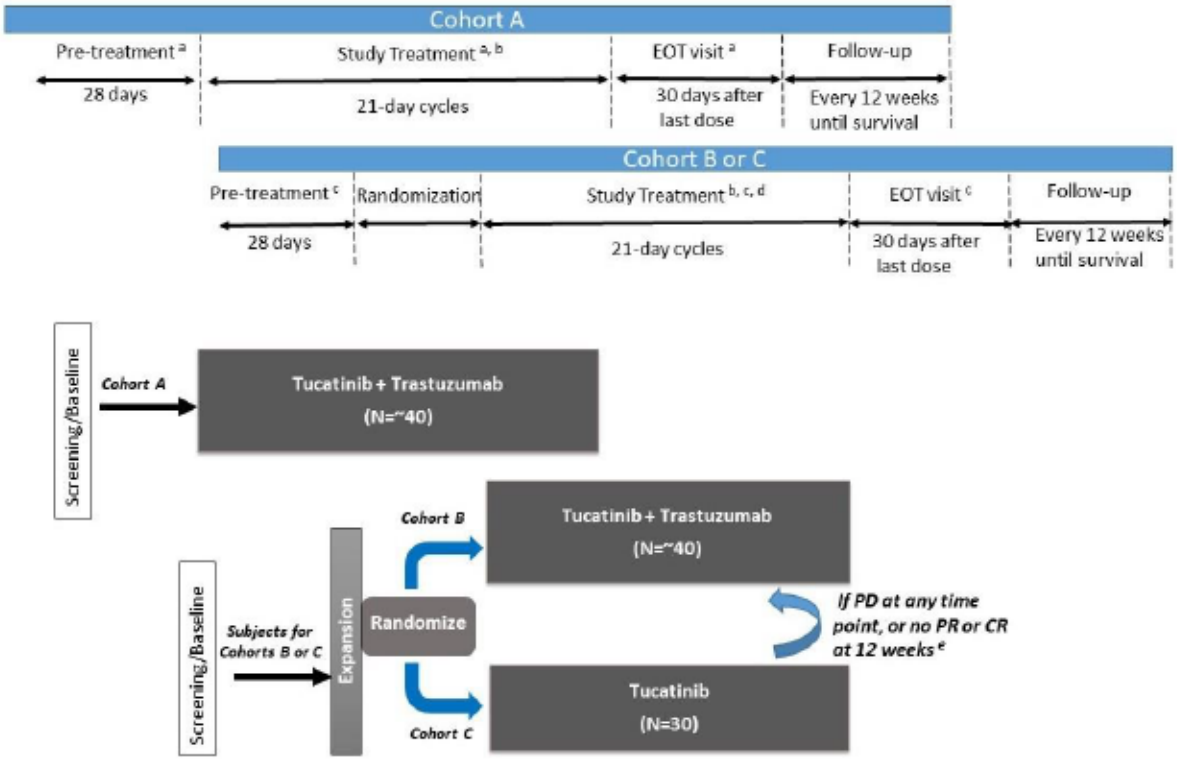

Note: Subjects enrolled in Cohort A or Cohort B will be treated with tucatinib and trastuzumab doublet combination therapy, and subjects enrolled in Cohort C will be treated with tucatinib monotherapy.

CR = complete response, EOT = end of treatment, PD = progressive disease, PR = partial response

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

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

c For Cohorts B and C, an optional pre-screening is available. Tissue based HER2 testing can be performed within 90 days prior to the anticipated screening visit. Collection of tissue for confirmatory HER2+ and biomarker testing can be done at pre-screening or screening. Radiological disease assessment (CT or MRI of chest, abdomen, and pelvis) and CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects who discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

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

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

Inclusion Criteria

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

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

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

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

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

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

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

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

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

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

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

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

e. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

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

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

b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration

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

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

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Exclusion Criteria

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

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

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12. Inability to swallow pills or any significant gastrointestinal disease which would preclude the adequate oral absorption of medications

13. Have used a strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP2C8 or CYP3A4 inducer within 5 days prior to first dose of study treatment.

14. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

15. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer)

16. Subjects with known active CNS metastasis (irradiated or resected lesions are permitted, provided the lesions are fully treated and inactive, subject is asymptomatic, and no steroids have been administered for at least 30 days)

17. Have a hypersensitivity to tucatinib or any of its excipients, to trastuzumab or any of its excipients, or to murine proteins.

Number of Planned Subjects

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

Study Design

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

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

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

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

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

The primary efficacy analysis set will comprise all treated subjects in Cohorts A+B.

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

Secondary efficacy endpoints include duration of confirmed response, PFS, and OS for all subjects enrolled on the doublet regimen (Cohort A+B). In addition, in order to assess the contribution of tucatinib to the doublet regimen, ORR by 12 weeks will be assessed in Cohorts A+B, as well as in Cohort C; however, there will be no formal statistical comparisons between cohorts.

End of Study

The primary analysis for this trial was conducted based on a data cut-off date of 28 March 2022. As the primary objective was met, the decision was made to close the trial. For subjects remaining on study, a last visit / contact will occur and subjects who are still receiving treatment will revert to physician care. When applicable, the Sponsor will assist with post-trial access to tucatinib and trastuzumab.

Investigational Product, Dose, and Mode of Administration

All Cohorts

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

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

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

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

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Duration of Treatment

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

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

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

Efficacy Assessments

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

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

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

The determination of antitumor activity will be based on confirmed objective response assessments as defined by RECIST 1.1. Disease assessments will be evaluated by both the BICR and investigators. The investigator will make treatment decisions based on site assessments of scans. For Cohort A, confirmation of response was initially not required per protocol. For the purposes of the primary analysis, the disease assessment timepoint after the first response documented by the BICR will be used to determine confirmed response. For Cohort A, responses (CR or PR) will be confirmed at the next re-staging timepoint, 9 weeks (±14 days) after first documentation of response. For Cohorts B and C, responses (CR or PR) will be confirmed at the next re-staging

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timepoint, 6 weeks (±7 days) after first documentation of response. Subjects will be followed for survival every 12 weeks (±14 days) until PD, death, or end of study.

Pharmacokinetic Assessments

PK assessments of trough levels of tucatinib drug levels will be performed on Day 1 of Cycles 2 to 6 prior to administration of tucatinib in both Cohorts B and Cohort C. On Day 1 of Cycle 3, PK assessments of peak levels of tucatinib drug levels will be performed 1 to 4 hours after administration of tucatinib in both Cohort B and Cohort C. Subjects in Cohort C who crossover to the tucatinib + trastuzumab regimen should continue PK assessments, if crossover occurs prior to Cycle 6. If the crossover happens after Cycle 6, no PK collections are required.

Biomarker Assessments

Biomarker assessments may include the confirmation of HER2 status by IHC, FISH, and NGS as well as an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved or CE-marked IHC test following the package insert's interpretational manual for breast cancer. NGS analysis may be performed to interrogate the mutation status of a panel of oncogenes and tumor suppressor genes that are associated with tumor growth, survival and resistance to targeted therapeutics. This assessment may enable the correlation of treatment outcome to either preexisting or acquired cancer gene mutations and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor genotype in the future.

Patient-Reported Outcomes and Health Economic Assessments

PRO measures will be completed at protocol-specified time points using the EORTC QLQ-C30. Health economic assessments will be explored with the EQ-5D-5L instrument and health resource utilization. EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered for Cohorts B and C at: pre-dose Cycle 1 Day 1 (C1D1), C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.

Safety Assessments

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

Concomitant Therapies

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

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dose of study treatment and during the study. Use of moderate or weak inhibitors of CYP2C8 are permitted but should be used with caution.

Statistical Methods

Safety and efficacy endpoints will be summarized with descriptive statistics.

Data collected in this study will be presented using summary tables, subject data listings, and figures. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Confidence intervals (CI), 95% 2-sided, will be presented where needed to gauge the strength of evidence for a corresponding estimated treatment effect. For time-to-event endpoints, the median survival time will be estimated using the Kaplan Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation. Subjects from the initial, non-randomized Cohort A and those randomized to Cohort B during the expansion will be analyzed together (Cohorts A+B). Demographic and baseline characteristics will be summarized separately by cohort.

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

Sample Size Considerations

Cohort A

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

Cohorts B and C

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

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

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For illustration purposes, a summary of the expected 95% CIs for subjects treated in Cohorts A+B and subjects treated in Cohort C at the proposed sample sizes of 80 and 30, respectively. No formal statistical comparisons between cohorts are planned.

Confirmed ORR	95% Exact CI. (Cohorts A+B, N = 80)
40%	(29%, 52%)
50%	(39%, 61%)
60%	(48%, 71%)

Confirmed ORR	95% Exact CI. (Cohort C, N = 30)
10%	(2%, 27%)
15%	(5%, 33%)
20%	(8%, 39%)

Efficacy Analyses

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

The timing of the primary analysis will be based on the time to confirmed ORR per BICR. DOR according to BICR assessment will also be analyzed at this time. PFS and OS will also be analyzed at the time of the primary ORR and DOR analyses; additional analysis of these time-to-event endpoints may be undertaken when mature progression and survival data become available.

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

Interim Futility Efficacy Analyses

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

Pharmacokinetic Analyses

Individual (subject) 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. These analyses will be described in a separate analysis plan.

Patient-Reported Outcomes and Health Resource Utilization Analyses

PRO assessments based on the EQ-5D-3L and EORTC QLQ-C30 will be summarized using descriptive statistics. PRO scores will be analyzed descriptively. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment time point may be presented.

Safety Analyses

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

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	twice daily
BSD	Baseline sum of diameters BSD
CBC	complete blood count
CCG	Case Report Form Completion Guidelines
CE	Conformité Européenne
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration observed
CNS	central nervous system
cORR	confirmed objective response rate
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
dMMR	deficient mismatch repair
DOR	duration of response
ED	emergency department
EEA	European Economic Area
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-Life 30-item Core Questionnaire
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
EU	European Union

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

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

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1 INTRODUCTION

1.1 HER2+ Colorectal Cancer

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

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

1.2 Treatment of HER2+ CRC

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

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

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

TTP = time-to-progression; WT = wild-type
a ORR 32%; ORR 40% (17/43) in KRAS WT; ORR 8% (1/13) in KRAS mutated

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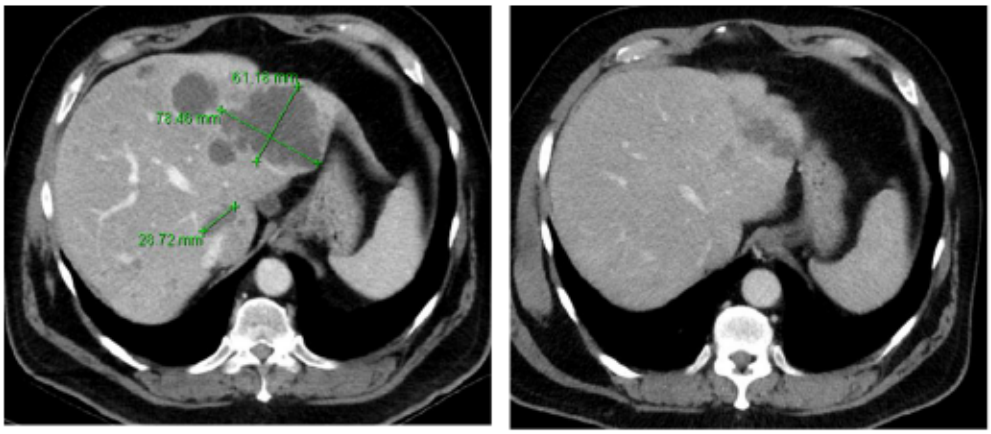
As part of an investigator-initiated trial at Duke University (NCT02008383), comprehensive molecular profiling is being performed on patients with EGFR-refractory, RAS wild-type mCRC. Three out of the first 24 patients (12.5%) had ERBB2 amplification confirmed by fluorescence in situ hybridization (FISH).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

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



Baseline (PPD) After 6 cycles lapatinib + trastuzumab (PPD)

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

1.2.1 Ongoing Medical Need in HER2+ Metastatic CRC

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

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

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

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

1.3 Tucatinib

1.3.1 Product Description and Mechanism of Action

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

1.3.2 Overview of Nonclinical and Clinical Pharmacology Studies

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

1.3.2.1 Preclinical Studies

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

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

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

Table 1-3: HER2 and HER1 Inhibition

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

In Vivo Pharmacology

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

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

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

Nonclinical Safety

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

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

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

1.3.2.2 Absorption, Distribution, Metabolism, and Excretion Studies

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

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

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

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

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

1.3.2.3 Clinical Studies

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

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

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

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

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

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including combination with ado-trastuzumab emtansine (T-DM1, Study ONT-380-004), and capecitabine, trastuzumab or capecitabine and trastuzumab (Study ONT-380-005). In addition, Study ONT-380-206 (HER2CLIMB) is an ongoing, Phase 2, randomized, double-blinded, placebo-controlled clinical trial that compares tucatinib versus placebo in combination with capecitabine and trastuzumab in patients with progressive, unresectable locally advanced or metastatic HER2+ breast cancer who have had prior treatment with trastuzumab, pertuzumab, and T-DM1. This trial recently reported topline results which showed a 46% reduction in the risk of disease progression or death (hazard ratio [HR]=0.54; p<0.00001), an improvement in overall survival with a 34% reduction in the risk of death (HR=0.66; p=0.0048) and a 52% reduction in the risk of disease progression or death in patients with brain metastases at baseline (HR=0.48; p<0.00001) (Murthy 2020). Additionally, a randomized, double-blind, Phase 3 study of tucatinib versus placebo in combination with T-DM1 in patients with unresectable locally advanced or metastatic HER2+ breast cancer is ongoing (SGNTUC-016; HER2CLIMB-02).

Several clinical trials evaluating tucatinib in multiple gastrointestinal cancers have recently been initiated. SGNTUC-022 (MOUNTAINEER-02) is a randomized, double-blind phase 2/3 study evaluating tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in HER2+ gastric or gastroesophageal junction adenocarcinoma; SGNTUC-024 is a phase 1b/2 dose escalation and expansion study of tucatinib in combination with trastuzumab and oxaliplatin-based chemotherapy in HER2+ gastrointestinal cancers; and SGNTUC-019 is a phase 2 basket study evaluating tucatinib and trastuzumab in solid tumors driven by HER2 alterations.

The SGNTUC-017 (MOUNTAINEER) study was initiated on 29-Mar-2017 as an investigator-sponsored trial (IST) in which approximately 40 subjects were to be enrolled and treated with tucatinib in combination with trastuzumab (Cohort A). The study was transferred to Seagen Inc. on 17 Sep-2019, and at that time, 37 subjects were enrolled. An additional 8 subjects were enrolled into Cohort A after the Investigational New Drug (IND) transfer and prior to expansion of the trial. A total of 45 subjects were enrolled to Cohort A (44 subjects treated with tucatinib+trastuzumab, and 1 subject treated with trastuzumab only prior to discontinuation from all study treatment). Following discussion with the FDA in September 2019, the protocol was amended (Protocol Amendment 8) to not only expand enrollment to include an additional 40 subjects (Cohort B) treated with tucatinib+trastuzumab (for a total of approximately 80 subjects in Cohorts A+B) but also to include randomization of approximately 30 subjects treated with tucatinib monotherapy (Cohort C).

Enrollment was continuous; there was no pause in enrollment when the trial was transferred to Seagen and there was no pause between completion of enrollment on Cohort A and initiation of randomization to Cohorts B and C. All subjects enrolled in the expansion portion of the trial were randomized in a 4:3 ratio to receive tucatinib+trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment continued until 41 subjects were randomized

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to Cohort B (41 subjects treated with tucatinib+trastuzumab) and 31 subjects were randomized to Cohort C (30 subjects treated with tucatinib monotherapy, and 1 subject withdrew consent prior to treatment).

Patients with HER2+ mCRC have a significant unmet need for efficacious and well-tolerated treatment options. Data from the MOUNTAINEER study, evaluating a dual HER2-targeted regimen for subjects with HER2+ CRC who had received at least one prior treatment regimen for unresectable or metastatic disease, demonstrated that treatment with tucatinib in combination with trastuzumab resulted in clinically meaningful and durable responses in this population. A robust independently assessed cORR of 38.1% (95% CI: 27.7%, 49.3%) was observed in subjects treated with tucatinib in combination with trastuzumab. Responses were durable, with a median duration of 12.4 months. Benefit was consistent across prespecified subgroups. The median PFS among subjects treated with tucatinib in combination with trastuzumab was 8.2 months and the median OS was 24.1 months.

MOUNTAINEER showed tucatinib+trastuzumab to be safe and well tolerated in this patient population with high unmet need. Discontinuations due to TEAEs were infrequent (5.8% and 3.5% for tucatinib and trastuzumab, respectively). Most reported events were low grade and manageable, and the types and rates of observed TEAEs were consistent with the established safety profile of tucatinib in the approved indication. There were no TEAEs leading to death, and no new safety risks were identified.

Overall, the results of this study demonstrated a positive benefit:risk for tucatinib in combination with trastuzumab and may represent a new standard of care for patients with HER2+ mCRC who have received at least one prior treatment regimen in the metastatic setting.

1.3.3 Summary of tucatinib

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

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1.4 Trastuzumab

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

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

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

1.5 Nonclinical Rationale for combination of tucatinib with trastuzumab

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

1.6 Clinical Rationale for combination of tucatinib with trastuzumab

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

HER2+ Metastatic Breast Cancer setting

Historical data for trastuzumab monotherapy in breast cancer demonstrate modest radiographic response rates of 14% (Cobleigh 1999; Burstein 2008; Cortes 2012; Martin 2013a). However, when anti-HER2 agents such as lapatinib or pertuzumab are added to trastuzumab-based regimens in HER2+ breast cancer, response rates not only increase

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(24%–31%), but significant gains in PFS and OS are also achieved (Baselga 2012; Johnston 2018).

Study ONT-380-206 (HER2CLIMB) evaluated tucatinib versus placebo in combination with capecitabine and trastuzumab in patients with progressive, unresectable locally advanced or metastatic HER2+ breast cancer who had prior treatment with trastuzumab, pertuzumab, and T-DM1. Topline results from this trial showed a 46% reduction in the risk of disease progression or death (HR=0.54; p<0.00001), an improvement in overall survival with a 34% reduction in the risk of death (HR=0.66; p=0.0048), and a 52% reduction in the risk of disease progression or death in patients with brain metastases at baseline (HR=0.48; p<0.00001) (Murthy 2020).

HER2+ mCRC setting

As discussed above (see Section 1.2), dual HER2-inhibition with trastuzumab-containing regimens have been examined in the setting of HER2+ mCRC, and the response rates seen in the HERACLES and MyPathway trials (Table 1-1) have led to a change in the widely adopted national (US) guidelines for the treatment of colon cancer, which now recommend (Category 2B) dual HER2-inhibition for treatment of HER2-amplified, RAS wild-type, mCRC patients. While there are no monotherapy arms included in the HERACLES and MyPathway trials (Table 1-1), it is worth noting that response rates are higher than what has historically been observed with anti-HER2 agents used as monotherapy in metastatic breast cancer, and compare favorably with response rates seen with dual inhibition in that setting.

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

1.7 Study Rationale

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

The activity of tucatinib monotherapy in HER2+ metastatic breast cancer patients that had failed prior HER2 directed therapies has been examined, with an ORR of 14% observed. Tucatinib has also shown single-agent activity in HER2+ CRC preclinical tumor models.

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However, the activity of tucatinib monotherapy in patients with mCRC is currently unknown. Therefore, a tucatinib monotherapy cohort has been included in order to explore this activity.

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

1.8 Rationale for Selection of Doses

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

- PK studies (ARRAY-380-102 and ARRAY-380-103)
- Results of the Phase 1 dose-escalation study of single-agent tucatinib in subjects with advanced solid tumors (ARRAY-380-101)
- Results of a Phase Ib study of tucatinib combined with T-DM1 (ONT-380-004)
- Results of a Phase Ib study of tucatinib combined with either capecitabine and/or trastuzumab (ONT-380-005); this study declared a RP2D of 300 mg BID in the tablet formulation, equivalent to the single-agent dose of tucatinib

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

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2 OBJECTIVES AND ENDPOINTS

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

Table 2-1: Objectives and corresponding endpoints

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

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Objective	Corresponding Endpoint[a]
Secondary Safety	
• To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B	• Frequency and severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria, of all treatment-emergent adverse events (TEAEs) and treatment-related TEAEs, in Cohorts A+B • Frequency of serious adverse events (SAEs) and deaths due to adverse events (AEs), in Cohorts A+B • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B • Frequency and severity of laboratory abnormalities, in Cohorts A+B • Vital signs and other relevant safety variables, in Cohorts A+B
• To assess the safety and tolerability of tucatinib monotherapy, in Cohort C	• Frequency and severity, according to CTCAE v4.03, of all TEAEs and treatment-related TEAEs, in Cohort C • Frequency of SAEs and deaths due to AEs, in Cohort C • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohort C • Frequency and severity of laboratory abnormalities, Cohort C • Vital signs and other relevant safety variables, in Cohort C
Exploratory	
• To evaluate the pharmacokinetics (PK) of tucatinib	• PK parameters of tucatinib
• To explore any correlations between tissue and blood-based biomarkers and clinical outcomes	• To explore potential biomarkers of response, resistance or toxicity from archived paraffin-embedded tumor samples and circulating tumor DNA (ctDNA) isolated from plasma samples.
• To assess the PFS in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment	• PFS (RECIST 1.1), according to BICR assessment, in Cohort C
• To assess the OS in subjects treated with tucatinib monotherapy, in Cohort C	• OS, in Cohort C
• To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with trastuzumab	• Change from baseline in PRO assessments of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L), and European Organization for Research and Treatment of Cancer Quality-of-Life 30-item Core Questionnaire (EORTC QLQ-C30)

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Objective	Corresponding Endpoint[a]
• To explore health resource utilization	• Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and emergency department (ED) visits

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

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3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

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

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

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

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

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

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

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Secondary efficacy endpoints include duration of confirmed response, PFS, and OS for all subjects enrolled on the doublet regimen (Cohort A+B). In addition, in order to assess the contribution of tucatinib to the doublet regimen, ORR by 12 weeks will be assessed in Cohorts A+B, as well as in Cohort C. There will be no formal statistical comparisons between cohorts.

PK assessments of tucatinib will be performed in subjects in Cohorts B and C. Blood samples will also be taken for possible evaluation of potential biomarkers of response, including ctDNA.

Health-related quality of life and health care economics will be assessed by use of the EQ-5D-5L and EORTC QLQ-C30 quality of life instruments and collection of health care resource utilization data.

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

3.1.1 Data & Safety Monitoring

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

3.1.2 Stopping Criteria

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

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

3.1.3 End of Study

The primary analysis for this trial was conducted based on a data cut-off date of 28 March 2022. As the primary objective was met, the decision was made to close the study. End of study will be defined as last patient, last visit. In addition, the sponsor may terminate the study at any time (see Section 10.4.1).

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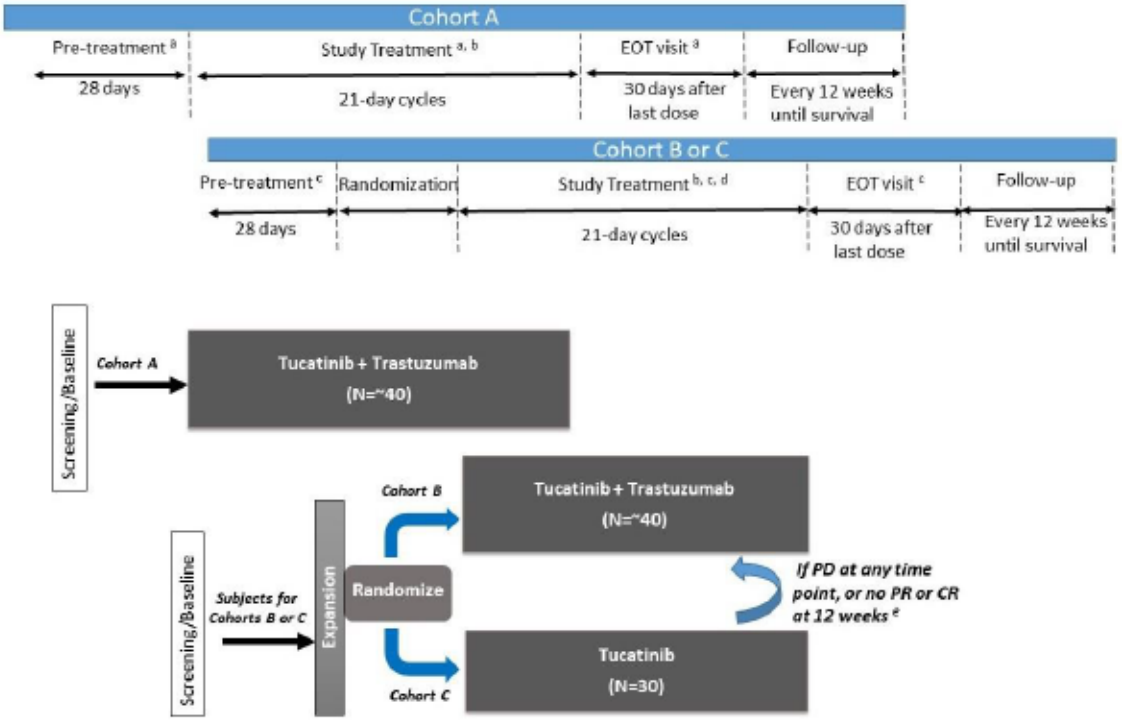
Figure 3-1: Study schematic



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

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

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

c For Cohorts B and C, an optional pre-screening is available. Tissue based HER2 testing can be performed within 90 days prior to the anticipated screening visit. Collection of tissue for confirmatory HER2+ and biomarker testing can be done at pre-screening or screening. Radiological disease assessment (CT or MRI of chest, abdomen, and pelvis) and CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Subjects who discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

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

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

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

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3.2 Discussion and Rationale for Study Design

3.2.1 Rationale for Selection of Doses and Regimen

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

Selection of the tucatinib dosing regimen for the current study was based upon the RP2D derived from two Phase 1b studies in HER2+ metastatic breast cancer that evaluated tucatinib in combination with T-DM1 (ONT-380-004), or capecitabine and trastuzumab (ONT-380-005). In those studies, tucatinib 300 mg was generally well-tolerated, and AEs were manageable by protocol-specified dose modifications and dose reductions. In addition, the efficacy and safety of tucatinib is currently being explored in a pivotal study in HER2+ metastatic breast cancer (ONT-380-206, HER2CLIMB), at 300 mg BID in combination with capecitabine and trastuzumab and an additional pivotal study in 2L metastatic breast cancer (SGNTUC-016) at 300 mg BID in combination with T-DM1.

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

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

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4 STUDY POPULATION

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

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

4.1 Inclusion Criteria

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

1. Have histologically and/or cytologically documented adenocarcinoma of the colon or rectum, which is metastatic and/or unresectable.
2. Unless otherwise contraindicated, subjects must have received and failed regimens containing the following agents: fluoropyrimidine (e.g., 5-fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF mAb (bevacizumab, ramucirumab, or ziv-aflibercept), and an anti-PD-(L)1 therapy (nivolumab or pembrolizumab) if the tumor has dMMR proteins or is MSI-H.

1. Have progression of unresectable or metastatic CRC after last systemic therapy (as confirmed by investigator), or be intolerant of last systemic therapy
2. Have RAS wild-type in primary or metastatic tumor tissue, based on expanded RAS testing including KRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146), and NRAS exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)
3. Subjects must be willing and able to provide the most recently available tissue blocks (or slides, with Medical Monitor's approval), obtained prior to treatment initiation, to a sponsor-designated central laboratory for biomarker analysis. If archival tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion is required.
4. Have confirmed HER2-positive mCRC, as defined by having tumor tissue tested at a Clinical Laboratory Improvement Amendments (CLIA)-certified or International Organization for Standardization (ISO)-accredited laboratory, meeting at least one of the following criteria:
   a. HER2+ overexpression (3+ immunohistochemistry [IHC]) by an FDA-approved or Conformité Européenne (CE)-marked HER2 IHC test following the package insert's interpretational manual for breast cancer
   b. HER2 2+ IHC is eligible if the tumor is amplified by an FDA-approved or CE-marked HER2 in situ hybridization assay (FISH or chromogenic in situ

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

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

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

   a. Absolute neutrophil count (ANC) ≥1.0 × 10^3/µL

   b. Platelet count ≥75 × 10^3/µL

   c. Hemoglobin ≥8.0 g/dL

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

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

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

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

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

10. For subjects of childbearing potential, as defined in Section 4.3, the following stipulations apply:

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

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

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c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 7 months after the final dose of study drug administration
d. May choose to practice complete abstinence, if consistent with the subject's preferred lifestyle, as an acceptable form of contraception
e. If sexually active in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control, as defined in APPENDIX C, starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of any study drug.

11. For subjects who can father children, the following stipulations apply:
    a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 7 months after the final study drug administration
    b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 highly effective methods of birth control, as defined in APPENDIX C, starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of any study drug
    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 contraception options, as defined in APPENDIX C, starting at time of informed consent and continuing throughout the study and for at least 7 months after the final dose of any study drug.
12. Subject must provide signed informed consent document that has been approved by an institutional review board/independent ethics committee (IRB/IEC) prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the subject's disease
13. Subject must be willing and able to comply with study procedures

4.2 Exclusion Criteria

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

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

Alopecia and neuropathy, which must have resolved to ≤ Grade 2

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

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Anemia, which must have resolved to ≤ Grade 2

Decreased ANC, which must have resolved to ≤ Grade 2

4. Have clinically significant cardiopulmonary disease such as:

Ventricular arrhythmia requiring therapy

Symptomatic hypertension or uncontrolled asymptomatic hypertension, as determined by the investigator

Any history of symptomatic CHF, left ventricular systolic dysfunction or decrease in ejection fraction

Severe dyspnea at rest (CTCAE Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy

Presence of ≥ Grade 2 QTc prolongation on screening ECG

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

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

4.3 Childbearing Potential

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

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

4.4 Removal of Subjects from Therapy or Assessment

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

4.4.1 Discontinuation of Study Treatment

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

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

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

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

4.4.2 Subject Withdrawal from Study

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

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

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5 TREATMENTS

5.1 Treatments Administered

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

Table 5-1: Treatment schedule

Agent	Dose Level	Route	Day(s)	Cycle(s)	Frequency	Drug Administration in Each Cohort (Y/N) Cohort A	Cohort B	Cohort C
Tucatinib	300 mg	PO	Days 1-21	All	Twice daily	Y	Y	Y
Trastuzumab[a]	8 mg/kg body weight	IV	Day 1	Cycle 1 (loading dose)	Once	Y	Y	N
Trastuzumab[ab]	6 mg/kg body weight	IV	Day 1	Cycle 2 and beyond	Once	Y	Y	N

a Use actual weight or estimated dry weight if fluid retention

b Trastuzumab may also be given on a weekly basis at 2 mg/kg IV or Q2 week basis at 4 mg/kg IV, but only in circumstances where the trastuzumab infusion schedule has been interrupted or suspended, and these infusions are required to resynchronize the cycle length to 21 days.

It is a requirement of the nurse to perform instruction on tucatinib administration techniques and drug diary prior to Cycle 1 Day 1 (C1D1) (APPENDIX G). The nurse will need to ensure that the subject understands these instructions before granting treatment independence. It is not a requirement that the first dose be given in clinic.

5.1.1 Investigational Study Drug (Tucatinib)

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

Tucatinib is supplied as yellow oval (150 mg) or round (50 mg) capsule-shaped tablets for oral administration.

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

5.1.1.1 Description

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The

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tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

5.1.1.2 Method of Procurement

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

5.1.1.3 Dose and Administration

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

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

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

5.1.1.4 Storage and Handling

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

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

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Refer to the Pharmacy Instructions for more information.

5.1.1.5 Packaging and Labeling

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

5.1.1.6 Study Drug Accountability

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

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

5.1.2 Trastuzumab

5.1.2.1 Description

Trastuzumab is a humanized IgG-1 kappa monoclonal antibody which binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2); it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which over express HER2 protein.

5.1.2.2 Method of Procurement

The investigational study drug (trastuzumab) will be provided by the sponsor.

5.1.2.3 Dose, Preparation, and Administration

Trastuzumab will be given as a loading dose of 8 mg/kg IV followed by 6 mg/kg once every 21 days. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q 7 days, but only in the circumstance that trastuzumab infusion has been delayed, and weekly infusions are required to resynchronize the cycle length to 21 days, after discussion with the Medical Monitor. Trastuzumab infusion rates will be per institutional guidelines. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose of 8 mg/kg should be given per approved dosing instructions.

Single-dose vial (150 mg/vial) as a lyophilized sterile powder for reconstitution is commercially available and should be prepared and administered per instructions in the trastuzumab (Herceptin®) package insert for administration instructions. Trastuzumab will be administered IV under the direction of the investigator.

Trastuzumab should be stored according to the package insert.

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5.1.2.4 Risk Associated with Trastuzumab

Risks associated with trastuzumab include fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, myalgia, and CHF. Please see the trastuzumab (Herceptin®) package insert/national prescribing information for more details.

- Management of cardiac, gastrointestinal, and skin/subcutaneous tissue disorders may require temporary interruption or treatment discontinuation of trastuzumab as per guidelines provided in the package insert and of infusion-related reactions (IRR) in Table 5-3.

5.1.2.5 Storage and Handling

Refrigeration should be set at 2–8°C for storage of vials containing trastuzumab. Follow the package insert for more information.

5.1.2.6 Packaging and Labeling

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

5.1.2.7 Study Drug Accountability

Trastuzumab used during the course of the study should be handled according to its package insert. Trastuzumab vials are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction. All supplies, including partially used or empty vials, should be tracked.

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

5.2 Dose Modifications

5.2.1 Tucatinib Dose Reductions

Refer to Table 5-2 for the tucatinib dose reduction levels. Dose reductions larger than those required by these tables may be made at the discretion of the investigator. Up to 3 dose reductions of tucatinib are allowed, but dose reductions to below 150 mg BID are not allowed. Patients who, in the opinion of the investigator, would require a dose reduction to <150 mg BID, or who would require a potential fourth dose reduction of tucatinib, should discontinue study treatment.

The dose of tucatinib should not be re-escalated after a dose reduction is made. For further guidelines regarding dose modification of tucatinib due to AEs, please see Table 5-4.

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Table 5-2: Tucatinib: Recommended dose reduction schedule for AEs

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

Note: Tucatinib dose levels are based on AEs listed in Table 5-4. Dose reductions of greater increments than those listed in this table (i.e., more than 50 mg per dose reduction) may be made if considered clinically appropriate by the investigator. However, tucatinib may not be dose reduced below 150 mg BID

5.2.2 Trastuzumab Dose Modifications

There are no dose reductions for trastuzumab. Guidelines regarding dose delays and discontinuation of trastuzumab due to AEs are given in Table 5-4 and Table 5-6.

Trastuzumab may also be given on a weekly basis at 2 mg/kg IV q 7 days or biweekly at 4mg/kg IV, but only in the circumstance that trastuzumab infusion has been delayed, and these infusions are required to resynchronize the cycle length to 21 days, after discussion with the Medical Monitor. If trastuzumab cannot be restarted at the same dose after being held for an AE, it must be discontinued. If dosing of trastuzumab has been held for >4 weeks, the IV loading dose of 8 mg/kg should be given per approved dosing instructions. As trastuzumab may be given as an IV infusion, infusion-related reactions (IRRs), may occur.

5.2.2.1 Infusion-related Reaction and its Management

An IRR is characterized by an adverse reaction to the infusion of pharmacological or biological substances. IRRs occur within 24 hours of infusion and may manifest as a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain and/or hypotension (Kang 2007).

IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for IRR.

IRR related to trastuzumab have been observed. Refer to Table 5-3 for IRR-specific dose modification of trastuzumab. If a significant IRR occurs, the infusion should be interrupted and appropriate medical therapies should be administered (see Table 5-3). Permanent discontinuation should be considered in subjects with severe IRR. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction. The severity of IRRs should be graded according to NCI CTCAE v4.03 guidelines.

No standard premedication is required for future treatments if subjects have developed an infusion syndrome. Subjects may be given acetaminophen prior to treatments. Serious

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reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids, and withdrawal of study agent as indicated.

Table 5-3 Dose modifications for infusion-related reactions for trastuzumab

Infusion-related reactions	Dose Modification
Grade 2	INTERRUPT trastuzumab infusion immediately. Subjects should be treated according to the following guidelines, or according to institutional guidelines, at discretion of the study physician: Stop infusion and notify physician. Assess vital signs. Administer acetaminophen 650 mg PO. Consider administration of meperidine 50 mg intramuscular (IM) or equivalent, diphenhydramine 50 mg IV, ranitidine 50 mg IV or cimetidine 300 mg IV, dexamethasone 10 mg IV or famotidine 20 mg IV. If vital signs stable, RESTART trastuzumab at the same dose. No standard premedication is required for future treatments if subjects have developed an infusion syndrome. Subjects may be given acetaminophen prior to treatments. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of study agent as indicated.
≥ Grade 3	INTERRUPT infusion immediately Administer appropriate medical therapies. DISCONTINUE treatment.

5.2.2.2 Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE v4.03). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of trastuzumab. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, i.e., a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain and/or hypotension.

5.2.2.3 Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death. (NCI CTCAE v4.03 and (Rosello 2017).

If anaphylaxis occurs, administration of trastuzumab should be immediately and permanently discontinued.

5.2.3 Dose Modifications for Adverse Events

General dose modification guidelines for tucatinib and trastuzumab are provided in Table 5-4 for clinical AEs. Dose modifications for hepatotoxicity and left ventricular dysfunction are provided in Table 5-5 and Table 5-6, accordingly.

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AEs ≥ Grade 3 not specifically mentioned in the following tables but that are assessed as being related to tucatinib or trastuzumab should be managed by HOLDING treatment until event resolution to ≤ Grade 1 or pre-treatment level. Treatment should be RE-STARTED at next lower dose level.

Table 5-4 Dose modifications for clinical AEs related to either tucatinib or trastuzumab

	Tucatinib	Trastuzumab
Clinical Adverse Event	Related to tucatinib	Related to trastuzumab
≥ Grade 3 AEs other than Grade 3 fatigue lasting ≤ 3 days; alopecia[a]; nausea; vomiting; diarrhea; rash; correctable electrolyte abnormalities which return to ≤ Grade 1 within 7 days	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITHOUT optimal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 nausea, vomiting, or diarrhea WITH optimal use of anti-emetics or anti-diarrheals	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 vomiting, or diarrhea regardless of use of anti-emetics or anti-diarrheals	Do not administer until severity ≤ Grade 1. Reduce to next lowest dose level.	Do not administer until severity ≤ Grade 1. Restart without dose reduction.
Grade 3 rash WITHOUT maximal use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.	Do not administer until severity ≤ Grade 1 or pretreatment level. Initiate appropriate therapy. Restart without dose reduction.
Grade 3 rash WITH maximal use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reduction.
Grade 4 rash regardless of use of topical corticosteroids or anti-infectives.	Hold until severity ≤ Grade 1 or pretreatment level. Restart at next lowest dose level.	Do not administer until severity ≤ Grade 1 or pretreatment level. Restart without dose reductions.

a No dose modifications are required for alopecia

5.2.3.1 Dose Modifications for Hepatotoxicity

Dose modification may be required in the case of liver function abnormalities. For dose modifications of tucatinib for liver function abnormalities see Table 5-5. Dose modification of trastuzumab is not required but dosing can be held at investigator's discretion. For subjects with documented Gilbert's disease, please contact the Medical Monitor for guidance regarding dose modifications in these subjects.

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Table 5-5 Dose modifications of tucatinib for liver function abnormalities

Liver Function Abnormalities	Action for tucatinib, Regardless of Relationship to Drug
Grade 3 elevation of ALT and/or AST (> 5 to 20 × ULN)	Hold until severity ≤ Grade 1 or until return to pretreatment level in subjects with known liver metastases Restart at next lowest dose level
Grade 4 elevation of ALT and/or AST (> 20 × ULN)	Discontinue drug
Elevation of ALT and/or AST (> 3 × ULN) AND Bilirubin (> 2 × ULN)	Discontinue drug
Grade 3 elevation of bilirubin (> 3 to ≤ 10 × ULN) and both ALT and AST <3.0 × ULN	Hold until severity ≤ Grade 1 or until return to pretreatment level in subjects with known liver metastases Restart at next lowest dose level
Grade 4 elevation of bilirubin (> 10 x ULN)	Discontinue drug

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

5.2.3.2 Dose Modifications for Left Ventricular Dysfunction

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause asymptomatic decline in LVEF.

Trastuzumab dose modification guidelines for left ventricular dysfunction are provided in Table 5-6.

Table 5-6: Trastuzumab dose modifications guidelines for left ventricular dysfunction

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

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

5.3 Concomitant Therapy

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

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5.3.1 Potential Concomitant Drug Interactions

5.3.1.1 Tucatinib

Tucatinib is cleared predominantly by CYP2C8 and to a lesser extent by CYP3A4. Strong CYP2C8 inhibitors and strong CYP2C8 or CYP3A4 inducers are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment.

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

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

Treatment with tucatinib is associated with mild increases in serum creatinine which were reversible upon treatment discontinuation. A dedicated DDI study demonstrated no impact on renal function.

5.3.1.2 Trastuzumab

Please refer to the package insert for trastuzumab potential drug interactions.

In PK studies, trastuzumab, a monoclonal antibody therapeutic, did not alter the plasma concentrations of other small molecule therapeutics such as paclitaxel, docetaxel, or doxorubicin. It is therefore very unlikely that trastuzumab would have an effect on the pharmacokinetics of tucatinib. There was no DDI between tucatinib and trastuzumab observed in Studies ONT-380-005 and ONT-380-206 (HER2CLIMB), which evaluated the combination of tucatinib with capecitabine and trastuzumab.

5.3.2 Required Concomitant Therapy

There is no required concomitant therapy.

5.3.3 Allowed Concomitant Therapy

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

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- During study treatment, subjects may receive supportive care to include bisphosphonates, hematologic and anti-infectious support and pain management
- Supportive care medications such as anti-diarrheals, anti-emetics, antacids, and laxatives are permitted. Prophylactic use of anti-diarrheals are permitted at the discretion of the investigator
- Prophylactic and symptomatic treatment of nausea and vomiting may be used per standard-of-care
- Thoracentesis or paracentesis may be performed, if needed for comfort
- If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor), these interventions should be avoided if clinically feasible until after the second response assessment and the Medical Monitor should be consulted prior to the intervention occurring.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO) Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline (Smith 2006).
- Subjects should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as anti-diarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea free (maximum 16 mg/day).
- In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and anti-diarrheals.
- If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Subjects with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

5.3.4 Concomitant Therapies to be Used with Caution

Subjects on anti-coagulant treatment should be closely monitored during study treatment.

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

Moderate CYP2C8 inhibitors should be used with caution.

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

5.3.5 Prohibited Concomitant Therapy

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

- Investigational drugs and devices
- Anti-cancer therapy, including but not limited to chemotherapy and hormonal therapy
- Radiation therapy, except for palliative radiotherapy at focal non-CNS sites which are not considered target lesions per RECIST 1.1, which may be given after consultation with the Medical Monitor. Radiation therapy directed at target lesions per RECIST 1.1 requires prior approval by the Medical Monitor. Tucatinib must be held 7 days prior to and 7 days post radiation therapy.
- Vaccination with live vaccines
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of study treatment (see APPENDIX E)
- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib treatment (see APPENDIX F)
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (see APPENDIX H). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study.

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5.4 Management of Overdose

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

Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of tucatinib.

Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of tucatinib administered, subject weight) and AEs, if any.

Overdose events (with or without associated AEs) are to be captured on the AE electronic case report form (eCRF)

Refer to the package insert for overdose information for trastuzumab.

5.5 Treatment Compliance

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

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

Data regarding the administration and dose of trastuzumab will also be collected by the site after each cycle. Dose modifications and interruptions of any study drug will be documented in the source documents and the CRF.

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6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (pre-dose) through the safety reporting period (see Section 7.7.1.3). Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, liver function tests (LFTs), complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.7.3], urinalysis, physical exam, weight, and performance status) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Tumor biopsies performed during the study should be made available to the sponsor if feasible (see Section 7.1).

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

6.2 Screening Period

6.2.1 Pre-screening (Up to 3 Months Before Anticipated Screening Visit)

If HER2 overexpression/amplification status is unknown in pre-study assessments, subjects may consent to submit an archival tumor specimen or new lesion biopsy for local IHC/in situ hybridization (ISH) testing for assessment of HER2 status. Subjects should be known wildtype by expanded RAS testing and should be expected to be eligible for MOUNTAINEER after completion of their current chemotherapy regimen. Subjects must be informed that HER2 testing consent is not informed consent for the study and participation in HER2 testing does not guarantee study eligibility.

> HER2 alterations testing informed consent
>
> Submission of archival tissue for local IHC/ISH testing for HER2 status following the package insert's interpretational manual for breast cancer; if archival tissue blocks are not available, a fresh tumor biopsy may be obtained for HER2 pre-screening.

6.2.2 Screening Visit (Days [-28] to [-1])

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Documented disease history (See Section 7.1)
- Radiological Disease Assessment (CT/MRI)
- Blood Tumor Marker (carcinoembryonic antigen [CEA])
- Hepatitis B and C screening (anti-HCV will only be collected for Cohorts B and C)
- Concomitant medications

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- AEs
- ECHO/MUGA
- Confirm availability of archival tissue for submission to central laboratory (formalin fixed paraffin-embedded [FFPE]); if archival tissue blocks that meet requirements are not available, a fresh tumor biopsy must be obtained and submitted for HER2 testing (see Section 7.1).
- Biomarker Plasma collection for Cohorts B and C (Table 11-3)

6.2.3 Baseline Visit (Days [-7] to [-1])

Physical examination, including height

Vital signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)

ECOG PS (APPENDIX B)

Urinalysis

Blood samples for laboratory testing (as listed in Section 7.7.3)

- Blood chemistries and LFTs
- CBC with differential and platelets
- Coagulation panel (including INR, prothrombin time (PT), and aPTT)

For persons of childbearing potential, serum β-hCG pregnancy test within 7 days of first study treatment

12-lead ECG

Concomitant medications

AEs

Submit Eligibility Worksheet to sponsor for approval to enroll

With sponsor's approval, access randomization system for treatment assignment (Cohorts B and C only)

6.3 Treatment Period (21-day cycles)

6.3.1 Cycle 1 Pre-dose Day 1

Physical Examination (pre-dose, may not be performed if done within 1 day prior to C1D1)

Vital signs: weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation (pre-dose, may not be performed if done within 1 day prior to C1D1)

Drug Diary Review

EQ-5D-5L questionnaire (Cohorts B and C only)

EORTC QLQ-C30 questionnaire (Cohorts B and C only)

ECOG PS (pre-dose, may not be performed if done within 1 day prior to C1D1)

Concomitant medications

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AEs

Biomarker Plasma and Serum Collection (Cohort A only) (Table 11-2) (pre-dose, may not be performed if done within 1 day prior to C1D1)

Blood chemistries and LFTs (pre-dose, may not be performed if done within 7 days prior to C1D1)

CBC with differential and platelets (pre-dose, may not be performed if done within 7 days prior to C1D1)

Serum pregnancy test (pre-dose, may not be performed if done within 7 days prior to C1D1)

Trastuzumab administration (for Cohorts A, B, and subjects from Cohort C who crossover to dual combination therapy)*

Tucatinib administration and dispensation (all cohorts)*

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

6.3.2 Cycle 1 Days 8 & 15 (±3 days)

Blood chemistry and LFTs

CBC with differential and platelets

EQ-5D-5L questionnaire (Cohorts B and C only)

EORTC QLQ-C30 questionnaire (Cohorts B and C only)

Concomitant medications

AEs

6.3.3 Cycle 2 (and All Subsequent Cycles) Day 1 (±3 days)

Physical Examination

Vital Signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)

Drug Diary Review

ECOG PS

Concomitant medications

AEs

Blood chemistries and CBC with differential and platelets

Serum β-HCG pregnancy test for females of childbearing potential

PK samples for Cohorts B and C only (pre-dose Cycles 2, 3, 4, 5, & 6 and post-dose Cycle3) (Table 11-3)

Only on Cycles 2, 3, and 4; and every 3 cycles thereafter

- EQ-5D-5L questionnaire (Cohorts B and C only)
- EORTC QLQ-C30 questionnaire (Cohorts B and C only)

Biomarker Plasma and Serum collections (for Cohort A only) at Cycle 4 and every 3 cycles thereafter (i.e., Cycles 4, 7, 10, etc.) (Table 11-2)

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Trastuzumab administration (Cohorts A, B, and subjects from Cohort C who crossover to dual combination therapy)*

Tucatinib administration and dispensation (all cohorts) *

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

6.3.4 Cycle 2 (and All Subsequent Cycles) Every 6 or 9 weeks (±7 days)

Radiological Disease Assessment

- Cohort A: every 9 weeks (±14 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (± 7days). Subjects who discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.
- Cohorts B and C: every 6 weeks (±7 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects who discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.

Blood Tumor Marker (CEA)

- CEA assays will be performed on the same schedule as radiographic scanning.

6.3.5 Every 12 weeks (±14 days)

- ECHO/MUGA

6.3.6 Subjects Crossing-Over to Doublet Regimen

Subjects randomized to tucatinib monotherapy (Cohort C) will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy, if they experience radiographic progression at any time point (as determined by investigator assessment using RECIST 1.1), or if they have not achieved a PR or CR by the Week 12 assessment.

- Submit Request for Approval to Change Treatment Regimen form to sponsor
- With sponsor's approval, access randomization system to register the change in treatment assignment

Immediately proceed with new study treatment regimen and continue to follow study procedures outlined in Section 6.3.3.

Investigators must do a new baseline RECIST assessment on Cohort C subjects who crossover from monotherapy to doublet therapy. Investigators must use the RECIST scans that were used to qualify the subject for crossing over (Week 12 scans or first PD scans as applicable) to establish a new baseline. Investigators must select target and non-target lesions per RECIST v1.1 guidance. Selection of target and non-target lesions will be based solely upon the crossover scans, and, therefore, may include new lesions that appeared while the subject was on monotherapy. Establishing a new baseline at the time of crossover will allow

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these subjects to achieve an objective response (CR/PR) per RECIST while on doublet therapy, which is relative to the new baseline. Subjects who have radiographic progressive disease while on doublet therapy per the new baseline should discontinue therapy unless the investigator believes the subject has signs of clinical benefit, as described in Section 7.7.7.1.

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

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

- Physical Examination
- Vital Signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation)
- ECOG PS
- CBC with differential and platelets
- Serum blood chemistries
- Coagulation tests
- ECHO/MUGA (may not be performed if done on-treatment 12 weeks previously)
- Radiological Disease Assessments
- Blood Tumor Marker (CEA)
- EQ-5D-5L (Cohorts B and C only)
- EORTC QLQ-C30 questionnaire (Cohorts B and C only)
- Concomitant medications
- AEs
- Blood samples for biomarker analyses:
  - Cohort A: Biomarker Plasma and Serum (Table 11-2)
  - Cohorts B and C: Biomarker Plasma (Table 11-3)

6.5 Follow-up

- Further anti-cancer therapy and survival (every 12 weeks ±14 days)
- If a subject discontinues trastuzumab for any reason, assessment of cardiac function (ECHO or MUGA) must be conducted every 6 months (±14 days) until 24 months from the last administration of trastuzumab

6.6 End of Study/End of Follow-up

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

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6.7 Post-Study Care

At the time of study closure, subjects who are still receiving treatment will revert to physician care. When applicable, the Sponsor will assist with post-trial access to tucatinib and trastuzumab.

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7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

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

Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing (by an FDA-approved or CE-marked HER2 IHC test following the package insert's interpretational manual for breast cancer). Confirmatory HER2 testing may be performed on archival tissue or a newly-obtained baseline biopsy of an accessible tumor lesion that has not been previously irradiated.

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

A physical exam, height, vital signs, CT with contrast/MRI scan for baseline response efficacy assessment, biopsy collection, CBC with differential and platelets, urinalysis, ECHO/MUGA, Hepatitis B and C screening, biomarker serum chemistry panel, coagulation tests including, INR, PT, and aPTT, ECOG PS, ECG and serum pregnancy test (for females of childbearing potential) are required for all subjects at screening and/or baseline as described in Section 6.2 and APPENDIX A.

Tissue Collection

The availability of archival tissue is to be confirmed at pre-screening or screening. If archival tissue blocks that meet requirements are not available, a fresh tumor biopsy must be obtained and submitted for HER2 testing. For fresh tissue, core needle or excisional biopsy is preferred. If neither is possible, discuss with sponsor whether biopsy obtained via alternative methods may be appropriate.

7.2 Response/Efficacy Assessments

The determination of antitumor activity will be based on confirmed objective response assessments made by a BICR according to the RECIST 1.1 (Eisenhauer 2009). Treatment decisions will be based on objective response assessments made by the investigator. Clinical response of CR, PR, SD, or PD will be determined at each assessment. In addition, images will be collected by an independent review facility.

Measures of anticancer activity will be assessed by either CT with contrast or MRI scans at protocol-specified time points. **Subjects must be evaluated using the same imaging method throughout the study for efficacy assessments.**

For Cohort A, responses (CR or PR) will be confirmed at the next re-staging timepoint, 9 weeks (±14 days) after first documentation of response. For Cohorts B and C, responses (CR or PR) will be confirmed at the next re-staging timepoint, 6 weeks (±7 days) after first

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documentation of response. Tumor imaging should also be performed whenever disease progression is suspected.

Subjects who discontinue for reasons other than documented PD will continue to have disease assessments (CT/MRI scans) approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy (see APPENDIX A). However, subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment.

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee), upon request.

7.2.1 Schedule of Events

For the purposes of this study, subjects should be re-evaluated as follows:

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

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

Radiographic disease assessments for subjects with documented PD who have continued on study treatment for clinical benefit must continue per the protocol defined assessment schedule; continued disease assessments will not be required after treatment is discontinued.

7.2.2 Definitions of Measurable and Non-Measurable Disease

1. Measurable Disease

   - A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with computed tomography (CT) scan, CT component of a positron emission tomography (PET)/CT, or MRI.
   - A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended
   - A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm).

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- Tumor lesions in a previously irradiated area are not considered measurable disease.

2. Non-Measurable Disease

- All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

- NOTE: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

7.2.3 Guidelines for Evaluation of Measurable Disease

1. Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For subjects having only lesions measuring ≥1 cm to <2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

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

2. Acceptable Modalities for Measurable Disease

- Conventional CT and MRI

- This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤5 mm. If CT scans have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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- PET-CT
- If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

3. Measurement at Follow-up Evaluation

   In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 9 weeks (see Section 7.2.4.3).

7.2.4 Measurement of Effect

Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 7.2.2) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (see Section 7.2.2), where ≤2 lesions are from the same organ and ≤2 malignant nodal lesions are selected. NOTE: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline sum of diameters (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of diameters (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Diameters (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the PBSD. If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is <0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned.

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If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

Non-Target Lesions & Non-Target Lymph Nodes
Non-measurable sites of disease (see Section 7.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accordance with Section 7.2.4.2.

7.2.4.1 Evaluation of Target Lesions

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 7.2.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

- CR: All of the following must be true:
  - Disappearance of all target lesions.
  - Each target lymph node must have reduction in short axis to <1.0 cm.
- PR: At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 7.2.4).
- PD: At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (see Section 7.2.4). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the MSD.

7.2.4.2 Evaluation of Non-Target Lesions & Non-Target Lymph Nodes

Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may

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need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

- CR: All of the following must be true:
  - Disappearance of all non-target lesions.
  - Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
- PD: At least one of the following must be true:
  - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

7.2.4.3 Overall Objective Status

The overall objective status for an evaluation is determined by combining the subject's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

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Table 7-1: Evaluation of overall objective status

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated[a]	No	PR[b]
SD	CR Non-CR/Non-PD Not All Evaluated[a]	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[a]	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated[a]	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated[a]	Yes	PD

a See Section 7.2.4.1

NOTE: This study uses the protocol RECIST 1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the protocol RECIST 1.1 template as of 2/16/2011 and to match RECIST 1.1 requirements.

7.3 Pharmacokinetic Assessments

In subjects randomized to Cohorts B or C, PK assessments of trough drug levels will be performed on Day 1 of Cycles 2 to 6 prior to administration of tucatinib. On Day 1 of Cycle 3, PK assessments of peak levels of tucatinib drug levels will be performed 1 to 4 hours after administration of tucatinib (Table 11-3).

Trough PK samples should continue to be collected on schedule regardless of dose holds or interruptions. The Day 1 Cycle 3 post-dose sample should not be collected during dose hold or interruptions.

Subjects in Cohort C who crossover to the tucatinib + trastuzumab regimen should continue PK assessments per Table 11-3, if crossover occurs prior to Cycle 6. If the crossover happens after Cycle 6, no PK collections are required.

7.4 Biomarker Studies

Biomarker assessments may include the confirmation of HER2 status by IHC, FISH, and NGS as well as an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved or CE-marked IHC test following the package insert's

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interpretational manual for breast cancer. Next generation DNA sequence analysis may be performed to interrogate the mutation status of a panel of oncogenes and tumor suppressor genes that are associated with tumor growth, survival and resistance to targeted therapeutics. This assessment may enable the correlation of treatment outcome to either preexisting or acquired cancer gene mutations and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor genotype in the future.

Sampling timepoints for body fluid biospecimens are listed in APPENDIX A (Table 11-2 and Table 11-3).

7.4.1 Biospecimen Collection

Blood and blood product samples collected for this study are the following:

4. Soluble protein (blood-based) biomarkers

   Blood (platelet poor plasma, serum, and white blood cells [buffy coat]) will be collected as summarized in Table 11-2 and Table 11-3. Analyses may include, but are not limited to soluble HGF, c-MET, EGF, HBEGF, HER1-3, VEGFA-D, PlGF, VEGFR2, GAS6, AXL, SDF1, Ang2, and TIE-2. Additional biomarkers may also be explored using multiplex array technology. Final biomarker selection will reflect the best science at the time of analysis.
5. Biomarker Plasma (Mutational and Blood NGS) analyses

   Blood (platelet poor plasma) to assess the molecular profile of ctDNA will be collected as summarized in Table 11-2 and Table 11-3. Analyses may include, but are not limited to HER2 amplification, EGFR amplification, BRAF mutations, and extended KRAS/NRAS testing (exons 2, 3, and 4). Final biomarker selection will reflect the best science at the time of analysis.

7.4.2 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the subjects or their family members, the genetic results will not be disclosed to the subjects or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB/IEC review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

7.4.3 Pathology Considerations/Tissue Biospecimens

Submission of the most recently available tumor block is necessary to support HER2 confirmation. Confirmatory HER2 testing will be done in the central laboratory for IHC following the package insert's interpretational manual for breast cancer. Additionally, testing will include NGS and FISH for mutational status including but not limited to HER2.

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Tissue Biospecimen Submission

FFPE tissue block with largest amount of invasive tumors from primary tumors present prior to study entry (if available) must be submitted upon enrollment. If no primary tumor tissue is available, metastatic biopsies should be used.

If there is no suitable FFPE block available, contact the Medical Monitor.

Blocks requested to accommodate individual subject management will be returned promptly upon request.

Refer to the Central Laboratory Manual for instructions on preparation and submission of tissue biospecimens.

7.5 Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seagen and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of antibody-drug conjugate sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.6 Patient-Reported Outcomes and Health Economic Assessments

PROs measures will be completed at protocol-specified time points using the EORTC QLQ-C30. Health economic assessments will be explored with the EQ-5D-5L instrument and health resource utilization. EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered for Cohorts B and C at: pre-dose Cycle 1 Day 1 (C1D1), C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.

7.7 Safety Assessments

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

Safety of all cohorts will be monitored over the course of the study by an SMC. Periodic cumulative data (AEs and laboratory results) review meetings will be held every 6 months. The meetings will provide a forum for decisions regarding whether to continue with the study as-is, to continue the study with modifications, to suspend enrollment, or to terminate the study.

The site principal investigator is responsible for reporting any/all AEs to the sponsor as described within the protocol. Refer to Section 7.7.1 for detailed information.

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7.7.1 Adverse Events

7.7.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a patient or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

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

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing pre-dose on study Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing pre-dose on study Day 1 that worsen in severity, increase in frequency, become related to study drug, or worsen in any other way but do not meet the threshold for increase in CTCAE grade should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

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Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant/important:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.1.2 for the definition of potential DILI.)

Adverse Event Characteristics

Adverse event monitoring and reporting is a routine part of every clinical trial.

AE characteristics should be defined using the following criteria:

a. Identify the severity grade of the event (Section 7.7.1.1).

b. Determine if the AE is related to the study intervention (agent, treatment or procedure)

c. Determine if AE is serious or non-serious (Section 7.7.1.1).

d. Determine the appropriate timeframe and mechanism of reporting (Sections 7.7.1.3 and 7.7.1.4).

Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) are defined by Seagen as a potential safety problem identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs MUST be undertaken at each treatment evaluation. Development of one of these AESIs (≥ Grade 1 unless otherwise noted) MUST be reported in terms of CTCAE v4.03 grade and attribution.

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

AESIs for this study are:

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1. Potential drug-induced liver injury

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

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

2. Asymptomatic left ventricular systolic dysfunction

In general, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and must be reported as an AE to the sponsor ≤1 business day of discovery of the event.

Adverse Event Severity

AE severity should be graded using the NCI CTCAE v4.03. These criteria are provided in the study manual.

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

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in Section 7.7.1.1.

Relationship of the Adverse Event to Study Treatment

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

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

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7.7.1.2 Procedures for Eliciting and Recording Adverse Events

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

Eliciting Adverse Events

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

Recording Adverse Events

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

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

Diagnosis vs. Signs or Symptoms

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

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

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

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

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Progression of Underlying Malignancy

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

Pregnancy

Notification to Drug Safety

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

Collection of data on the CRF

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

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

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

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

Definition

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

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

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AND

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

AND

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

Reporting Requirements

Any potential Hy's Law case should be handled as a serious adverse event (SAE) and reported promptly to the sponsor.

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

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening. Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

Left Ventricular Ejection Fraction Decreased

For asymptomatic declines in LVEF leading to a change in study treatment or discontinuation of study treatment, the term "ejection fraction decreased" should be used, and severity Grades 2 to 4 used to report asymptomatic LVEF decrease.

For symptomatic CHF, the term "heart failure" should be used, and severity Grades 2 to 5 used to report symptomatic CHF.

7.7.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

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

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

7.7.1.4 Serious Adverse Events Require Immediate Reporting

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

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

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

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

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

7.7.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.7.1.4). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs), to regulatory authorities as required per local legislation or regulatory reporting requirements.

7.7.2 Vital Signs

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

7.7.3 Clinical Laboratory Tests

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

- The serum chemistry panel is to include the following tests: albumin, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, calculated creatinine clearance

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using Cockcroft-Gault (at baseline and as clinically indicated), glucose, potassium, sodium, total protein.

- Hepatitis B and C screening (anti-HCV will only be collected for Cohorts B and C only)
- LFTs include ALT/serum glutamic pyruvic transaminase (SGPT), AST/ serum glutamic oxoloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin (and direct bilirubin when total bilirubin is >ULN)
- The CBC with differential is to include the following tests: CBC with differential that includes hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with 5-part differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- The coagulation panel is to include the following tests: INR, PT, and PTT
- The urinalysis is to include the following tests: color, appearance, pH, protein, glucose, ketones, blood, specific gravity, bilirubin, leukocyte esterase, nitrites, urobilinogen
- A serum β-hCG pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units) for subjects of childbearing potential

7.7.4 Physical Examination

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

7.7.5 Pregnancy Testing

For subjects of childbearing potential, a serum β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline and within 7 days prior to Day 1 of each treatment cycle. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests may also be repeated as requested per IRB/IEC or if required by local regulations.

7.7.6 Cardiac Function

7.7.6.1 MUGA or ECHO

Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. Additionally, if a subject discontinues trastuzumab for any reason, assessment of cardiac

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function (ECHO or MUGA) must be conducted every 6 months until 24 months from the last administration of trastuzumab. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

7.7.6.2 Electrocardiogram

ECGs will be performed at baseline. To correct for heart rate, QT intervals should be calculated using the Fridericia formula.

7.7.7 Treatment/Follow-up Decision at Evaluation of Subject

7.7.7.1 Treatment

Subjects will continue to receive study treatment per protocol until discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation from trial will be recorded.

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

Reasons for subject discontinuation may include, but are not limited to, the following:

- Death
- PD/treatment failure without ongoing clinical benefit
- Significant noncompliance by subject or treating physician
- AEs that are considered intolerable and unmanageable (relation to all drugs should be noted)
- Investigator determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted barrier methods of contraception (e.g., male condom, female condom) during the course of the study and for 7 months following discontinuation of study treatment
- Women who become pregnant or are breast feeding

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- Treatment-related adverse events which do not resolve to Grade ≤2 within 6 weeks, in which case the subject will have study treatment discontinued unless there is unequivocal evidence that the subject is benefiting
- Dosing delay greater than 6 weeks
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Withdrawal of consent
- Study termination by sponsor

7.7.7.2 Observation and Follow-up (Cohort A)

Observation

If subject discontinues treatment because of disease progression, they will have 1 Observation visit 30 (±7) days post last study intervention. After this time, subject will enter follow-up.

For subjects who go off study treatment with no documented disease progression and no subsequent anticancer treatment, the subject will be observed every 12 weeks (±14 days) or as clinically indicated until PD, at which time they will enter follow-up. Subjects remaining in observation for ≥5 years from first study treatment will go off study without entering follow-up.

Follow-up

Subjects in follow-up will have status evaluation every 12 weeks (±14 days) until PD, death, or end of study. Evaluation may be by telephone call, email, or in-person assessment. Review of medical records may be used to obtain this information if reasonable efforts to make phone/personal contact are unsuccessful. For subjects remaining on study at the time of study closure, a last visit / contact will occur and subjects who are still receiving treatment will revert to physician care.

Follow-up is the time period when the subject is no longer following the protocol test schedule. During follow-up, the data collection schedule is dictated by the protocol, but the subject visit schedule is determined by clinical practice at each participating site.

During the follow-up phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death.

Subjects cannot be required to return to the consenting site for study-related reasons or be required to have research-related tests performed. Samples from biospecimens collected in the course of clinical care may be requested but cannot be required of the participant.

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Progression of Disease (PD)

Subjects in Cohort A who develop PD at any time will have one observation visit 30 (±7) days post last study intervention and then to follow-up. These subjects should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

7.7.7.3 Follow-up Disease Assessment

Subjects in all cohorts will undergo:

- Further anti-cancer therapy and survival

7.8 Appropriateness of Measurements

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

Response will be assessed according to RECIST 1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The schedule for tumor imaging is consistent with general oncological practice and appropriately balances measurement of tumor control with the expense and subject inconvenience associated with CT and PET scanning.

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

The QLQ-C30 (Version 3.0) is a validated questionnaire developed by the EORTC to assess the quality of life of cancer subjects (Aaronson 1993; Sneeuw 1998). The EQ-5D-5L is a validated instrument for use as a measure of health-related QoL. These PROs have been incorporated into previous clinical trials that seek to quantify the QoL in subjects.

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8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

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

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

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

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8.2 Data Management Procedures

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

8.3 Access to Source Data

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

8.4 Accuracy and Reliability of Data

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

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

8.5 Quality Assurance Procedures

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

8.6 Data Handling and Record Keeping

Refer to the Case Report Form Completion Guidelines (CCG) for the methods of data collection.

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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 Seagen, whichever is longer. The investigator must contact Seagen 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 Seagen.

8.7 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

For purposes of timing of the Results Reporting, the estimated completion date for the Primary Endpoint of this study is approximately 50 months after the study opens to enrollment.

The definition of "Primary Endpoint Completion Date" for this study is 8 months from the time the last subject is registered.

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9 DATA ANALYSIS METHODS

An overview of study outcome measurements is provided in Table 9-1.

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Table 9-1: Overview of study outcome measurements

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
Primary			
• To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by cORR (per RECIST 1.1), according to BICR assessment	• cORR (confirmed CR or PR), per RECIST 1.1, according to BICR assessment, in pooled Cohorts A+B	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
Secondary Efficacy			
• To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohorts A+B	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment	• ORR (RECIST 1.1) by 12 weeks of treatment, according to BICR assessment, in Cohort C	• ORR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the duration of response (DOR) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohorts A+B	• DOR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment	• DOR (RECIST 1.1), according to BICR assessment, in Cohort C	• DOR, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years

Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• To assess the PFS in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment b	• PFS (RECIST 1.1), according to BICR assessment, in Cohorts A+B	• PFS, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the OS in subjects treated with tucatinib given in combination with trastuzumab, in Cohorts A+B	• OS, in Cohorts A+B	• OS	• Up to approximately 5 years
Secondary Safety			
• To assess the safety and tolerability of tucatinib given in combination with trastuzumab, in Cohorts A+B	• Frequency and severity, according to CTCAE v4.03 criteria, of all TEAEs and treatment-related TEAEs, in Cohorts A+B • Frequency of SAEs and deaths due to AEs, in Cohorts A+B • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B • Frequency and severity of laboratory abnormalities, in Cohorts A+B • Vital signs and other relevant safety variables, in Cohorts A+B	• Incidence of AEs • Incidence of dose modification and treatment discontinuation • Incidence of laboratory abnormalities	• Through 1 month following last dose; up to approximately 9 months overall per subject

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Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• To assess the safety and tolerability of tucatinib monotherapy, in Cohort C	• Frequency and severity, according to CTCAE v4.03, of all TEAEs and treatment-related TEAEs, in Cohort C • Frequency of SAEs and deaths due to AEs, in Cohort C • Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohort C • Frequency and severity of laboratory abnormalities, Cohort C • Vital signs and other relevant safety variables, in Cohort C	• Incidence of AEs • Incidence of dose modification and treatment discontinuation • Incidence of laboratory abnormalities	• Through 1 month following last dose; up to approximately 9 months overall per subject
Exploratory			
• To evaluate the PK of tucatinib	• PK parameters of tucatinib	• PK parameters of tucatinib	• Through Cycle 6
• To explore any correlations between tissue and blood-based biomarkers and clinical outcomes	• To explore potential biomarkers of response, resistance or toxicity from archived paraffin-embedded tumor samples and ctDNA isolated from plasma samples.	• Biomarker readouts from liquid biopsies	• Up to approximately 3 years
• To assess the PFS in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment	• PFS (RECIST 1.1), according to BICR assessment, in Cohort C	• PFS, per RECIST 1.1, by BICR assessment	• Up to approximately 5 years
• To assess the OS in subjects treated with tucatinib monotherapy, in Cohort C	• OS, in Cohort C	• OS	• Up to approximately 5 years

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Objective	Corresponding Endpoint	Corresponding Measurement	Timeframe
• To assess PROs associated with tucatinib given in combination with trastuzumab	• Change from baseline in PRO assessments of the EuroQOL-5 Dimensions (EQ-5D-5L), and European Organization for Research and Treatment of Cancer Core QoL Questionnaire (EORTC QLQ-C30)	• Changes in PRO scores	• Up to approximately 3 years
• To explore health resource utilization	• Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and ED visits	• Incidence of health care utilization	• Up to approximately 3 years

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9.1 Determination of Sample Size

Approximately 110 subjects will be enrolled in the study. Subjects are considered enrolled if they give informed consent and meet all eligibility criteria. Approximately 40 subjects will be enrolled in Cohort A. Approximately 70 subjects, enrolled in the expansion portion of the trial, will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment will continue until approximately 40 subjects have been randomized to and treated in Cohort B, and approximately 30 subjects have been randomized to and treated in Cohort C.

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

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

For illustration purposes, Table 9-2 summarizes the expected 95% CIs for subjects treated with tucatinib given in combination with trastuzumab (Cohort A+B) and subjects treated with tucatinib monotherapy (Cohort C) at the proposed sample sizes of 80 and 30 respectively. No formal statistical comparisons between cohorts are planned.

Table 9-2: Estimated ORR

Confirmed ORR	95% Exact CI. (Cohorts A+B, N=80)
40%	(29%, 52%)
50%	(39%, 61%)
60%	(48%, 71%)

Confirmed ORR	95% Exact CI. (Cohort C, N=30)
10%	(2%, 27%)
15%	(5%, 33%)
20%	(8%, 39%)

Accrual Time and Study Duration

Approximately 2 subjects per month will be enrolled over 42 months. Subjects may continue to receive study treatment until they experience unacceptable drug-related toxicity or disease progression. Subjects will be followed for survival up to 5 years from first study treatment.

The final analysis can begin approximately 50 months after the trial begins.

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9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

The primary endpoint in this study is the confirmed ORR per BICR. The ORR is defined as the proportion of subjects with confirmed CR or PR, per RECIST 1.1. Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments as described in Section 7.2 of the protocol will be counted as non-responders.

There have been minimal changes to eligibility criteria for Cohort A and Cohort B, and all patients will be centrally confirmed as being HER2+ with the same testing methodology (IHC/breast criteria), therefore the primary efficacy analysis set will be comprised of all treated subjects in Cohorts A+B.

9.2.2 Objective Response Rate by Week 12

ORR by Week 12 per BICR is defined as the proportion of subjects with CR or PR by 12 weeks of treatment, and before time of crossover (Cohort C), whichever comes earlier, as determined by BICR assessment per RECIST 1.1. Responses do not need to be confirmed to be scored as responders for the purpose of determining ORR by Week 12. Subjects whose disease response cannot be assessed as CR, PR, or SD by Week 12 or later will be scored as non-responders for calculating the ORR by Week 12.

ORR by Week 12 will be summarized for subjects treated solely with tucatinib monotherapy (Cohort C) and subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B).

9.2.2.1 DOR

The DOR is defined as the time from first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD (per RECIST 1.1) or to death due to any cause, whichever comes first.

DOR will be calculated for the subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B) and subjects treated solely with tucatinib monotherapy (Cohort C).

9.2.2.2 PFS

PFS is defined as the time from start of study treatment (Cohort A) or randomization (Cohorts B and C) to first documentation of tumor progression (clinical progression or PD per RECIST 1.1), as determined by BICR assessment, or to death due to any cause, whichever comes first. PFS data will be censored on the date of the last disease assessment documenting absence of PD for subjects who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, or are removed from study prior to documentation of tumor progression. Subjects lacking an evaluation of tumor response after their start of study treatment (Cohort A) or randomization (Cohorts B and C) will have their event time censored at 1 day.

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9.2.2.3 OS

OS is defined as the time from start of study treatment (Cohort A) or randomization (Cohorts B and C) to date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive. Subjects lacking data beyond their start of study treatment (Cohort A) or randomization (Cohorts B and C) will have their survival time censored at 1 day.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

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

Unless otherwise specified, CIs will be calculated at 2-sided 95% level.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (e.g., ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Subjects enrolled in the initial Cohort A and those randomized to Cohort B during the expansion will be analyzed together (Cohorts A+B). Demographic and baseline characteristics will be summarized by cohort.

9.3.1.1 Randomization and Blinding

All subjects enrolled in the expansion portion of the trial will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Randomization will be stratified by:

- Left sided primary versus all other primary types (i.e., right, transverse, overlapping primary)

Blinding will not be performed.

9.3.1.2 Adjustments for Covariates

No adjustment for covariates is planned in the analyses.

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9.3.1.3 Handling of Dropouts and Missing Data

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

9.3.1.4 Multicenter Studies

This study will be conducted at multiple study centers, however it is not anticipated that site-to-site variation will be adjusted in the analyses.

9.3.1.5 Multiple Comparisons and Multiplicity

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

9.3.1.6 Data Transformations and Derivations

Time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section. Unless otherwise specified, baseline values used in all analyses will be the most recent nonmissing measurement prior to the first dose of study drug.

9.3.1.7 Analysis Sets

The intent-to-treat (ITT) set will include all enrolled subjects in Cohort A and all randomized subjects in Cohorts B and C. A subject is considered enrolled if he/she has met all criteria for participation in the study.

The full analysis set (FAS) set will include all subjects who are enrolled and receive any amount of study treatment.

The safety analysis set will include all subjects who receive any amount of study treatment. The safety analysis set will be used for all safety analyses.

The PK analysis set will include all subjects in Cohorts B and C who received study treatment and from whom at least one PK assessment was reported. The PK analysis set will be used for PK analyses.

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

9.3.1.8 Examination of Subgroups

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

9.3.1.9 Timing of Analyses

The timing of the primary analysis will be based on the time to confirmed ORR per BICR. DOR according to BICR assessment will also be analyzed at this time. Detailed information regarding the timing of the analysis will be provided in the SAP.

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9.3.2 Subject Disposition

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

9.3.3 Subject Characteristics

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

9.3.4 Treatment Compliance

Treatment administration will be summarized for safety analysis set. Summary statistics for duration of therapy (weeks) and the number of cycles per subject will be presented, as well as the number and percentage of subjects who were treated at each cycle and completed each cycle. Details will be provided in the SAP.

9.3.5 Efficacy Analyses

9.3.5.1 Primary Efficacy Analyses

The primary endpoint of this study is the confirmed ORR per BICR. The ORR is defined as the proportion of subjects with confirmed CR or PR according to RECIST 1.1. Subjects who do not have at least 2 (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders.

The ORR and its exact 2-sided 95% CI, using the Clopper-Pearson method (Clopper 1934), will be calculated.

The primary efficacy analysis will be performed for subjects treated solely with tucatinib in combination with trastuzumab (Cohorts A+B).

9.3.5.2 Secondary Efficacy Analyses

The analyses on secondary endpoint, ORR by 12 weeks of treatment, and the exact 2-sided 95% CIs, using the Clopper-Pearson method (Clopper 1934), will be calculated.

Secondary endpoints, such as DOR per BICR, PFS per BICR, and OS, are time-to-event endpoints, and they will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. Details on the censoring algorithm will be provided in the SAP.

ORR by Week 12 will be summarized for subjects treated solely with tucatinib monotherapy (Cohort C) and subjects treated solely with tucatinib given in combination with trastuzumab (Cohorts A+B).

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9.3.5.3 Other Efficacy Analyses

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

9.3.6 Pharmacokinetic Analyses

Individual (subject) 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. These analyses will be described in a separate analysis plan.

9.3.7 Biomarker Analyses

Relationships of biomarker parameters (e.g., baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters will be explored. Relationships and associated data that are determined to be of interest will be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.8 Patient-Reported Outcomes and Health Resource Utilization Analyses

PRO assessments based on the EQ-5D-3L and EORTC QLQ-C30 will be summarized using descriptive statistics. PRO scores will be analyzed descriptively. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment time point may be presented. Further investigation of missing patterns and details of imputation will be provided in the SAP. Additional statistical modeling for PRO measures may be performed separately as exploratory analyses.

9.3.9 Safety Analyses

Safety will be assessed through summaries of AEs, changes in laboratory test results, changes in vital signs, physical examination findings, changes in ECOG PS, and changes in cardiac ejection fraction results. AEs will be classified by SOC and preferred term using Medical Dictionary for Regulatory Activities (MedDRA); AE severities will be classified using the CTCAE v4.03 criteria.

9.3.9.1 Extent of Exposure

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

Details will be provided in the SAP.

9.3.9.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will

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be defined as treatment emergent if they are newly occurring or worsen following study treatment.

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

All collected AE data will be listed by cohort, study site, subject number, and cycle. Separately, all serious AEs and AEs of special interest (e.g., any DILI, and asymptomatic left ventricular systolic dysfunction) will be listed. A separate listing of all on-study deaths will be presented.

9.3.9.3 Deaths and Serious Adverse Events

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

9.3.9.4 Clinical Laboratory Results

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

9.3.9.5 Other Safety Analyses

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

ECOG Status
ECOG status will be summarized for each visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG
ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG, and shifts from baseline may be tabulated.

MUGA or ECHO
Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation, and at EOT (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac ECHO or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. Additionally, if a subject discontinues trastuzumab for any reason, assessment of cardiac function (ECHO or MUGA) must be conducted every 6 months until 24 months from the last

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administration of trastuzumab. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison.

9.3.10 Interim Analyses

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

No formal interim analyses are planned for Cohorts B and C.

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10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (World Medical Association 2013), and all applicable regulatory requirements. For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations.

10.1 Informed Consent

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

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

10.2 Ethical Review

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

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

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

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

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.

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- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3 Regulatory Considerations

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

10.4 Investigator Information

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

10.4.1 Protocol Amendments and Study Termination

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

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

10.5 Study Documentation, Privacy and Records Retention

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

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

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

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10.6 Clinical Trial Agreement

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

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APPENDIX A: SCHEDULE OF EVENTS

Table 11-1: Schedule of events

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Study Period/Treatment Cycle	Pre-screening[v]	Screening/Baseline		Treatment					EOT[a]	F/U[b]
	Up to 3 months prior to screening			Cycle 1		Cycles >1	Every 6 or 9 wks	Every 12 wks	30 days post last dose	Every 12 wks
Day		D–28 to –1	D–7 to –1	Pre-dose D1	D8 and 15	Pre-dose D1				
Visit Window					±3 days	±3 days	±7 days	±14 days	+7 days	±14 days
HER2 alterations testing informed consent[v]	X									
Study informed consent[c]		X								
Inclusion/exclusion criteria		X								
Document disease history		X								
FFPE Tumor Specimen[d]	X	X								
Physical examination[e]			X	X		X			X	
Height			X							
Vital signs[f]			X	X		X			X	
Drug Diary review				X		X				
Adverse event collection		Related to study procedures		Collect from C1D1 pre-dose through safety reporting period of study drugs						
Concomitant medication										
ECOG PS			X	X		X			X	
CBC with differential and platelets[g]			X	X	X	X			X	
Blood chemistries and LFTs[h]			X	X	X	X			X	
Coagulation tests[i]			X						X	
Urinalysis			X							
12-lead ECG[j]			X							
ECHO/MUGA[k]		X						X	X[l]	X
Serum β-HCG pregnancy test[m]			X[m]	X[m]		X				
Hepatitis B and C screening[n]		X								
Radiological disease assessment[o, u]		X					X[o]		X	
Blood tumor marker – CEA[p]		X					X[p]		X	
EQ-5D-5L/EORTC QLQ C30 questionnaire[q]				X	X	X			X	
Study drug treatment – Tucatinib[r]				X		X				
Study drug treatment – Trastuzumab[s]				X		X				
PK and Biomarker sample		See Table 11-2 and Table 11-3 for PK and biomarker samples collection schedule								
Further anticancer therapy and survival[t]										X

a For Cohort A, if subject discontinues treatment because of PD, they will have 1 Observation visit 30 (±7) days post last study intervention. After this time, subject will enter follow-up. For subjects who go off study treatment with no documented disease progression and no subsequent anticancer treatment, the subject will be observed every 12 weeks (±14 days) or as clinically indicated until PD, at which time they will enter follow-up. Subjects remaining in observation for ≥5 years from first study treatment will go off study without entering follow-up.

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b Treatment decisions/patient care for subjects who have discontinued study treatment is at the discretion of the treating physician.

c Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the site's institutional review board (IRB)/independent ethics committee (IEC) policies.

d Initiate collection of tissue for submission for confirmatory HER2+ and biomarker testing at pre-screening or screening. If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment.

e Pre-dose, may not be performed if done within 1 day prior to C1D1

f Vital signs to be collected are weight, body temperature, heart rate, systolic and diastolic blood pressure, pulse, and oxygen saturation. Pre-dose, may not be performed if done within 1 day prior to C1D1.

g If CBC is performed within 7 days prior to C1D1, it does NOT need repeating on C1D1.

h Creatinine, calculated creatinine clearance using Cockcroft-Gault (at baseline and as clinically indicated), total bilirubin (and direct bilirubin when total bilirubin is >ULN), ALT, AST, alkaline phosphatase, albumin, calcium, sodium, potassium, chloride, bicarbonate, BUN, glucose, and total protein. If chemistries are performed within 7 days prior to C1D1, they do NOT need to be repeated on C1D1.

i PT, INR, aPTT

j ECG assessments will be performed with standard 12-lead ECG equipment according to standard institutional procedures. Pre-treatment ECGs should be performed after vital signs are obtained and before any blood draws.

k Cardiac ejection fraction will be assessed by transthoracic ECHO will be performed at screening, every 12 weeks until treatment discontinuation irrespective of dose delays or interruption, and at the EOT visit. ECHO is the preferred modality for assessment of LVEF. If clinically indicated, MUGA scan may be used in place of ECHO. If a subject discontinues trastuzumab for any reason, assessment of cardiac function (ECHO or MUGA) must be conducted every 6 months until 24 months from the last administration of trastuzumab. The same method for LVEF assessment should be employed at each assessment.

l The EOT assessment of ECHO does not need to be performed if an on-treatment ECHO had been performed within 12 weeks previously.

m Women of childbearing potential only. If pregnancy test is performed within 7 days prior to C1D1, it does not need to be repeated on C1D1.

n Blood samples for Hepatitis B surface antigen (hBsAg), antibodies to Hepatitis B core (anti-HBc), and antibodies to Hepatitis C (anti-HCV will only be collected for Cohorts B and C).

o CT or MRI of the chest, abdomen, and pelvis to assess sites of measurable disease as per RECIST 1.1. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original schedule. Unless clinically indicated, the same method for tumor assessment should be employed at every restaging. For Cohort A, radiological disease assessment will be performed at the screening/baseline, every 9 weeks/3 cycles (±14 days) during study treatment (every 12 weeks/4 cycles [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. For Cohorts B and C, radiological assessment will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. Radiographic assessments for subjects with documented PD who have continued on study treatment for clinical benefit must continue to be performed per the protocol defined assessment schedule; continued disease assessments will not be required after treatment is discontinued. Subjects who discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.

p CEA assays will be performed on the same schedule as radiographic scanning. For Cohort A, CEA assays will be performed at the screening/baseline, every 9 weeks (every 3 cycles, ±14 days) during study treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. For Cohorts B and C, CEA assays will be performed at screening/baseline, every 6 weeks (±7 days) during treatment (every 12 weeks [±7 days] after 12 months of treatment, if the subject is clinically stable), and at the EOT visit. If cycles are delayed for any reason or there is an interim unscheduled assessment, CEA assays should continue to be performed according to the original schedule.

q EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered for Cohorts B and C at: pre-dose C1D1, C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.

r Tucatinib is administered PO BID, on each 21-day cycle.

s Trastuzumab is administered IV, once every 21 days for Cohorts A and B, or subjects in Cohort C who are approved to crossover to doublet treatment.

t Following progression or initiation of further anticancer therapy, subjects will be contacted every 12 weeks (±2 weeks) to obtain information on subsequent anticancer therapy, and survival status until death, study closure, or withdrawal of consent.

u Subjects from Cohort C must have a new baseline RECIST assessment, as described in Section 6.3.6, prior to crossover from monotherapy to doublet therapy using the Week 12 scans or the first PD scans as applicable.

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v If HER2 overexpression/amplification status is unknown in pre-study assessments, subjects may consent to submit an archival tumor specimen or new lesion biopsy for local Immunohistochemistry/In situ hybridization testing for assessment of HER2 status. Subjects must be informed that HER2 testing consent is not informed consent for the study and participation in HER2 testing does not guarantee study eligibility.

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Table 11-2: Pharmacokinetic and biomarker sample collection time points – Cohort A

Visit	Study day	Time	Window	Relative Time	Blood Samples		Tumor
					Biomarker Plasma (Mutational Analysis)	Biomarker Serum	FFPE Tumor Specimen
Screening	-28 to -1	N/A	N/A	N/A			X[a]
Cycle 1	Day 1	Pre-dose	Within 24 hours	Time of administration	X	X	
Cycle 4 and every third cycle thereafter	Day 1	Pre-dose	Within 24 hours	Time of administration	X	X	
End of Treatment					X	X	

a If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment

Table 11-3: Pharmacokinetic and biomarker sample collection time points – Cohorts B and C

Visit	Study day	Time	Window	Relative Time	Blood Samples		Tumor
					PK	Biomarker Plasma	FFPE Tumor Specimen
Screening	-28 to -1	N/A	N/A	N/A		X	X[a]
Cycle 2	Day 1	Pre-dose	Within 2 hours	Time of administration of tucatinib	X		
Cycle 3	Day 1	Pre-dose	Within 2 hours	Time of administration of tucatinib	X		
		Post-dose	Within 1-4 hours	Post-dose of tucatinib	X		
Cycle 4, 5 & 6	Day 1	Pre-dose	Within 2 hours	Time of administration of tucatinib	X		
End of Treatment						X	

a If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment

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APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

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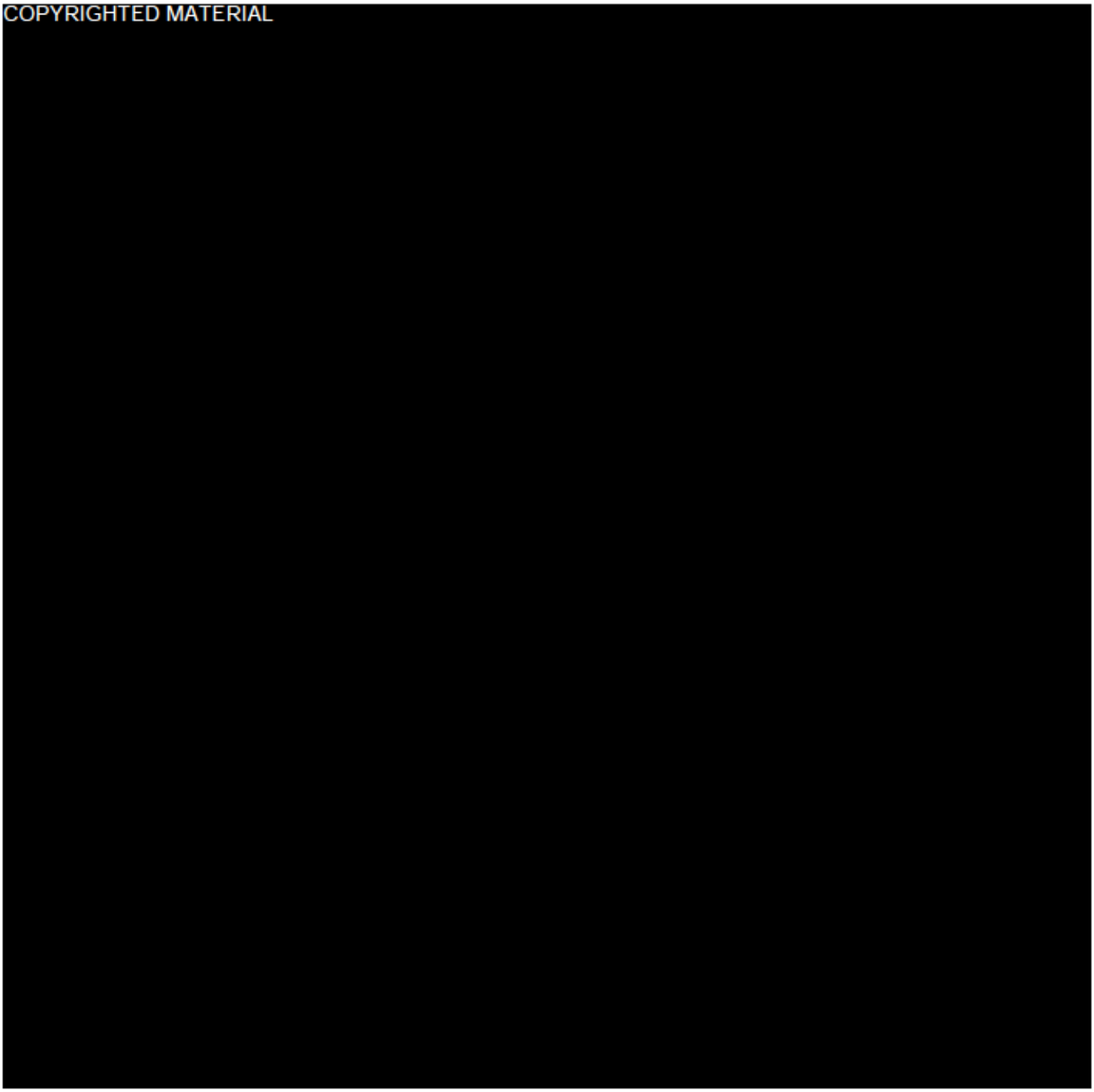

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APPENDIX C: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 7 months after the final dose of study drug administration; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

Subjects who are of childbearing potential[a] or whose partners are of childbearing potential[a] and who are sexually active in a way that could lead to pregnancy may choose any TWO of the following methods:

- Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
- Intrauterine device with failure rate <1%
- Tubal ligation
- Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)
- Barrier method/s (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)

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

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:

- Option 1: Male condom (with or without spermicide) and cervical cap
- Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

- Periodic abstinence
- No method
- Withdrawal
- Rhythm
- Spermicide only
- Progestin-only pills
- Concomitant use of female and male condoms

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APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

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On-line source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

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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)

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

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

Drug[a, b]	Elimination Half-life[c]
Strong Inhibitors	
Gemfibrozil	1–2 hours
Moderate Inhibitors	
Clopidogrel	6 hours
Deferasirox	8-16 hours
Teriflunomide	18-19 days
Moderate Inducer	
Rifampin	3–5 hours

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

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

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

c Drug package insert

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APPENDIX G: PATIENT DRUG DIARY

Tucatinib

Cycle:	Patient ID Number:	Name:
Pill strength dispensed:	☐ 50 mg tablets	You will take _____ tablets in the MORNING, and _____ tablets in the EVENING.
	☐ 150 mg tablets	

ORAL MEDICATION DIARY

Patient Instructions

- Store your study drug in the refrigerator and keep out of the reach of children and pets. The individual unit dose of the tucatinib tablet may be exposed to room temperature for up to 6 hours prior to dose. If left out of refrigeration for a longer period of time, please contact your study team.
- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should stop taking your medication or continue it.
- To correct an error or mistake, please make a single line through that entry and write your initials and date next to the error or mistake.
- Please record each dose as soon as you take it and fill in the date as directed.
- Please indicate on the calendar below every day that you take your study medication by placing the time dose was taken on the line under the date.
- Please do not consume grapefruit, grapefruit juice, star fruit, or Seville oranges while taking tucatinib.
- Tucatinib tablets should be taken twice each day (once in the morning, and once in the evening) approximately 8-12 hours between doses in the same calendar day. It is recommended that if you miss a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, you should not take the missed dose but should wait and take the next regularly scheduled dose. If you miss a dose, place a check "0" under the date.
- Take tablets by mouth twice daily as prescribed on days 1–21 of each cycle
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose or double up the next dose.
- Pills must be swallowed whole. Do not crush, chew, or dissolve pills in liquid.

- If you vomit a dose, and the pill is visible in the vomit, you can take a replacement pill. If the pill is not visible in the vomit, please wait until your next scheduled time before taking the medication again.

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 8	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
	Day 15	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date:							
Time of Morning Dose	AM	AM	AM	AM	AM	AM	AM
Time of Evening Dose	PM	PM	PM	PM	PM	PM	PM
Each cycle has 21 days. In cases where a patient is unable to return to clinic at the end of a cycle, a 3-day window is allowed in the study. Tucatinib tablets taken during this time will be recorded here.					***+Day 1***	***+Day 2***	***+Day 3***
Date:							
Time of Morning Dose					AM	AM	AM
Time of Evening Dose					PM	PM	PM

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APPENDIX H: EXAMPLES OF CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

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

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

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

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

OATP1B1 = organic anion transporting polypeptide 1B1.

d Listed based on pharmacogenetic studies.

e Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.

f Usually administered to patients in combination with ritonavir, a strong CYP3A inhibitor.

g Acid form is an OATP1B1 substrate

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

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APPENDIX I: DEFINING LINES OF THERAPY

A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the investigator's opinion, maximum benefit has been achieved. Disease progression can be either clinical or radiographic and does not have to be based on a formal RECIST assessment.

- Maintenance therapy (e.g., continuation of 5-fluorouracil [5FU] after discontinuation of oxaliplatin or irinotecan) does not count as a separate line.

- Hepatic arterial infusion (HAI) pump therapy counts as a separate line.

- Restarting a chemotherapy backbone counts as a line if:
  - There is an addition of a biologic not previously used
  - The patient previously had progressive disease (clinical or radiographic) on this regimen

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APPENDIX J: INVESTIGATOR SIGNATURE PAGE

Protocol Number:	Study SGNTUC-017
Protocol Title:	A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer **(MOUNTAINEER)**
Investigational Product:	Tucatinib (ONT-380)
Version:	Amendment 12; 06-Mar-2023

Investigator Statement and Signature

I have read the attached protocol entitled "A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer (MOUNTAINEER)"

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

Investigator Signature _____ Date _____

Investigator Name, Printed _____

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APPENDIX K: DOCUMENT HISTORY

Version*	Date
Original	5 May 2017
Amendment 1	23 June 2017
Amendment 2	20 October 2017
Amendment 3	02 March 2018
Amendment 4	21 September 2018
Amendment 5	19 April 2019
Amendment 6	05 July 2019
Amendment 7	10 September 2019
Amendment 8	01 November 2019
Amendment 8.1	22 November 2019
Amendment 8.2	14 February 2020
Amendment 9	10 September 2020
Amendment 10	21 December 2020
Amendment 11	30 June 2021
Amendment 12	09 March 2023

*Up through "Amendment 6" the investigator-sponsored trial documents were also known as "Addendums" instead of "Amendments."

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Summary of Changes in Amendment 1

Protocol section updated	Nature of change
Title Page	• IND number corrected • Draft date removed • Document history updated to reflect Activation/Amendment 1
Protocol Resource Page	• Removed from protocol
Schema	• Correction made to Tucatinib dosing schedule • Clarifications made to study schema
Section 3.0, Patient Eligibility	• Editorial changes • Change to length of birth control requirements
Section 4.0, Test Schedule	• Changes to pre-registration tests and procedures • Correction to Clinical Follow-up and Event Follow-up visits • Clarifications to visit timing • Consolidation of like biospecimen collections • Footnotes updated to reflect above-mentioned edits and to add further clarifications
Section 13.0, Treatment/Follow-up Decision at Evaluation of Patient	• Change to length of birth control requirements
Section 14.0, Body Fluid Biospecimens	• Biospecimen submission table updated to reflect Test Schedule changes • Additional guidelines added to kit instructions
Section 15.0, Drug Information	• IND number corrected • Tucatinib section updated based on Pharmacy review of template • Nursing guidelines added
Section 17.0, Pathology Considerations/Tissue Biospecimens	• Removal of redundant information • Correction of form name
Section 18.0, Records and Data Collection Procedures	• Initial Materials table updated to reflect final forms build • Test Schedule Materials updated to reflect final forms build • Follow-up Materials table updated to reflect final forms build
Appendix I, Informed Consent Template	• Side effects of Tucatinib updated based on Pharmacy review of IB • Side effects of Trastuzumab updated based on Pharmacy review of IB • Change to length of birth control requirements • Risks of TTE removed • Timeframe for reporting of pregnancy of partner of male patient revised
Appendix VII, Patient Drug Diary	• Correction made to drug storage instructions
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 2

Protocol section updated	Nature of change
Title Page	• Editorial and administrative changes have been made regarding the Protocol Resource Page communication.
Schema, Page 3	• Tucatinib and Trastuzumab have been updated with administrative and editorial changes.
Section 3.0, Patient Eligibility	• 3.13 have been updated with an editorial change. • 3.18 have been updated with administrative and editorial changes. • 3.19c has been updated with an editorial change and to define amenorrhea as ≥12 consecutive months. • 3.19d have been updated with administrative and editorial changes.
Section 4.0, Test Schedule	• Under Cycle 1, days 8 & 15 was modified as required. • Under the Active Treatment section, the cycles were modified with editorial changes. • Footnote 10 has been deleted; thus renumbering footnotes 10-13 has changed. • The mandatory tissue sample was moved to the observation section as required.
Section 7.0, Protocol Treatment	• Section 7.1 Treatment Schedule has been updated with an administrative change. • Section 7.2 has been updated with administrative and editorial changes.
Section 11.0, RECIST Measurement Guidelines	• Section 11.1 has been updated with administrative and editorial changes.
Section 14.0, Body Fluid Biospecimens	• Section 14.115 has been deleted regarding the days of shipment for specimens.
Section 15.0, Drug Information	• Section 15.14 has been updated with added information regarding the administration of Tucatinib. • Section 15.16, additional information was added to the Potential Drug Interactions paragraph. • Sections 15.297-98 Nursing Guidelines have been added for Trastuzumab.
Section 18.0, Records and Data Collection Procedures	• Section 18.1 Submission Timetable, the specimen submission tissue for baseline has been moved from the active-monitoring phase to the observation phase and footnotes have been updated to reflect these changes.
Section 19.0, Budget	• Section 19.2 has been updated with editorial changes.
Appendix I, Informed Consent Template	• Pages 7, 8, and 9 have been updated to reflect Tucatinib to be taken twice daily. • Page 10 has been updated with administrative and editorial changes. • Pages 14, 15; Reproductive Risks have been updated with administrative and editorial changes. • Page 18; the verbiage regarding drug cost has been updated. • Page 19; Travel Reimbursement language has been added.
Appendix IV	• Page 1; Administrative and editorial changes have been made.

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Protocol section updated	Nature of change
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 3

Protocol section updated	Nature of change
Schema	• Trastuzumab availability has been changed to Biologics.
Section 7.0, Protocol Treatment	• Section 7.3 was updated to clarify that the patient does not necessarily need to get treatment where they signed consent.
Section 9.0, Ancillary Treatment/Supportive Care	• Section 9.5 was updated with an editorial change. • Section 9.9a was updated to clarify radiation and RECIST.
Section 14.0, Body Fluid Biospecimens	• Footnote #2; cycle numbers were corrected.
Section 15.0, Drug Information	• Section 15.13 was updated to clarify the shelf life of Tucatinib. • Section 15.17; More verbiage has been added to the toxicities for Tucatinib. • Section 15.18; Drug procurement language has been added for Tucatinib. • Section 15.19a; Temperature Excursion language has been added to clarify the process for sites. • Section 15.19b; Nursing Guidelines have been changed due to the updated IB for Tucatinib. • Section 15.19c; Drug Accountability has been updated for sites clarity. • Section 15.28 Drug procurement for trastuzumab has been updated to clarify funding and the updated process.
Appendix I, Informed Consent Template	• Appendix I; Pages 3, 5, 6, 8, 9, 10, 11, 18, 19 were updated with an administrative and editorial changes.
Appendix VII, Drug Diary	• The Patient Drug Diary has been updated to clarify instructions for the patient regarding the drug.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 4

Protocol section updated	Nature of change
Title Page	• The IND Holder has been changed from Dr. PPD to Dr. PPD . • The Statistician's for this trial has been edited.
Index	• The header was changed to reflect Amendment 4.
Schema	• Biologics was changed to McKesson on the availability for tucatinib and trastuzumab.
Section 1.0, Background	• Administrative and editorial changes were made throughout Section 1.0.
Section 3.0, Patient Eligibility	• Administrative and editorial changes were made throughout Section 3.0.
Section 4.0, Test Schedule	• Footnote #6 was changed for clarification regarding imaging. • Footnote #8 was modified to clarify tissue submission.
Section 8.0, Dosage Modification Based on Adverse Events	• Added language was inserted for clarification regarding Adverse Event-Specific Dose Modifications.
Section 10.0, Adverse Event (AE) Reporting and Monitoring	• Cascadian was changed to Seattle Genetics throughout section 10.0.
Section 13.0, Treatment/Follow-up Decision at Evaluation of Patient	• The follow-up period was changed in section 13.1 for clarification. • Verbiage regarding dosing delays was added for clarification.
Section 15.0, Drug Information	• Section 15.1 Tucatinib; Cascadian was changed to their new name Seattle Genetics. • The temperature excursion email was modified. • Section 15.2 Trastuzumab; had administrative and editorial changes throughout for clarification on Cascadian's name change to Seattle Genetics and based on the package insert. • Section 15.26 language removed from the protocol as it was not related to this study. • Section 15.27 has editorial and administrative changes for clarification.
Section 16.0, Statistical Considerations and Methodology	• Section 16.2 Primary Endpoint; has been edited for clarification. • Section 16.31 Decision Rule; Administrative and editorial changes have been made. • Section 16.34 Power and Significance Level; administrative and editorial changes have been made.
Appendix I, Informed Consent Template	• The header has been changed to reflect Amendment 4 • Cascadian has been changed to Seattle Genetics. • Verbiage regarding study testing was modified for clarification. • Side Effects associated with Trastuzumab were changed based on the package insert. • Tumor assessments have been modified regarding RECIST imaging.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 5

Protocol section updated	Nature of change
Title Page	• Amendment 5 has been added to the title page.
Section 1.0, Background	• Section 1.2 references and language was changed based on new findings. • Section 1.323 was edited based on the trastuzumab package insert.
Section 4.0, Test Schedule	• Footnote 6, language had added language for clarification.
Section 8.0, Dosage Modification Based on Adverse Events	• 8.2; Administrative and editorial edits have been added for clarifications. • Edits have been made to the table regarding Left Ventricular Systolic Dysfunction.
Section 11.0, RECIST Measurement Guidelines	• 11.213; An editorial change was made for clarification regarding measurable disease.
Section 14.0, Body Fluid Biospecimens	• 14.0, Footnote 1 had an administrative change regarding blood collection for C1 day 1.
Section 18.0, Records and Data Collection Procedures	• NGS or FISH/CISH are now added as reports to be uploaded for baseline.
Section 20.0 References	• An outdated reference was removed and replaced.
Appendix I, Informed Consent Template	• Trastuzumab Reproductive Risks; language was added for precautionary measures for pregnant females. • Seattle Genetics was added to receive data for this protocol.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 6

Protocol section updated	Nature of change
Title Page	• Amendment 6 was changed on the Title Page.
Section 1.0, Background	• Section 1.2 was modified with the current reference. • Section 1.2; language was removed and an editorial changes was made. • Section 1.323; CYP language was added for study clarification. • Section 1.6; Administrative changes were made for clarification.
Section 3.0, Patient Eligibility	• Numbering was modified due to insertion and deletion of language. • Administrative and editorial changes were made throughout Section 3.0
Section 4.0, Test Schedule	• Footnote 6 &7 had an editorial changes for study clarification. • The mandatory blood sample on the test schedule was changed from baseline to prior to dosing on Day 1, per the PI.
Section 7.0, Protocol Treatment	• Additional language has been added to the treatment schedule for study purposes.
Section 8.0, Dosage Modification Based on Adverse Events	• Editorial changes were made to Section 8.1 for clarification.
Section 9.0, Ancillary Treatment/Supportive Care	• Additional language was inserted throughout for precautionary measures for this trial regarding medications and CYP substrates.
Section 14.0; Body Fluid Specimens	• Footnote 1; additional language was added for clarification.
Section 15.0, Drug Information	• Section 15.15; an editorial change was made. • Section 15.16; Language was removed and replaced for updated potential drug interactions. • 15.17; an editorial change was made.
Section 16.0, Statistical Considerations and Methodology	• Administrative and editorial changes were made throughout Section 16.0 for study clarification.
Section 17.0, Pathology Considerations/Tissue Biospecimens	• The table and sections were edited to change tissue information needed for study purposes.
Section 20.0, References	• A reference was edited to reflect the most current information.
Appendix I, Informed Consent Template	• Appendix I was edited to reflect the most current amendment.
Appendix VIII, List of Selected Substrates or Inhibitors of P-gp and Substrates of BCRP Oral Drugs	• This appendix was added for study purposes.
Appendix IX, Examples of Clinical Substrates for CYP3A-Mediated Metabolism	• This appendix was added for study purposes.
Appendix X, Drugs Accepted or Possibly Associated with Risk of QT Prolongation or Torsade de Pointes	• This appendix was added for study purposes.
Appendix XI, List of Selected Potential Sensitive Substrates for UGT1A1	• This appendix was added for study purposes.
Editorial and administrative changes have been made throughout the protocol but do not affect the scientific content or meaning.	

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Summary of Changes in Amendment 7

Section(s)	Change	Rationale
Throughout	Replaced "ACCRU" with "Seattle Genetics, Inc." or "sponsor"	Sponsor name change
Throughout	Added new protocol number: ACCRU-GI-1617, SGNTUC-017	Added Seattle Genetics protocol number.
Cover Page	• Changed the name of the IND Holder from "PPD , MD" to "Seattle Genetics" • Removed study co-chair • Added Sponsor Medical Monitor • Replaced ACCRU Statistician with Seattle Genetics Statistician • Added Seattle Genetics confidentiality statement • Removed the following text: ~~*For any communications regarding this protocol, please contact the person indicated on the Protocol Resource Page. This is a stand-alone document found on the ACCRU web site (www.ACCRU.org)*~~~~Study Chairs~~ ~~√ Study contributor(s) not responsible for patient care.~~ ~~Research Coordinating Center~~ ~~Academic and Community Cancer Research United~~ ~~200 First Street Southwest~~ ~~Rochester, MN 55905~~ ~~FAX# 507-538-0906~~	Updated, as after the IND transfer to Seattle Genetics, the company assumed sponsorship of the study and specific information pertaining to ACCRU processes no longer applies. Added Sponsor Medical Monitor and Sponsor Statistician due to change in responsibilities.
Throughout	Removed references to the ACCRU website.	Removed, to reflect the updated resources.
Throughout	Minor editorial corrections: spelling, formatting, addition of missing items to the TOC (Index) table	To provide more clarity and consistency throughout the document.
Schema	Switched the notes on each side of the Schema diagram: "Off study for Disease Progression, Alternative Therapy, or Withdrawal/Refusal" was moved to the right side and "Off study for any reason other than Disease Progression, Alternative Therapy, or Withdrawal/Refusal" was moved to the left side. Changed "availability" of trastuzumab: ~~McKesson~~Seattle Genetics	Corrected mislabeling. Correction made to reflect changes in the drug procurement

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Section(s)	Change	Rationale
3.17	ECOG Performance Status (PS) of 0, 1, or 2. ~~(Form is available on the ACCRU web site https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html)~~An example form is available in the Study Operations Manual.	Correction made to specify the designated location (Study Operations Manual) of the updated forms
4.0	In the Test Schedule Table: 1. Removed "Mandatory blood sample – whole blood for pharmacogenomics analysis" row 2. Amended text in the Footnote 8: Submission will be ~~once within 12 months of the analysis of the primary endpoint when requested by study chair or designee~~ done upon enrollment. See section 17.0.	Change made to reflect the reduction in blood collection. The footnote update was also captured in Section 17.11 and was performed to reflect the changes in the process.
6.1	Procedures for registering patients are available in the Study Operations Manual. ~~To register a patient, access the ACCRU web page at https://www.accru.org/accru/group/cra.html, go to the Remote Application section, click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at (507) 284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).~~ ~~Instructions for the registration/randomization application are available on the above web page under the Remote Application section, "Remote Application Training."~~ ~~Prior to initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:~~ ~~• Contact the ACCRU Registration Office (507) 284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.~~ ~~• Refer to "Remote Registration, Installation & Entry Instructions" under "Training Material Manuals."~~	Removed, as specific details about procedures for registering patients are outlined in the Study Operations Manual.

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Section(s)	Change	Rationale
6.3	Documentation of IRB approval must be on file with ~~ACCRU~~ the sponsor before an investigator may register any patients. ~~Approvals should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~ In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file with ~~ACCRU~~the sponsor no less than annually. ~~Approvals should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~ If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved. Annual IRB approval must continue to be submitted to ~~ACCRU~~ the sponsor until site receives notification from ~~ACCRU~~the sponsor that IRB closure can commence and approval of such is granted. ~~IRB approval of study closure should be uploaded through the electronic ACCRU Regulatory Management System (ARMS) at https://accru.vacava.com/.~~	Removed specific information regarding ACCRU electronic regulatory system as it is no longer relevant.
6.4 to 6.9	Removed Sections 6.4 through 6.9. ~~6.4 Prior to accepting the patient registration, the registration application will verify the following:~~ ~~• IRB approval at the registering institution~~ ~~• Patient eligibility~~ ~~• Existence of a signed consent form~~ ~~• Existence of a signed authorization for use and disclosure of protected health information~~ ~~6.5 At the time of registration, the following will be recorded:~~ ~~• Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.~~ ~~• Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.~~	Removed as specific details about registration processes are outlined in the Study Operations Manual, as specified in Section 6.1.

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Section(s)	Change	Rationale
	~~6.6 Treatment cannot begin prior to registration and must begin 7 days after registration.~~ ~~6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.~~ ~~6.8 All required baseline symptoms (see Section 10.62) must be documented and graded.~~ ~~6.9a Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.~~ ~~6.9b Study drug is available on site.~~ ~~6.9c Blood draw kit is available on site.~~	
10.0	**10.0 Adverse Event (AE) Reporting and Monitoring** The site principal investigator is responsible for reporting any/all adverse events to ~~ACCRU~~the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information. ~~ACCRU is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:~~ ~~• Any suspected adverse reaction that is both serious and unexpected.~~ ~~• Any findings from laboratory animal or in vitro testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.~~ ~~• Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.~~ ~~• Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).~~	Removed specific information regarding ACCRU's processes, as following updated sponsorship, all regulatory authority reporting is performed per Seattle Genetics Standard Operating Procedures (SOPs).
10.1	Removed the following definitions: ~~Suspected Unexpected Serious Adverse Reaction (SUSAR)~~	Removed, as information related to Suspected Unexpected Serious Adverse Reactions (SUSAR), Suspected Adverse Reaction, and

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Section(s)	Change	Rationale
	~~A SUSAR is a serious adverse reaction or event, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or package insert). The Investigator must determine the relationship of the event to study agent based on information available at the time of the initial reporting. The initial assessment may be revised as new information becomes available.~~ ~~Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.~~ ~~NOTE: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).~~ ~~Suspected Adverse Reaction~~ ~~Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.~~ ~~Expedited Reporting~~ ~~Events reported to sponsor within 24 hours, 5 days, or 10 days of study team becoming aware of the event.~~ ~~Routine Reporting~~ ~~Events reported to sponsor via case report forms~~ ~~Events of Interest~~ ~~Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).~~	Expedited and Routine Reporting are covered by Seattle Genetics SOPs and are outside of the scope of the individual site(s). Removed Events of Interest as ACCRU's definition does not align with Seattle Genetics' definition.
10.2	Added the following text: Diagnosis vs. Signs or Symptoms	Added the Seattle Genetics standard language for more clarity.

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Section(s)	Change	Rationale
	In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event. If applicable: Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI Common Terminology Criteria for Adverse Events (CTCAE) terms of "cytokine release syndrome," "acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion related event, each sign or symptom should be recorded separately with its level of severity. Progression of Underlying Malignancy Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or serious adverse event (SAE). The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.	
Prior 10.4	~~10.4 Expectedness~~ ~~Determination of whether an event is expected or unexpected should be determined as outlined below.~~ ~~10.41 Expected events~~	Removed, as assessment of expectedness will not be performed by the clinical sites, but will be performed by Seattle Genetics.

Section(s)	Change	Rationale
	~~Those events described within the Section 15.0 of the protocol, the study-specific consent form, package insert and/or the investigator brochure, or otherwise described in the general investigational plan.~~ ~~10.42 Unexpected adverse events~~ ~~Those events not listed in Section 15.0 of the protocol, the study specific consent form, package insert and/or in the investigator brochure (or are not listed at the specificity or severity that has been observed), or is not consistent with the risk information described in the general investigational plan.~~ ~~Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.~~ ~~10.43 Suspected Unexpected Serious Adverse Reaction (SUSAR)~~ ~~A SUSAR is a serious adverse reaction or event, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure or package insert). The Investigator must determine the relationship of the event to study agent based on information available at the time of the initial reporting. The initial assessment may be revised as new information becomes available. SUSARs include any incident, experience, or outcome that meets all of the following criteria:~~ ~~• Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;~~ ~~• Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and~~ ~~• Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.~~	

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Section(s)	Change	Rationale
	~~Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.~~ ~~If the event meets the criteria for a SUSAR, submit to your IRB as required by your institutional policies.~~	
10.41	~~Investigational Agents and Commercial Agents on the SAME Arm~~ ~~When commercial agents are used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.~~ ~~These aEs should be assessed as specified in the appropriate IND/IDE Reporting Table in Section 10.822.~~ Relationship of the Adverse Event to Study Treatment The relationship of each AE to each study treatment (tucatinib and trastuzumab) should be evaluated by the investigator using the following criteria: Related: There is evidence to suggest a causal relationship between the drug and the AE, such as: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture) Unrelated: Another cause of the AE is more plausible (e.g., due to underlying disease o occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatmer a causal relationship is considered biologically implausible	Replaced the content of the Section 10.41 (prior 10.51), as relatedness will be reported in relations to each study drug (tucatinib and trastuzumab) in the combination treatment, as opposed to the regimen in general.

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Section(s)	Change	Rationale
10.5111	Reportable categories of death: • Death attributable to a CTCAE term • Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life • Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF. • ~~Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5~~ • ~~Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5~~ • ~~Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.~~	Updated the language on death to align with the Seattle Genetics standard language.
10.513	An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.	Added the language on reporting of serious events to align with the Seattle Genetics standard language.
Prior 10.62, 10.621, and 10.622	~~10.62 Non-Serious Events~~ ~~A non-serious adverse event is defined as any of the following that do not meet serious criteria as previously outlined:~~ ~~10.621 Grade 2 aEs deemed possibly, probably, or definitely related to the study treatment or procedure.~~ ~~10.622 Grade 3 and 4 aEs regardless of attribution to the study treatment or procedure~~.	Removed, as this definition does not align with Seattle Genetics' definition.
10.62	In general, an asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment is considered an event of special interest and must be	Removed specific information regarding ACCRU's processes to

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Section(s)	Change	Rationale
	reported as a serious adverse event to ~~ACCRU~~ the sponsor ≤1 business day of discovery of the event. ~~ACCRU will notify Seattle Genetics ≤1 business day of site notification.~~	reflect the changes associated with the updated sponsorship.
10.7	Removed the table for Reporting Timeframes and Mechanisms and added the following language: Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen. For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included: • Patient number • Date of event onset • Description of the event • Study treatment, if known • Investigator's causality assessment The completed SAE form is to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form). Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.	Removed the table for Reporting Timeframes and Mechanisms and added the updated information on SAEs (per Seattle Genetics standard SAE reporting language) in Section 10.7, on Adverse Events of Special Interest (AESI) in Section 10.73, and on pregnancies in Section 10.83.
10.72 (prior 10.82)	~~Expedited Reporting Timeframe and Mechanism~~ ~~10.821 Expedited Reporting Mechanism~~ ~~For adverse events meeting criteria for expedited reporting and occurring within 30 days of the last dose of investigational agent:~~ ~~• Complete the ACCRU Adverse Event Expedited Report Form, located on the ACCRU website: (https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html) and submit the completed form to the ACCRU SAE Coordinator via fax (507.284.9628) within the timeframe outlined in the table(s) below.~~	Removed the section, as all Expedited Reporting.to regulatory authorities will be performed by Seattle Genetics as per Seattle Genetics SOPs.

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Section(s)	Change	Rationale
	• The ACCRU SAE Coordinator will notify Industry Partner via email to Drug.safety@seagen.com and ACCRU IND Coordinator as required. • The ACCRU IND Coordinator will assist ACCRU sponsor-investigator in notifying FDA if required. • Complete all required site-specific reporting procedures.	
Prior 10.822	10.822 Expedited Reporting Timelines for Investigational Agents **FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)** **NOTE:** Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in **ANY** of the following outcomes: 1. Death 2. A life-threatening adverse event 3. An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5. A congenital anomaly/birth defect. 6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). **ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.	Removed the section, as all Expedited Reporting to regulatory authorities will be performed by Seattle Genetics as per Seattle Genetics SOPs.

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Section(s)	Change	Rationale

~~Hospitalization~~	~~Grade 1 and Grade 2 Timeframes~~	~~Grade 3-5 Timeframes~~
~~Resulting in Hospitalization ≥24 hrs~~	~~7 Calendar Days~~	~~24 Hour; 3 Calendar Days~~
~~Not resulting in Hospitalization ≥24 hrs~~	~~Not required~~	

~~**Expedited AE reporting timelines are defined as:**~~

- ~~"24 Hour; 3 Calendar Days" – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24 hour report.~~
- ~~"7 Calendar Days" – A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.~~

~~[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:~~

~~**Expedited 24 hour notification followed by complete report within 3 calendar days for:**~~

- ~~All Grade 3, 4, and Grade 5 aEs~~

~~**Expedited 7 calendar day reports for:**~~

1. ~~Grade 2 aEs resulting in hospitalization or prolongation of hospitalization~~

~~[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.~~

~~Effective Date: May 5, 2011~~

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Section(s)	Change	Rationale
10.73 (prior 10.84)	~~10.841 AESI Reporting Mechanism~~ Within 24 hours of observing or learning of an event meeting criteria for an AESI (Section 10.7), investigators are to report, email or fax (see email or fax number specified on the SAE report form), the event to the sponsor's Drug Safety Department, regardless of the relationship of the event to the study treatment regimen. ~~For events meeting criteria for adverse event of special interest (AESI) reporting and occurring within 30 days of the last dose of investigational agent (Section 10.7):~~ ~~1. Complete the ACCRU Adverse Event Expedited Report Form, located on the ACCRU website: (https://www.accru.org/accru/forms/NonProtocolSpecificForms/index.html) and submit the completed form to the ACCRU SAE Coordinator via fax (507.284.9628) within the timeframe outlined below.~~ ~~2. The ACCRU SAE Coordinator will notify Industry Partner via email to Drug.safety@seagen.com within the timeline outlined below.~~ ~~NOTE: For events that meet criteria for both an AESI and a severe adverse event (Section 10.61), only the SAE reporting mechanism and timeline should be used.~~ ~~10.842 AESI Reporting Timeline~~ ~~3. Events meeting criteria for AESI should be reported to ACCRU within 21 days of learning of them.~~ 4. ~~ACCRU will forward all AESI forms to Seattle Genetics within 24 hours of their receipt.~~	Updated the language on reporting of AESIs to align with Seattle Genetics standard language.
10.83	The investigator should report, email or fax (see email or fax number specified on the SAE report form), all pregnancies, including those of the partners of male patients, within 24 hours to ~~ACCRU~~the sponsor's Drug Safety Department using Pregnancy Report form. ~~The funding sponsor will be notified by ACCRU within 2 business days.~~ The sponsor may ask for follow up evaluation of the pregnancy, fetus, and child.	Updated the information on reporting of pregnancies.
Throughout	Replaced CTCAE v4.0 to CTCAE version 4.03	Updated the version of CTCAE.
13.1	NOTE: Subjects with signs of clinical benefit (e.g., mixed response, symptom improvement, demonstrable slowing of progression, progression rate of <20% over 6 months) who are tolerating treatment may be allowed to continue treatment past formal radiologic progression (i.e. RECIST) if such treatment is considered in the subject's best	Updated, to reflect the changes in the process.

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Section(s)	Change	Rationale
	interest by the subject, the treating physician, and the ~~ACCRU study chair~~Sponsor Medical Monitor.	
13.7	A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. ~~On study material and the End of Active Treatment/Cancel Notification Form must be submitted.~~ The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.	Removed, as the specific instructions on which forms to complete for this population are provided in CCGs.
14.1	14.1 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol: 1. Removed "Mandatory - EDTA K2 (purple) - Whole Blood" row 2. Changes in the footnote: 4. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions found in the Central Laboratory Manual ~~(see Section 14.2 for detailed shipping instructions.)~~	Updated, to reflect the reduction in the blood collection and location of shipping instructions.
14.111 to 14.114	~~14.111~~ The kit contains supplies and instructions for collecting, processing, and shipping specimens. Refer to the Central Laboratory Manual for instructions regarding the kit supply, re-ordering, specimen collection, processing, and shipping. ~~14.112 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. A small but sufficient supply of the specimen collection kits should be ordered prior to patient entry. Unused/expired kits should be disposed of per institution policy. Do not send unused kits back to BAP. Supply Order Forms must be filled in completely and legibly for quick processing.~~ ~~14.113 Kits will be sent via FedEx Ground at no cost to the participating institutions. Allow up to two weeks to receive the kits. Kits will arrive inside the shipping boxes.~~ ~~14.114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx account number or alternate billing number for express service. ACCRU will not cover the cost for rush delivery of kits.~~	Removed, as the specific instructions on procurement of kits is listed in the Central Laboratory Manual.

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Section(s)	Change	Rationale
14.2	14.2 Shipping and Handling Refer to the Central Laboratory Manual for details on shipping and handling. ~~14.21 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit, and specimen collection labels are completed and filled in correctly.~~ ~~14.22 Specimens must be shipped the same day they are drawn.~~ ~~14.23 Ship tubes with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.~~ ~~14.24 Ship specimens via Priority Overnight service, Monday – Thursday, to BAP Freezer according to kit instructions. Do not send samples on weekends or just prior to federal holidays. If a patient can only be seen on Fridays, email the Biospecimen Manager (found on resource page) with the sample information and FedEx tracking number.~~ ~~14.25 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an air bill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Freezer.~~ ~~14.26 BAP Freezer will receive the samples and immediately forward specimens to the ACCRU Research Base BAP Shared Resource, Hilton SL 21, Attention: BAP Supervisor.~~	Removed specific information regarding shipping and handling of body fluid biospecimens as the updated information is provided in the Central Laboratory Manual.
14.311 and 14.312	~~14.311 Whole blood for pharmacogenomics~~ ~~DNA will be extracted from whole blood and stored for future pharmacogenetic assays (e.g., genetic polymorphisms such as those known to regulate angiogenesis, inflammation, immunity, auto-immunity, and antibody or drug action of clearance) that may correlate with efficacy and tolerability. The Duke Phase I Biomarker Laboratory located at Duke University may analyze the DNA for the presence of markers of interest using standard laboratory protocols.~~ 14.31~~2~~1 Soluble protein (blood-based) biomarkers	Change made to reflect the reduction in blood collection. Analyses of biospecimens will be performed by the central laboratory and no longer by the Duke Phase I Biomarker Laboratory.

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Section(s)	Change	Rationale
	Blood (platelet poor plasma, serum, and white blood cells (buffy coat)) will be collected at baseline, every restaging, and progression for future analysis. ~~The Duke Phase I Biomarker Laboratory located at Duke University may analyze for the following.~~ Analyses may include, ~~-~~but are not limited to soluble HGF, c-MET, EGF, HBEGF, HER1-3, VEGFA-D, PlGF, VEGFR2, GAS6, AXL, SDF1, Ang2, and TIE-2. Additional biomarkers may also be explored using multiplex array technology. Final biomarker selection will reflect the best science at the time of analysis. 14.31~~3~~2 Plasma for mutational analysis Blood (platelet poor plasma) to assess the molecular profile of circulating tumor DNA (ctDNA) will be collected at baseline, every restaging, and at the 30-day post-treatment visit. ~~The Duke Phase I Biomarker Laboratory located at Duke University may analyze for the following, Analyses may include,~~ Analyses may include, but are not limited to HER2 amplification, EGFR amplification, BRAF mutations, and extended KRAS/NRAS testing (exons 2, 3, and 4). Final biomarker selection will reflect the best science at the time of analysis.	
15.0	Investigator brochure will be provided to participating sites ~~and stored on the ACCRU website~~.	Removed, to reflect the administrative changes.
15.18	An initial supply of tucatinib will be auto-shipped to participating sites upon ~~receipt by ACCRU of signed Pharmacy Contact Form and initial IRB approval~~site activation by the sponsor. Thereafter, each participating ~~ACCRU~~ treating location will order the drug from Seattle Genetics. Email the ~~Drug Order Request~~ Investigational Drug Request/Shipment Record Form (found in the ~~forms packet~~ Pharmacy Binder) to: ~~IST@seagen.com~~ mountaineer@seagen.com Each participating ~~ACCRU~~ treating location will be responsible for monitoring the supply of tucatinib and will use the ~~Drug Order Request~~ Investigational Drug Request/Shipment Record Form to order additional supplies as needed. ~~Outdated~~Expired or remaining drug is to be destroyed on-site as per procedures in place at each institution. Contact the sponsor prior to destroying investigational product.	Updates made to reflect the administrative changes in the process of drug procurement.
15.19a	Temperature Excursions Temperature excursions that occur at the site should be reported by the site using the Investigational Product Quality Complaints and Temperature Excursions Form ~~insert~~	Updates made to reflect the administrative changes in the process of drug procurement

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Section(s)	Change	Rationale
	~~sponsor deviation/temperature excursion form name~~ found ~~on the ACCRU web site for this study~~ in the Pharmacy Binder~~and emailed to: IST@seagen.com~~	
15.28	~~Seattle Genetics will provide funding for the procurement of trastuzumab by McKesson. Each participating ACCRU treating location will order the drug from McKesson. Fax the Drug Order Request Form (found on the ACCRU web site) to:~~ ~~McKesson~~ ~~Attn. Clinical Research Services~~ ~~Fax: (919) 256-0794~~ ~~Each participating ACCRU treating location will be responsible for monitoring the supply of trastuzumab and will use the Drug Order Request Form to order additional supplies as needed.~~ Each participating treating location will be responsible for monitoring the supply of trastuzumab and will use the Investigational Drug Request/Shipment Record Form (found in the Pharmacy Binder) to order additional supplies as needed. ~~Outdated~~Expired or remaining drug is to be destroyed on-site as per procedures in place at each institution. Contact the sponsor prior to destroying the investigational product.	Updates made to reflect the administrative changes in the process of drug procurement
16.51	The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. ~~The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.~~	Removed specific information regarding ACCRU's processes of data monitoring to reflect the administrative changes associated with the updated sponsorship.
16.73	Based on prior ~~ACCRU~~ studies involving similar disease sites, ~~we expect about~~ it is estimated that 10% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:	Reworded for clarity.
17.0 and 17.11	• Added language to Section 17: Refer to the Central Laboratory Manual for instructions on preparation and submission of tissue biospecimens. • Changes made to the Summary Table of Tissue Biospecimens for This Protocol (Section 17.11): • To the "Type of tissue biospecimen to submit" column: FFPE tissue block ~~with corresponding H&E slide or up to fifty (50) 5-micron, unstained slides and up to three (3) corresponding H&E slides~~ from **primary tumors present prior to**	Updates made to reflect the changes in the processes.

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Section(s)	Change	Rationale
	study entry (if available). If no primary tumor tissue is available, metastatic biopsies should be used. • To the "when to submit" column: ~~Within 12 months of the analysis of the primary endpoint when requested by study chair or designee~~Upon enrollment	
17.2, 17.21 to 17.29	17.2Paraffin Embedded Tissue Blocks~~/Slides~~ ~~17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) from original surgery at the time of diagnosis. Biopsy material obtained at the time of metastatic diagnosis may be submitted. A corresponding H&E slide for each submitted block must be provided to permit quality assessment of each tissue block. The H&E slide for each block should be reviewed by the institution's pathologist to assess tissue quality prior to submission.~~ If there is no suitable FFPE block available, contact the medical monitor.~~17.22 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, cut up to 50 (fifty) 5 micron sections and mount on charged glass slides. Label the slides with ACCRU patient ID number, accession number, and order of sections, and thickness of sections. NOTE: do not place "sticky" labels directly on slides. H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). The H&E slides should be reviewed by the institution's pathologist to assess tissue quality prior to submission. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. Ideally, each slide should have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides.~~ 17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment: ~~• Paraffin embedded tissue blocks with corresponding H&E slide(s) (OR up to 50 (fifty) unstained slides with corresponding H&E slide(s).~~ ~~• Specimen Submission: Tissue form~~ ~~• Surgical Pathology Report~~ ~~• Operative Report (optional)~~ ~~NOTE: Please include the ACCRU patient ID number on all materials listed above.~~	Removed, as specific information regarding shipping and handling of tissue specimens is provided in the Central Laboratory Manual, as specified in Section 17.0.

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Section(s)	Change	Rationale
	17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. 17.25 Tissue specimens must be shipped ≤30 days from date of submission request by study chair or designee. 17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet). 17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base: ~~ACCRU Operations Office~~ ~~Attn: PC Office (ACCRU-GI-1617)~~ ~~RO_FF_03_24 CC/NW Clinic~~ ~~200 First Street SW~~ ~~Rochester, MN 55905~~ 17.28 When an appropriate request is submitted, the ACCRU Operations Office will forward the block(s) to the ACCRU Research Base PRC, 2915 Valley high Drive, Mayo Clinic Rochester (Attn: PRC Supervisor) for processing as outlined in Section 17.3. ~~17.29 If a corresponding H&E wasn't submitted by the institution with the block, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block and will be forwarded to the ACCRU Research Base PRC for review under the research base's protocol for assessing tissue quality for the proposed correlative studies, unless the tumor size is too small. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed. After ACCRU research base pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the ACCRU Operations Office.Operations Office.~~	
17.3	17.31 At the completion of the study, any unused/remaining material will be stored ~~in the ACCRU Central Operations Office or Duke Phase I Biomarker Laboratory (Attn.: Pathology Coordinator)~~ for future research ~~according to the patient consent permission (see Section 6. 5)~~. Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy,	Updated the biospecimen repository information per Seattle Genetics SOPs.

Section(s)	Change	Rationale
	and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval. 17.32 For patients who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seattle Genetics and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of sensitivity and resistance mechanisms to tucatinib, and the identification of biomarkers of HER2+ metastatic colorectal disease and response/resistance to therapy. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met. ~~Banking of tumor tissue, according to the patient consent permission (see Section 6. 5), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU studies).~~ ~~17.33 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.~~	
18.0	Removed all 3 Submission Timetables: • Initial Material(s) • Test Schedule Material(s) • Follow-up Material(s) Removed tables were replaced with the following language: Refer to the Case Report Form Completion Guidelines (CCG) for the methods of data collection.	Removed, as specific information regarding methods of data collection are provided in the CCG.

Appendix I	• Removed a sample of Informed Consent Template for Cancer Treatment Trials as Appendix I, and
	• Original Appendices II through XI were renumbered to Appendix I through X.
	  • Added text to the Appendix I (ACCRU-GI-1617, SGNTUC-017 [MOUNTAINEER] Study Assessment)
	  Local laboratories will perform all laboratory tests, and results will be provided to the investigator. Blood and urine samples for hematology, serum chemistry, and urinalysis will be prepared using standard procedures. With the exception of pregnancy testing, results of clinical laboratory tests are to be submitted to the central laboratory. Laboratory results will be reviewed by the investigator for clinical significance.
		ICF template was removed from the protocol to provide consistency with Seattle Genetics document development.
		Added text to reflect the administrative change in the Laboratory Assessment process.

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Section(s)	Change	Rationale
Appendix II	Tumor Assessments Tumor response will be assessed using RECIST 1.1 Criteria. Radiographic imaging will be performed with CT or MRI. The same method for tumor assessment should be employed at every assessment. Imaging will be performed every 9 weeks (every 3 cycles). If the patient is clinically stable after ~~two years (34 cycles)~~12 month of treatment, CT or MRI of the chest, abdomen, and pelvis may be performed once every 12 weeks (every 4 cycles +/- 14 days).	Updated for the consistency with Section 4 (Test Schedule).
Appendix VI	•It is recommended that if you miss a scheduled dose of tucatinib and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, you should not take the missed dose but should wait and take the next regularly scheduled dose. If you miss a dose, place a check "0" under the date~~, but remember to take your prescribed dose at the next regularly scheduled time~~.	Added text to the Patient Drug Diary to provide more clarity.
Appendix XI	Added appendix XI	Added to align with Seattle Genetics document development.
Appendix XII	Added Summary of Changes for Amendment 2 through 7.	Added to align with Seattle Genetics document development.

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Summary of Changes in Amendment 8

Section(s)	Change	Rationale
Title page	Added a brief title.	To align with protocol template
Throughout	Revised ACCRU (IST) language with the standard Seattle Genetics template language	To have the protocol that better reflects company's processes and to accommodate changes due to updated sponsorship (the IND transfer to Seattle Genetics occurred on the 17-Sep-2019), the document was transferred into the Seattle Genetics protocol template
Synopsis	Addition of synopsis	To align with the protocol template. There was no synopsis in the ACCRU template (original protocol through the Protocol Amendment A07)
Synopsis, 2, 3.1, 4	Added indication: • Patients with HER2-positive, RAS wild-type, unresectable or metastatic CRC who, unless contraindicated, have previously received systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients whose disease has dMMR proteins or is MSI-H must also have received an anti-PD-(L)1 mAb, if indicated.	To add clarity
Throughout	Addition of 2 cohorts to the study: tucatinib given in combination with trastuzumab (Cohort B) and tucatinib monotherapy (Cohort C).	Cohort B was added to assess efficacy (confirmed Objective Ressponse Rate [cORR]) and safety of the dual therapy for mCRC subjects. Cohort C was added to better characterize the antitumor activity of tucatinib when used as a monotherapy.
1.3.2 and 1.3.3	Updated the text pertaining to the overview of clinical tucatinib studies.	Reflects the latest updates for tucatinib clinical trials
1.4 and 1.6	Addition of the "widely adopted national (US) guidelines for the treatment of colon cancer".	Reflects an update to the current guidelines for treatment of colon cancer patients
1.6	Addition of the interim data from the current MOUNTAINEER protocol.	Reflects the latest data update for the MOUNTAINEER study
Synopsis, 2, 9	Amendment of the primary objective (to cORR) and addition of new study objectives (secondary, and exploratory) for the combination therapy and monotherapy cohorts of the study as follows: • To determine the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, as measured by cORR (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria), according to blinded independent central review (BICR) assessment	Evaluation of tucatinib given in combination with trastuzumab and tucatinib monotherapy

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Section(s)	Change	Rationale
	• To evaluate the antitumor activity of tucatinib given in combination with trastuzumab, in Cohorts A+B, by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment • To evaluate the antitumor activity of tucatinib monotherapy, in Cohort C, as measured by ORR by 12 weeks of treatment (RECIST 1.1), according to BICR assessment • To assess the DOR in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment • To assess the safety and tolerability of tucatinib monotherapy, in Cohort C • To assess the PFS in subjects treated with tucatinib monotherapy (RECIST 1.1), in Cohort C, according to BICR assessment • To assess the OS in subjects treated with tucatinib monotherapy, in Cohort C • To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with trastuzumab, in Cohorts A+B • To explore health resource utilization Removed clinical benefit rate (CBR) from the objectives. Updated objectives and endpoints to state that all assessments will be done by BICR. Amended endpoints to reflect the objectives.	
Synopsis, 3	Planned enrollment was increased from 40 to 110 subjects. As of Amendment 8, 70 newly enrolled subjects will be randomized to either tucatinib given in combination with trastuzumab (40 subjects randomized to Cohort B) or tucatinib monotherapy (30 subjects randomized to Cohort C).	Evaluation of tucatinib given in combination with trastuzumab and tucatinib monotherapy
3.1.1, and 7.7	As of Amendment 8, safety over the course of the study will be evaluated by safety monitoring committee (SMC).	Reflects transfer of data and safety monitoring function from Study Chair to SMC
3.1.2	Addition of stopping criteria.	Reflects changes to the study design
Synopsis, 3.1.3	Updated the study schematic.	Reflects changes to the study design
3.2.1	Reworded the rationale for selection of doses and regimen.	Clarification
Synopsis, 4.1, 7.1, 7.4, 7.4.3, and APPENDIX A	Specified that: • IHC testing must be done following the package insert's interpretational manual for breast cancer. • Confirmatory HER2 testing will be done in the central laboratory. Added:	Reflects changes to the study design.

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Section(s)	Change	Rationale
	• If archived tissue is not available, then a newly-obtained baseline biopsy of an accessible tumor lesion is required.	
Synopsis, 4.1	The baseline platelet count was changed from "≥75,000/mm^3" to "≥100 x 10^3/µL; subjects with stable platelet count from 75-100 × 10^3/µL may be included with approval from medical monitor"	Clarification
Synopsis, 4.1	The baseline laboratory hemoglobin level was changed from "≥8.0 g/dL" to "≥9.0 g/dL"	Added flexibility
Synopsis, 4.1	The inclusion criteria for pregnancy was clarified to include an agreement for females of childbearing potential not to try to become pregnant during the study and for at least 7 months after the final dose of study drug, and agreement to not donate ova, starting at the time of informed consent and continuing through 7 months after the final dose of study drug. Added hormonal methods of contraception. In addition, the timing of males who agreed not to donate sperm during the study was clarified to "starting at the time of informed consent, continuing throughout the study period and for 7 months after discontinuation of study drug."	Added flexibility, clarification, and alignment with the protocol template
Synopsis, 4.2	Added "decreased absolute neutrophil count, which must have resolved to ≤ Grade 2" clause to the Toxicity Related to Prior Cancer Therapies criterion"	Clarification
Synopsis, 4.2, 5.2.2.1, 5.3.4, APPENDIX E and APPENDIX F	Updated the Concomitant Medication Exclusion criterion to as follows: Have used strong CYP2C8 inhibitor within 5 half-lives of the inhibitor, or have used a CYP2C8 inducer within 5 days prior to first dose of study treatment. CYP3A4 or CYP2C8 inducers and strong CYP2C8 inhibitors are also prohibited as concomitant medications within 2 weeks of discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks before enrollment and during study treatment. Removed "Require therapy with warfarin or other coumarin derivatives (non-coumarin anticoagulants are allowed)" criterion. Updated information on CYP3A4 and CYP2C8 inhibitors/inducers, Appendix E and Appendix F, respectively.	Reflects the latest updates from tucatinib clinical studies

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Section(s)	Change	Rationale
Synopsis, 4.2	Updated the history of another malignancy exclusion criterion from "≤2 years prior to registration which required systemic treatment" to "within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy"	Alignment with the protocol template
Synopsis, 4.2	Updated Hepatitis C exclusion criterion to as follows: Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks	Added flexibility for enrollment
5.1, 5.2	Updated treatment administration to include Cohorts B and C	Reflects changes to the study design
5.2.3	AE-specific Dose Modification table for tucatinib and trastuzumab was modified to reflect the latest updates from the clinical studies and separated into 4 tables: • Table 5-3 Dose modifications for infusion-related reactions for trastuzumab • Table 5-4 Dose modifications for clinical AEs related to either tucatinib or trastuzumab • Table 5-5 Dose modifications of tucatinib for liver function abnormalities • Table 5-6 Dose modifications guidelines for left ventricular dysfunction	Clarification
5.2.3	Dose modification for "Blood bilirubin increased at Grade 2" was removed and at an instance of "Blood bilirubin increased at Grade 3" it is now recommended to "HOLD until severity ≤ Grade 2", instead of "≤ Grade 1".	Changes to the dose modification were performed to reflect the updates to the safety practices
5.3.3, 5.3.4	Updated the language in Concomitant Therapies to be Used with Caution and Prohibited Concomitant Therapies.	Reflects the latest updates from tucatinib clinical studies
5.4, 5.5	Added language for Management of Treatment-Emergent Adverse Events (TEAE) and Treatment Compliance.	Alignment with the protocol template
6, APPENDIX A	Added: EQ-5D-5L and EORTC QLQ C30 questionnaires (C1D1, C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, disease progression, death, toxicity, withdrawal of consent or study closure, and at the EOT). Added only for Cohorts B and C: • Biomarker Plasma collection (at screening) • Randomization (At screening)	Reflects changes to the study design

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Section(s)	Change	Rationale
	• Antibodies to Hepatitis C (anti-HCV) • PK assessment (pre-dose Cycles 2, 3, 4, 5, & 6 and post-dose Cycle 3) • Radiological assessment: every 6 weeks (±7 days) during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy Added for all cohorts: • If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if medically feasible. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are not eligible for enrollment Updated for Cohort A: • Radiological assessment: every 9 weeks during treatment; every 12 weeks after 12 months of treatment if clinically stable (±7 days). Subjects that discontinue for reasons other than documented PD will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy. • Biomarker Plasma and Serum collections at Cycle 1, Cycle 4 and every 3 cycles thereafter (i.e., Cycles 4, 7, 10, etc.) Added: "Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy, if they experience radiographic progression at any time point (as determined by investigator assessment using RECIST 1.1), or if they have not achieved a PR or CR by the week 12 assessment."	
7.3, APPENDIX A	Added information for PK assessments for Cohorts B and C, and for subjects in Cohort C who crossover to the tucatinib + trastuzumab regimen.	Reflects changes to the study design
7.6, APPENDIX A	Added Patient-Reported Outcomes.	Reflects changes to the study design
7.7, 7.8, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7	The standard Seattle Genetics template language was incorporated throughout the section.	Alignment with the protocol template
9.1	Added information on determination of sample size of 110 subjects.	Reflects changes to the study design
9.2	Added the definitions for cORR and ORR by Week 12	Reflects changes to the study design
9.3	Added and updated the information on Statistical and Analytical Plans to reflect changes in the objectives.	Reflects changes to the study design

Section(s)	Change	Rationale
10	Added the standard Seattle Genetics language.	Alignment with the protocol template
APPENDIX B	Added the Lansky Performance Status scale	Alignment with the protocol template
APPENDIX C	Added the appendix per Seattle Genetics template.	Alignment with the protocol template
Appendix IX (removed)	Removed the appendix titled Drugs Accepted or Possibly Associated with Risk of QT Prolongation or Torsade De Pointes.	Results from a clinical pharmacology thorough QT study in healthy volunteers evaluating the potential for tucatinib to prolong the QT interval indicated that multiple doses of tucatinib 300 mg BID did not have a significant effect on the QT interval in healthy volunteers.
5.3.3 and Appendix X (removed)	Removed "sensitive substrates for the UGT1A1 transporter" from the list of Concomitant Therapies to be Used with Caution. Removed the appendix titled List of Selected Potential Sensitive Substrates for UGT1A1.	Reflects the latest updates from tucatinib clinical studies
Throughout	Administrative changes made, as necessary	To fix errors and ensure clarity

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Summary of Changes in Amendment 8.1

Section(s)	Change	Rationale
Synopsis, 4.2	13. Have used a strong CYP2C8 inhibitor within 5 half-lives of the ***inhibitor, or*** have used a CYP2C8 ***or CYP3A4*** inducer within 5 days prior to first dose of study treatment. ~~***CYP3A4 or CYP2C8 inducers and strong***~~ ***Strong*** CYP2C8 inhibitors ***and CYP2C8 or CYP3A4 inducers*** are also prohibited ~~as concomitant medications within 2 weeks of~~ ***in the 2 weeks following*** discontinuation of tucatinib treatment. Use of sensitive CYP3A substrates should be avoided 2 weeks ~~before enrollment~~ ***prior to first dose of study treatment*** and during study treatment.	Clarify the use of concomitant drug that are specific CYP inhibitors or inducers.
Synopsis, 5.3.1.1	Strong ~~inhibitors or inducers of~~ CYP2C8 ***inhibitors and CYP2C8 or CYP3A4 inducers*** are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of tucatinib treatment. ~~Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 2 weeks of discontinuation of study treatment.~~	Clarify the use of concomitant drug that are specific CYP inhibitors or inducers.
5.1.1.6	Tucatinib used during the course of the study should be handled according to the Pharmacy Instructions. Tucatinib ***tablets*** are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction.	Clarify the collection of tucatinib tablets
5.1.2.7	Trastuzumab used during the course of the study should be handled according to its package insert. Trastuzumab ***vials*** are to be tracked and documented from the time of receipt at the site, through subject dosing, and until the sponsor approves of the final return or destruction.	Clarify the collection of trastuzumab vials

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Summary of Changes in Amendment 8.2

Section(s)	Change	Rationale
Title page	Added EudraCT number	Administrative change.
Synopsis, 4.1, APPENDIX C	Appendix C was updated. The inclusion criteria number 12 was updated to align with Appendix C. *d. May choose to practice complete abstinence, if consistent with the subject's preferred lifestyle, as an acceptable form of contraception* ~~d.~~ *e.* If sexually active in a way that could lead to pregnancy, must consistently use highly effective methods of birth control (i.e., methods that achieve a failure rate of <1% per year when used consistently and correctly) starting at the time of informed consent and continuing throughout the study and for at least 7 months after the final dose of study drug administration. *For the full list of highly effective methods of birth control and guidance on contraception r*~~R~~efer to APPENDIX C. ~~for guidance on contraception.~~ ~~Highly effective methods of birth control include:~~ ~~• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)~~ ~~• Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)~~ ~~• Intrauterine device~~ ~~• Bilateral tubal occlusion/ligation~~ ~~• Vasectomized partner~~ ~~• Sexual abstinence when it is the preferred and usual lifestyle choice of the subject~~	Reflects the latest updates of Seattle Genetics guidance on contraception.

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Section(s)	Change	Rationale
Synopsis, 4.1, 7.1, 7.4	HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved ***or CE-marked*** IHC test following the package insert's interpretational manual for breast cancer. 6. Have confirmed HER2-positive mCRC, as defined by having tumor tissue tested at a Clinical Laboratory Improvement Amendments (CLIA)-certified ***or International Organization for Standardization (ISO)-accredited*** laboratory, meeting at least one of the following criteria: a. HER2+ overexpression (3+ immunohistochemistry [IHC]) by an FDA-approved ***or Conformité Européenne (CE)-marked*** HER2 IHC test following the package insert's interpretational manual for breast cancer b. HER2 2+ IHC is eligible if the tumor is amplified by an FDA-approved ***or CE-marked*** HER2 in situ hybridization assay (FISH or chromogenic in situ hybridization [CISH]) following the package insert's interpretational manual for breast cancer c. HER2 (*ERBB2*) amplification by CLIA-certified ***or ISO-accredited*** Next Generation Sequencing (NGS) sequencing assay. Tumor tissue must be submitted to the sponsor-designated central laboratory for confirmatory HER2 testing (by an FDA-approved ***or CE-marked*** HER2 IHC test following the package insert's interpretational manual for breast cancer). HER2 status will be verified by central laboratory analysis using IHC by an FDA-approved ***or CE-marked*** IHC test following the package insert's interpretational manual for breast cancer.	Added EU-specific language for the local IHC testing.
7.4.2	If at any time, genetic results are obtained that may have clinical relevance, IRB/***IEC*** review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required.	Aligned with the rest of the protocol.

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Section(s)	Change	Rationale
1.1, 1.2.1, 1.7, 1.8	Removed US-specific language as appropriate. There are currently no ~~FDA-~~approved therapies for patients with ERBB2 amplified metastatic CRC. After progression on first and second line chemotherapy (FOLFOX and FOLFIRI), the clinical benefit of ~~FDA-~~approved therapies is limited. Once patients with mCRC have progressed on all standard chemotherapy and biological therapies, current ~~FDA-~~approved treatment options include regorafenib and trifluridine/tipiracil (TAS-102). Additionally, trastuzumab is ~~FDA-~~approved as a single-agent and in combination with either chemotherapy or pertuzumab. Trastuzumab will be given at the dose approved ~~by the FDA~~ for single-agent use when administered on a Q3 week cycle.	Removed US-specific language to accommodate the trial expansion in the EU.
3.1.3, 6.6	Updated the End of Study definition ~~The study ends when the last subject completes the last visit, or last contact, discontinues from the study, or is lost to follow-up, whichever occurs first.~~ *The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.4.1).*	Clarifies the definition of End of Study.
4.3	Menopause is defined clinically as 12 months of amenorrhea in a person *born female* over age 45 in the absence of other biological, physiological, or pharmacological causes.	Clarifies the definition of menopause.
Synopsis, 6.3.1, 6.3.2, 6.3.3, 6.4, 7.6, APPENDIX A	Specified that EQ-5D-5L and EORTC QLQ-C30 questionnaires apply to Cohorts B and C only. EQ-5D-5L and EORTC QLQ-C30 questionnaires will be administered *for Cohorts B and C* at: pre-dose Cycle 1 Day 1 (C1D1), C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles thereafter, until treatment discontinuation, PD, death, toxicity, withdrawal of consent or study closure, and at the EOT.	Clarifies the use of questionnaires.
10.0	*For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations.*	Added regulatory considerations for EU/EEA countries.

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Summary of Changes in Amendment 9

Section(s)	Change	Rationale
Synopsis, Sections 3.1.3 (Figure 3-1 footnotes a and c), 6.3.4, 7.2, 7.2.1, and Appendix A footnote o.	In these sections text was updated to indicate subjects with documented PD who have continued on study treatment for clinical benefit will not require continued disease assessments after discontinuing treatment. In the synopsis this included updated text in the study schema footnotes a and c, and in the "Efficacy Assessments" section.	Procedural clarification describing disease assessments for subjects with documented PD who have continued on study treatment for clinical benefit only. Consistency with detailed updates in Section 6.3.6 about disease assessment procedures.
Synopsis, Sections 3.1.3 (Figure 3-1, footnote e), 7.2.1, and Appendix A footnote u.	In these sections text about requiring new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy was added. In the synopsis this included updates to text in the study schema (footnote e), study design, and duration of treatment sections. In Appendix A, footnote u was added.	Consistency with detailed update about new baseline RECIST assessment added to Section 6.3.6 (see below).
Synopsis, Sections 4.1, and 7.4.3	Inclusion criterion 5 and Section 7.4.3: Added text to indicate subjects must be willing and able to provide most recently available tissue blocks.	To account for instances where latest tissue block is exhausted or not available.
Synopsis, Section 4.1	Inclusion criterion 11 was adjusted as follows: • Platelet count change from 100 to 75 × 10^3/uL and note to contact medical monitor for counts from 75 to 100 × 10^3/uL was deleted as it is no longer relevant. • Hemoglobin values were changed from 9 to 8 g/dL	Adjusted to align with original values used in the investigator-sponsored trial protocol.
Synopsis, Sections 4.2, Section 5.3.1.1, and 5.3.5	Exclusion criterion (EC) 13, Concomitant Therapies (in synopsis), and Sections 5.3.1.1 and 5.3.5 were updated with text about CYP2C8 and CYP3A4 inducers to include the qualifier "strong" and adjusted prohibition of use of strong CYP2C8 inhibitors, strong CYP2C8 or CYP3A4 inducers, or sensitive CYP3A substrates following discontinuation from 2 weeks to 1 week. In Synopsis and Section 4.2 EC 13, removed CYP related text that was covered in Section 5.3.1.1. In Section 5.3.1.1 added text about avoiding sensitive CYP3A substrates 1 week prior to first dose of study treatment and during study treatment. In Section 5.3.5 added new bullet: Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment	Consistency with other tucatinib protocols and current harmonized drug-drug interaction recommendations.

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Section(s)	Change	Rationale
	(see APPENDIX H). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.	
Synopsis, Section 4.2	Exclusion criterion 17 was added: Have a hypersensitivity to tucatinib or any of its excipients, to trastuzumab or any of its excipients, or to murine proteins.	New text to align with updates made in tucatinib responses to requests for information.
Sections 3.1, 5.1,	Added cross-reference to Section 6.3.6	Clarification to align with changes made in Section 6.3.6
Section 5.2.3.2	In Table 5-6, removed tucatinib from dose modification guidelines for left ventricular ejection fraction	Based on evaluation of HER2CLIMB data, a causal association between tucatinib and decreased LVEF was not established
Section 5.3.4	Added text indicating moderate CYP2C8 inhibitors should be used with caution.	Consistency with other tucatinib protocols and current harmonized drug-drug interaction recommendations.
Section 5.4	Added text to be consistent with other tucatinib protocols indicating overdose events should be captured on adverse event eCRF per Section 5.4 and reported as discussed in Section 7.7.1.2.	Consistency with other tucatinib protocols
Sections 6.2.2, 6.3.1, 6.3.3, 6.4, 7.7.2, Appendix A footnote f	Aligned vital sign text between these sections.	Consistency between sections
Section 6.3.6 (See Row 2 above as well for related updates)	Added clarification about tucatinib monotherapy and added more detailed text about requiring new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy. As mentioned on Row 2, updates were made throughout the protocol where crossover was discussed to either refer back to this section (Section 6.3.6) and/or to mention requirement for new baseline RECIST assessment for subjects from Cohort C who crossover from monotherapy to doublet therapy.	Detailed procedural clarifications about new baseline assessments for subjects in Cohort C who crossover from monotherapy to doublet therapy. Consistency with updates in Synopsis, Sections 3.1.3 (Figure 3-1, footnote e), 7.2.1, and Appendix A footnote u.

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Section(s)	Change	Rationale
Section 7.7.1.1	Added text to mandate that AESIs be reported within 24 hours to be consistent with other tucatinib studies. Clarified DILI related text – rewrote into text form because table form was potentially ambiguous. Added statement about measuring conjugated and unconjugated bilirubin in cases of hyperbilirubinemia.	Clarifications to be consistent with other tucatinib protocols Clarification only Clarification to assist in determining etiology in cases of hyperbilirubinemia.
Section 7.7.1.2	To "Follow-up for Abnormal Laboratory Results Suggesting Potential DILI", added text about measuring conjugated and unconjugated bilirubin Added text in section called "Dosing Errors" about tucatinib dosing errors and cross-referenced to Section 5.4 Management of Overdose Added text in section called "Left Ventricular Ejection Fraction Decreased" to address reporting for left ventricular ejection fraction decrease and congestive heart failure.	Consistency with updates to Section 7.7.1.1 Consistency with other tucatinib protocols Consistency with other tucatinib protocols
Appendix A	Table 11-2: Added footnote c 'Biomarker samples collected prior to dosing on Day 1 of Cycle 3 and every 3 cycles thereafter (i.e., Cycle 3, 6, 9 etc.) prior to Protocol Addendum 2 (effective date: 20OCT2017).'	Added to indicate that biomarker sample collection times in prior amendments were different. The added text makes it clear that under previous amendments procedures were done per protocol.
Appendix E	Removed text about CYP3A4 inhibitors	Consistency with other tucatinib protocols
Appendix F	The following changes were made: • Strong Inhibitors list: removed clopidogrel • Moderate Inhibitors List: added clopidogrel, deferasirox, teriflunomide Rifampin was changed to a moderate inducer (instead of strong inducer)	Changes to align with current CYP recommendations.
Appendix G	Added row for 50 and 150 mg pills in Instructions header Added +3 day window for end of cycle clinic visit Clarified text about missing/replacing a dose due to vomiting.	Changes to make the Patient Drug Diary more functional and to clarify missing/replaced doses due to vomiting.
Appendix H	Removed content about P-gp inhibitors (This was in Appendix H content). The former Appendix I "Examples of Clinical Substrates for CYP3A-Mediated Metabolism now becomes Appendix H.	These are no longer prohibited concomitant medications.

Section(s)	Change	Rationale
Appendix I	Added a new appendix to include information about Defining Lines of Therapy. This addition means the Investigator's Signature Page becomes Appendix J	Addition to provide clarifications about protocol specific definitions related to lines of therapy.
Throughout	Administrative changes made, as necessary	To fix errors and ensure clarity

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Summary of Changes in Amendment 10

Section(s)	Change	Rationale
Throughout	Seattle Genetics changed to Seagen throughout	Corporate name change
Section 1.3.2.3 and Section 1.6, Section 5.3.1.2	Added new ongoing studies with tucatinib and HER2CLIMB (ONT-380-206) primary results	To provide updated tucatinib clinical development information
Synopsis, Section 3.1, Section 9.1,	Clarified 'approximately' 30 subjects will be randomized to and treated in Cohort C	Clarification and consistency with Cohorts A and B
Synopsis Section 3.1 and Section 9.2.1	Updated primary efficacy analysis set	To clarify that the primary efficacy analysis set will consist of all patients in Cohorts A+B.
Synopsis and Section 4.1	Updated contraception language	For consistency with Appendix C
Section 4.4.1, Section 6.3.4, Section 7.2.1, Section 7.7.7.1 and Appendix A	Clarified timing of radiographic assessments for subjects with documented PD who continue on treatment	To ensure that assessments continue to be performed per the protocol defined assessment schedule
Section 5.4 and Section 7.7.1.2	Removed requirement to report overdose events or dosing errors following the SAE reporting process	Overdose and dosing errors will no longer be captured in the safety database.
Section 5.2.3.2	Revised trastuzumab dose modifications guidelines for LVEF	Consistency with other tucatinib protocols
Synopsis, Section 3.1.3, Section 6.2.1, Section 7.1, Appendix A	Added a pre-screening period	To allow patients on a current chemotherapy regimen who are expected to be eligible for MOUNTAINEER the option to submit a tumor specimen for assessment of HER2 status
Section 6.5, Section 7.7.6.1, Section 9.3.9.5, Appendix A	Added every 6-month assessment of cardiac function (ECHO or MUGA) until 24 months from the last administration of trastuzumab	For alignment with the trastuzumab summary of product characteristics
Section 7.7.1.5	Added requirement for investigator to report SAEs to sponsor	To satisfy SUSAR reporting regulations
Appendix G	Revised Oral Medication Diary	For clarity

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Summary of Changes in Amendment 11

Section(s)	Change	Rationale
Protocol Synopsis, Section 9.3.1.9	The timing of the primary analysis will be based on the time to confirmed ORR per BICR. DOR according to BICR assessment will also be analyzed at this time. ~~The final analysis of cORR and DOR will be conducted when all treated subjects 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.~~ Detailed information regarding the timing of the analysis will be provided in the SAP.	This change allows the primary analysis to be performed at a time when sufficient follow-up has occurred to ensure that all subjects enrolled will have the opportunity to achieve a confirmed response. The SAP will outline timing of the analysis based upon data maturity, taking into account the fact that at 6 months after LPI (last patient enrolled), ~90% of subjects are expected to have at least 8 months follow-up. This approach to the timing of the primary analysis will minimize the risk of excluding confirmed responses from subjects enrolled at the end of the study.
APPENDIX A: SCHEDULE OF EVENTS	~~b At time of radiographic assessments (i.e., prior to Cycle 4, prior to Cycle 7 etc.) which may occur ≤14 days prior to Day 1 of new cycle.~~ ~~c Biomarker samples collected prior to dosing on Day 1 of Cycle 3 and every 3 cycles thereafter (i.e., Cycle 3, 6, 9 etc.) prior to Protocol Addendum 2 (effective date: 20OCT2017).~~	Footnotes no longer apply since all Cohort A subjects have reconsented to a protocol version after Addendum 2.

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Summary of Changes in Amendment 12

Section(s)	Change	Rationale
Synopsis	Added new sub-section "End of Study": The primary analysis for this trial was conducted based on a data cut-off date of 28 March 2022. As the primary objective was met, the decision was made to close the trial. For subjects remaining on study, a last visit contact will occur and subjects who are still receiving treatment will revert to physician care. When applicable, the Sponsor will assist with post-trial access to tucatinib and trastuzumab.	To define the basis for ending the study and plan for last subject visit
Synopsis	Clarified that subjects will have status evaluation every 12 weeks until PD, death, or end of study.	To clarify the timing of follow-up evaluations
Section 1.3.2.3 Clinical Studies	Added results of analysis for primary endpoint.	To document the completion of the primary analysis of the MOUNTAINEER study
Section 3.1.3 End of Study	Deleted: "The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first." Added: "The primary analysis for this trial was conducted based on a data cut-off date of 28 March 2022. As the primary objective was met, the decision was made to close the study. End of study will be defined as last patient, last visit."	To define end of study
Section 6.6 End of Study/End of Follow-up	Deleted: "The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.4.1)."	Moved the end-of study definition to Section 3.1.3. End of Study.
Section 6.7 Post-Study Care	Added section: "At the time of study closure, subjects who are still receiving treatment will revert to physician care. When applicable, the Sponsor will assist with post-trial access to tucatinib and trastuzumab."	To ensure subjects continue to receive care as needed
Section 7.7.7.2 Observation and Follow-up (Cohort A)	Under Follow-up, clarified that subjects will have status evaluation every 12 weeks until PD, death, or end of study. Added: "For subjects remaining on study at the time of study closure, a last visit / contact will occur and subjects who are still receiving treatment will revert to physician care."	To clarify the timing of follow-up evaluations