Protocol Number:	SGNTUC-022
Version:	Amendment 2, 02-Apr-2021
Protocol Title:	**MOUNTAINEER-02:** A randomized, double-blind, placebo-controlled, active comparator Phase 2/3 study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)
Investigational Product:	Tucatinib
Brief Title:	Tucatinib, trastuzumab, ramucirumab, and paclitaxel versus paclitaxel and ramucirumab in previously treated HER2+ gastroesophageal cancer
Phase:	2/3
IND Number:	134840
EudraCT Number	2020-003249-12
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	PPD PharmD, BCOP Tel: PPD E-mail: PPD
SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number SGNTUC-022 **Version** Amendment 2, 02-Apr-2021 **Phase** 2/3	**Product Name** Tucatinib **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

MOUNTAINEER-02: A randomized, double-blind, placebo-controlled, active comparator Phase 2/3 study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)

Study Objectives

Phase 2

Primary Objectives	Corresponding Endpoints
• To determine the recommended dose of paclitaxel when administered in combination with tucatinib, trastuzumab, and ramucirumab	• Frequency of dose-limiting toxicities (DLTs) during the first cycle of treatment with tucatinib, trastuzumab, ramucirumab, and paclitaxel
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, paclitaxel, trastuzumab, and ramucirumab
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated locally-advanced unresectable or metastatic GEC that is HER2+ according to blood-based next generation sequencing (NGS) assay of circulating tumor DNA (ctDNA)	• Objective response rate (ORR; complete response [CR] or partial response [PR]) per Response evaluation criteria in solid tumors (RECIST) version 1.1 according to investigator assessment • Confirmed ORR per RECIST version 1.1 according to investigator assessment • Progression-free survival (PFS) per RECIST version 1.1 according to investigator assessment • Duration of response (DOR; CR or PR) per RECIST version 1.1 according to investigator assessment • Disease control rate (DCR; CR or PR or stable disease/non-CR, non-progressive disease as best objective response) per RECIST version 1.1 according to investigator assessment
• To evaluate the pharmacokinetics (PK) of tucatinib and the tucatinib metabolite ONT-993 • To evaluate the PK of paclitaxel and its metabolites in the presence and absence of tucatinib	• The PK parameters to be calculated for tucatinib, paclitaxel, and their respective metabolites (if applicable) may include but are not limited to: area under the plasma concentration-time curve (AUC) to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), time of C_{max} (T_{max}), trough concentration (C_{trough}), and metabolic ratio based on AUC (MR_{AUC})

Exploratory Objectives	Corresponding Endpoints
• To evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with disease that is HER2-negative according to blood-based NGS assay but HER2+ according to immunohistochemistry (IHC)/in situ hybridization (ISH) assay of a tumor tissue sample	• ORR per RECIST version 1.1 according to investigator assessment • Confirmed ORR per RECIST version 1.1 according to investigator assessment • PFS per RECIST version 1.1 according to investigator assessment • DOR per RECIST version 1.1 according to investigator assessment • DCR per RECIST version 1.1 according to investigator assessment
• To evaluate the correlation between HER2 alterations as detected by blood-based NGS assays and standard tissue-based assays	• Frequency of HER2 alterations according to blood-based NGS assay and according to assays on tumor tissue samples obtained after progression on the most recent line of therapy
• To explore correlations between blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in blood
• To evaluate the PK of tucatinib and ONT-993 in subjects with and without a gastrectomy	• The PK parameters of tucatinib and ONT-993 in subjects with and without a gastrectomy (without maintenance of the pylorus) may include but are not limited to: AUC_{last}, C_{max}, T_{max}, $C_{trough,}$ and MR_{AUC}

Phase 3

Primary Objective	Corresponding Endpoints
• To compare the efficacy of tucatinib and trastuzumab versus placebo, in combination with ramucirumab and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ GEC	*Dual primary endpoints* • Overall survival (OS) • PFS per RECIST version 1.1 according to investigator assessment *Key secondary endpoints* Confirmed ORR per RECIST version 1.1 according to investigator assessment *Other secondary endpoints* • PFS per RECIST version 1.1 according to blinded independent central review (BICR) assessment • Confirmed ORR per RECIST version 1.1 according to BICR assessment • ORR per RECIST version 1.1 according to investigator assessment • ORR per RECIST version 1.1 according to BICR assessment • DOR per RECIST version 1.1 according to investigator assessment • DOR per RECIST version 1.1 according to BICR assessment • DCR per RECIST version 1.1 according to investigator assessment • DCR per RECIST version 1.1 according to BICR assessment

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, trastuzumab, ramucirumab, and paclitaxel
• To evaluate the anti-tumor activity of tucatinib in combination with ramucirumab and paclitaxel	*Secondary Endpoints* • Confirmed ORR per RECIST version 1.1 according to investigator assessment • DOR per RECIST version 1.1 according to investigator assessment *Exploratory Endpoints* • OS • PFS per RECIST version 1.1 according to investigator assessment • PFS per RECIST version 1.1 according to BICR assessment • Confirmed ORR per RECIST version 1.1 according to BICR assessment • ORR per RECIST version 1.1 according to investigator assessment • ORR per RECIST version 1.1 according to BICR assessment • DOR per RECIST version 1.1 according to BICR assessment • DCR per RECIST version 1.1 according to investigator assessment • DCR per RECIST version 1.1 according to BICR assessment
• To assess PROs by treatment arm	• Time to deterioration of GEC symptoms as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and EORTC QLQ-OG25 questionnaires • Change from baseline in health-related quality of life (HRQoL) • Utility index values as assessed by the EQ-5D-5L
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of tucatinib in combination with ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, ramucirumab, and paclitaxel
• To evaluate the PK of tucatinib	• The PK parameter to be calculated for tucatinib (if applicable) includes: C_{trough}
• To explore correlations between blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in blood
• To assess HCRU by treatment arm	• Cumulative incidence of healthcare resource utilization, including length of stay, hospitalizations, and emergency department visits

Study Population

Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma
2. HER2+ disease documented since progression of the most recent line of systemic therapy, as follows:
   a. Phase 2 paclitaxel dose optimization stage:
   - HER2 amplification in a blood-based NGS assay performed at a central laboratory, or
   - HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) assay of a tumor tissue sample, processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory

   b. Phase 2 dose expansion stage:
      i. Cohort 2A: HER2 amplification in a blood-based NGS assay performed at a central laboratory
      ii. Cohort 2B: No HER2 amplification by blood-based NGS assay, but HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) assay of a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory

   c. Phase 3: HER2 amplification in a blood-based NGS assay performed at a central laboratory
3. Can supply archival tumor tissue for central review; if an archival sample is not available, the subject may be eligible, following approval by the medical monitor.
4. History of prior treatment with a HER2-directed antibody
5. Progressive disease during or after first-line therapy for locally-advanced unresectable or metastatic GEC
6. Phase 2: Measurable disease according to RECIST version 1.1
   Phase 3: Measurable or non-measurable disease according to RECIST version 1.1
7. Age ≥18 years, or considered an adult by local regulations, at time of consent
8. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1
9. Life expectancy of at least 3 months, in the opinion of the investigator
10. Adequate hepatic function as defined by the following:
    a. Total bilirubin ≤1.5 × upper limit of normal (ULN), except for subjects with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 × ULN
    b. Transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤2.5 × ULN (≤5 × ULN if liver metastases are present)
11. Adequate baseline hematologic parameters as defined by:
    a. Absolute neutrophil count ≥1.5 × 10^9/L
    b. Platelet count ≥100 × 10^9/L; subjects with stable platelet count from 75-100 × 10^9/L may be included with approval from the Medical Monitor
    c. Hemoglobin ≥9 g/dL; subjects with hemoglobin ≥8-9 g/dL may be included with approval from the Medical Monitor
    d. In subjects transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support
12. Estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation as applicable.

13. International normalized ratio (INR) ≤1.5, and prothrombin time (PT) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5 × ULN if not receiving anticoagulation therapy. Subjects on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin. If on warfarin, the subject must have an INR of ≤3 and have no active bleeding (within ≤14 days prior to enrollment or randomization, excluding trace hematuria) or pathological condition that carries a high risk of bleeding (i.e., tumor involving major vessels or known varices). Refer to Section 5.4.2 Prohibited Concomitant Therapy for potential drug interactions with tucatinib and oral anticoagulants.
14. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram or multi-gated acquisition (MUGA) scan documented within 4 weeks prior to first dose of study treatment
15. Urinary protein of ≤1+ on dipstick or routine urinalysis. If dipstick or routine analysis indicates proteinuria ≥2+, then either a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours or the urine protein/creatinine (UPC) ratio must be <1 to allow participation in study
16. For subjects of childbearing potential, the following stipulations apply:
    a. Must have a negative serum or urine pregnancy test (minimum sensitivity of 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 7 days prior to 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 any study drug
    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 any study drug
    d. 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.
17. 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 dose of any study drug
    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
18. The subject must provide written informed consent
19. Subject must be willing and able to comply with study procedures, laboratory tests, and other requirements of the study

Exclusion Criteria

1. Subjects with squamous cell or undifferentiated GEC
2. Having received more than 1 line of prior systemic therapy for locally-advanced unresectable or metastatic disease
3. Having received taxanes ≤12 months prior to enrollment, prior treatment with ramucirumab, or prior treatment with tucatinib, lapatinib, neratinib, afatinib, or any other investigational anti-HER2 and/or anti-EGFR tyrosine kinase inhibitor, or with trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), or any other HER2-directed antibody-drug conjugate

4. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin >360 mg/m²
    - Epirubicin >720 mg/m²
    - Mitoxantrone >120 mg/m²
    - Idarubicin >90 mg/m²
    - Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) >550 mg/m²
5. History of allergic reactions to paclitaxel, trastuzumab, ramucirumab, or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 infusion-related reactions to trastuzumab or ramucirumab that were successfully managed, or known allergy to any of the excipients in the study drugs or placebos
6. Phase 2 paclitaxel dose optimization stage only: history of prior partial or total gastrectomy
7. Treatment with any systemic anti-cancer therapy (including hormonal and biologic therapy), radiation, or an experimental agent, or participation in another interventional clinical trial ≤3 weeks prior to first dose of study treatment.
8. Major surgery within 28 days prior to enrollment or randomization, central venous access device placement within 7 days prior to enrollment or randomization, or planned major surgery following initiation of study treatment
9. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Anemia
    - Alopecia
    - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
10. Clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension ≥150/≥90 mmHg despite standard medical management, as determined by the investigator
    - Any symptomatic history of CHF, left ventricular systolic dysfunction or decrease in ejection fraction
    - Severe dyspnea at rest (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or above) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy, except when therapy is needed for obstructive sleep apnea
11. Known to be positive for hepatitis B by surface antigen expression. Known to be positive for hepatitis C infection (positive by polymerase chain reaction). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks
12. Presence of known chronic liver disease
13. Phase 2: Known to be positive for human immunodeficiency virus (HIV)
    Phase 3: Subjects known to be positive for HIV are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/uL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks
14. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study drug
15. Unable to swallow pills
16. Have used a strong cytochrome P450 (CYP)2C8 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.
17. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures

18. History of malignancy other than GEC within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS of ≥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.
19. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism during the 3 months prior to enrollment or randomization.
20. Chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs, e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide). Aspirin use at doses up to 325 mg/day is permitted.
21. Significant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal tract within 3 months prior to study entry.
22. History of any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment or randomization.
23. History of gastrointestinal perforation and/or fistulae within 6 months prior to enrollment or randomization.
24. Serious non-healing wound or peptic ulcer or bone fracture within 28 days prior to enrollment or randomization
25. History of bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis or chronic diarrhea
26. Active or uncontrolled clinically serious infection
27. Known active central nervous system metastases. 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.

Number of Planned Subjects

Phase 2: Up to approximately 78 subjects will be enrolled and treated

Phase 3: Approximately 500 subjects will be randomized to 3 arms

Study Design

This is an international, multicenter Phase 2/3 study in subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment with a HER2-directed antibody, and have received 1 prior line of therapy in the advanced disease setting.

The 2-stage, 2-cohort, open-label Phase 2 portion will include a paclitaxel dose optimization stage, in which paclitaxel dose escalation will be used to determine the recommended dose of paclitaxel to be given in combination with tucatinib, trastuzumab, and ramucirumab. Subsequently, enrollment will continue, to further evaluate the safety and activity of the regimen in a total of approximately 30 response-evaluable subjects in each of 2 cohorts, once the recommended paclitaxel dose is determined.

The randomized, double-blind, placebo-controlled Phase 3 portion is designed to compare the efficacy and evaluate the safety of tucatinib and trastuzumab versus placebo, in combination with ramucirumab and paclitaxel. The efficacy and safety of tucatinib combined with ramucirumab and paclitaxel will also be evaluated.

Phase 2 - Paclitaxel dose optimization stage

Six subjects will initially be enrolled and treated at paclitaxel 60 mg/m². Subjects can have HER2+ disease according to blood-based NGS assay or IHC/ISH assay of a tumor tissue sample (IHC3+ or IHC2+/ISH+). Once 6 subjects are evaluable for DLT, enrollment will be paused and the Safety Monitoring Committee (SMC) will undertake an evaluation of safety and PK. If necessary, additional subjects will be enrolled to replace subjects who are not evaluable for DLT.

In the 6 DLT-evaluable subjects receiving 60 mg/m²:

- If ≤1 DLT are observed in 6 subjects, the paclitaxel dose will be escalated to 80 mg/m² and evaluated in a further 6 subjects.
- If 2 DLTs are observed in 6 subjects, an additional 3 subjects will be treated at 60 mg/m², for a total of 9 subjects:
  - If ≤2 DLT are observed in 9 subjects, the paclitaxel dose will be escalated to 80 mg/m² and evaluated in a further 6 subjects.
  - If >2 DLT are observed in 9 subjects, the evaluation of the regimen will be halted, or an alternative dose level/schedule may be recommended by the SMC.
- If >2 DLTs are observed in 6 subjects, the evaluation of the regimen will be halted, or an alternative dose level/schedule may be recommended by the SMC.

In the 6 DLT-evaluable subjects receiving 80 mg/m²:

- If ≤1 DLT are observed in 6 subjects, 80 mg/m² will be the recommended dose.
- If 2 DLTs are observed in 6 subjects, an additional 3 subjects will be treated at 80 mg/m², for a total of 9 subjects:
  - If ≤2 DLT are observed in 9 subjects, 80 mg/m² will be the recommended dose.
  - If >2 DLT are observed in 9 subjects, the 60 mg/m² paclitaxel dose will be declared the recommended dose, and evaluation of the regimen will continue in the Dose Expansion stage.
- If >2 DLTs are observed in 6 subjects, the 60 mg/m² paclitaxel dose will be declared the recommended dose, and evaluation of the regimen will continue in the Dose Expansion stage.

The SMC may also recommend the inclusion of additional subjects in any dose level or the evaluation of an alternative dose level/schedule, if necessary. The SMC will continuously monitor subjects for AEs, deaths, other serious adverse events (SAEs), dose modifications, and laboratory abnormalities, with a specific focus on DLTs.

Phase 2 – Dose Expansion stage

Following the paclitaxel dose optimization stage, two cohorts will be opened to further evaluate the safety of the study regimen and undertake an initial assessment of anti-tumor activity. Cohort 2A will enroll subjects with HER2+ disease as determined by HER2 amplification in a blood-based NGS assay of ctDNA performed at a central laboratory at screening. The exploratory Cohort 2B will enroll subjects whose disease did **not** show HER2 amplification in the blood-based NGS assay, but did show HER2 overexpression/amplification by IHC and ISH assay of a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory.

For each type of HER2-positivity evaluated (blood-based NGS assay or IHC/ISH assay of a tumor tissue sample), approximately 30 response-evaluable subjects who have been treated at the recommended paclitaxel dose will be included in Cohort 2A or 2B, in order to further evaluate the safety of the study regimen and undertake an initial assessment of anti-tumor activity. Subjects who are not evaluable for response will be replaced. Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response -evaluable.

The SMC will evaluate the safety of the study regimen throughout the remainder of Phase 2, in the 2 cohorts. At least 6 subjects with a history of prior gastrectomy (without maintenance of the pylorus) will be enrolled in either cohort to evaluate the PK of tucatinib and ONT-993 in this population; alternative dose levels/schedules may be explored depending on the PK of tucatinib in subjects with gastrectomy.

After approximately 30 response-evaluable subjects who are HER2+ according to the blood-based NGS assay have been treated at the recommended paclitaxel dose in the dose optimization stage or in Cohort 2A, and have been followed for at least 6 weeks, a formal analysis of the activity of the regimen will be undertaken. If the ORR per RECIST v1.1 according to investigator assessment is ≥36%, the SMC may recommend that the Phase 3 evaluation of the regimen will be initiated, given that it is safe and tolerable.

Phase 3

Approximately 500 subjects will be randomized ~8:8:1 to either Arm 3A (tucatinib + trastuzumab + ramucirumab + paclitaxel; 235 subjects), Arm 3B (tucatinib placebo + trastuzumab placebo + ramucirumab + paclitaxel; 235 subjects), or Arm 3C (tucatinib + trastuzumab placebo + ramucirumab + paclitaxel; 30 subjects). Randomization will be stratified by region (Asia vs Rest of World), time to progression on first-line therapy for locally-advanced unresectable or metastatic disease (<6 months vs ≥6 months), and history of prior gastrectomy (yes vs no). Subjects, investigators, and staff, and the sponsor study team will be blinded to study arm allocation.

In the Phase 3 portion of the study, an Independent Data Monitoring Committee (IDMC) will periodically review relevant aggregate safety data and will make recommendations to the sponsor on the conduct of the study. Safety will also be monitored in an ongoing basis by the sponsor throughout the study.

Investigational Product, Dose, and Mode of Administration

In subjects in the Phase 2 undergoing PK assessment on Cycle 1 Day 8 and Cycle 2 Day 1, tucatinib should be dosed at approximately the same time as the start of the paclitaxel infusion. The administration order of intravenous (IV) study drugs is paclitaxel first, followed by trastuzumab and ramucirumab, or according to institutional standard of care.

Study treatment will be administered in 28-day cycles.

Phase 2

Tucatinib 300 mg will be administered orally (PO) twice-daily (BID) from Cycle 1 Day 1 onwards. In subjects undergoing Cycle 1 PK assessment, tucatinib will not be administered in the morning; the first dose will be in the evening, after all PK samples have been collected.

A trastuzumab 6 mg/kg IV loading dose will be administered on Cycle 1 Day 1, followed by trastuzumab 4 mg/kg IV on Cycle 1 Day 15 and then Days 1 and 15 of each cycle thereafter. Trastuzumab is not to be administered subcutaneously.

Ramucirumab 8 mg/kg will be administered IV on Days 1 and 15 of each cycle.

Paclitaxel will be administered on Days 1, 8, and 15 of each cycle. The paclitaxel dose will be as follows:

- Paclitaxel dose optimization stage: Planned paclitaxel dose levels are 60 and 80 mg/m² IV
- Dose Expansion stage: recommended dose determined in the dose optimization stage

Alternative dose levels/schedules may be evaluated, as recommended by the SMC.

Phase 3

Arm 3A

Tucatinib 300 mg PO BID starting on Day 1 of Cycle 1.

A trastuzumab 6 mg/kg IV loading dose will be administered on Cycle 1 Day 1, followed by trastuzumab 4 mg/kg IV on Cycle 1 Day 15 and then Days 1 and 15 of each cycle thereafter. Trastuzumab is not to be administered subcutaneously.

Ramucirumab 8 mg/kg will be administered IV on Days 1 and 15 of each cycle.

Paclitaxel will be administered on Days 1, 8, and 15 of each cycle at the recommended dose determined in the Phase 2.

Arm 3B

Tucatinib placebo PO BID from Cycle 1 Day 1 onwards

Trastuzumab placebo in an IV loading dose on Cycle 1 Day 1, followed by trastuzumab placebo IV on Cycle 1 Day 15 and then Days 1 and 15 of each cycle thereafter

Ramucirumab 8 mg/kg IV on Days 1 and 15 of each cycle.

Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 of each cycle

Arm 3C

Tucatinib 300 mg PO BID from Cycle 1 Day 1 onwards

Trastuzumab placebo in an IV loading dose on Cycle 1 Day 1, followed by trastuzumab placebo IV on Cycle 1 Day 15 and then Days 1 and 15 of each cycle thereafter

Ramucirumab 8 mg/kg IV on Days 1 and 15 of each cycle.

Paclitaxel on Days 1, 8, and 15 of each cycle at the recommended dose determined in the Phase 2

Duration of Treatment

Study treatment will continue until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure. If a study drug (tucatinib/placebo, trastuzumab/placebo, ramucirumab, or paclitaxel) is discontinued, study treatment can continue with remaining study drug(s).
In the absence of clear evidence of radiographic progression per RECIST version 1.1, all efforts should be made to continue treatment until unequivocal evidence of radiologic progression per RECIST version 1.1 occurs. No crossover will be allowed.

Efficacy Assessments

Disease response will be assessed by the investigator (in the Phase 2 and 3 portions) and the BICR (in the Phase 3 portion only) according to RECIST version 1.1. Treatment decisions will be made based upon local assessment of radiologic scans. Radiographic disease assessments will evaluate all known sites of disease, preferably using high quality spiral contrast computed tomography (CT), and covering, at a minimum, the chest, abdomen, and pelvis. Positron emission tomography (PET)-CT scans (if high quality CT scan is included) and/or magnetic resonance imaging (MRI) scans may also be used as appropriate, as well as additional imaging of any other known sites of disease (e.g., nuclear bone scan imaging for bone lesions). For each subject, the same imaging modality as used at baseline should be used throughout the study. Disease assessments will be done at screening, and every 6 weeks for the first 36 weeks then every 9 weeks, irrespective of dose holds or interruptions. Subjects that discontinue study treatment for reasons other than documented progressive disease will continue to have disease assessments every 9 weeks until the occurrence of documented progression per RECIST version 1.1, death, withdrawal of consent, or study closure. After disease progression is documented, subjects will be followed every 12 weeks for survival and further anti-cancer therapy.

Pharmacokinetic Assessments

Blood samples for tucatinib, ONT-993, paclitaxel, and paclitaxel metabolite PK assessments will be collected at protocol-defined timepoints (see **PK Sampling Schedule**). Tucatinib and ONT-993 concentrations will be sampled on Cycle 1 Day 8 and Cycle 2 Day 1, and concentrations of paclitaxel and its metabolites will be sampled on Cycle 1 Days 1 and 8 and Cycle 2 Day 1, in all subjects in the paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with gastrectomy. Subjects with a gastrectomy can come from either Cohort 2A or Cohort 2B. In all subjects in the Phase 2 and Phase 3 portions of the study, tucatinib trough drug concentrations will be sampled predose on Day 1 of Cycles 2 to 6. Plasma concentrations of tucatinib, paclitaxel, and their metabolites will be determined using validated liquid chromatography (LC)-mass spectrometry (MS)/MS methods. PK parameters of tucatinib, paclitaxel, and their respective metabolites will be calculated using standard noncompartmental methods. PK parameters to be estimated may include, but are not limited to: AUC_{last}, C_{max}, C_{trough}, T_{max}, and MR_{AUC}.

PRO and HCRU Assessments

The EORTC QLQ-C30, EORTC QLQ- OG25, and EQ-5D-5L patient-reported outcome measures will be administered to assess GEC symptoms and HRQoL/health status information. PROs will be assessed, in the Phase 3 portion, predose on Cycle 1 Day 1, predose on Day 1 of every second cycle (Cycles 2, 4, 6, etc.) until discontinuation of all study treatment, at the end-of-treatment (EOT) visit, and at each follow-up visit until the occurrence of documented progression, death, withdrawal of consent, or study closure. HCRU data will also be collected during treatment and follow-up, including procedures that occur on study, length of stay, hospitalizations, ED visits, planned/unplanned provider visits, medication use, radiology, and other treatments or procedures.

Biomarker Assessments

HER2 status will be determined by blood-based NGS assay or IHC/ISH assay of a tumor tissue sample (IHC3+ or IHC2+/ISH+) at screening. Additional biomarker assessments may include HER2 status by tissue-based NGS as well as an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. Additional exploratory analyses including but not limited to IHC and NGS analysis may be performed to interrogate biomarkers that are associated with tumor growth, survival, and resistance to targeted therapeutics. This assessment may enable the correlation of additional biomarkers with treatment outcome and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor phenotype/genotype in the future.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs and SAEs, physical examination findings, vital signs including weight, electrocardiograms (ECGs), concomitant medications, pregnancy testing, and laboratory tests. Assessment of cardiac ejection fraction will be performed using MUGA scan or echocardiogram.

Statistical Methods

Sample Size Considerations

Phase 2:

The preliminary activity of the study regimen will be formally evaluated in approximately 30 response-evaluable subjects from the dose optimization stage or the dose expansion stage (Cohort 2A) who are HER2+ by the blood-based NGS assay and who were treated at the paclitaxel recommended dose.

The Phase 3 may be initiated if the observed ORR per investigator is ≥36%. With the sample size of 30, it is expected that at least 11 responders will be observed if the underlying ORR is ≥36%. The point estimate and 95% CI for ORR under different underlying ORR for the sample size of 30 is as follows:

ORR	Number of responses in 30 subjects	Lower bound of 95% CI	Upper bound of 95% CI
30%	9	14.7%	49.4%
36%	11	19.4%	55.5%
40%	12	22.7%	59.4%
47%	14	28.6%	66.0%
50%	15	31.3%	68.7%

Response-evaluable subjects in the Phase 2 include all subjects who meet all following criteria: (1) had baseline disease assessment, and (2) received study treatment, and (3) had post baseline assessment or discontinued treatment due to documented disease progression, clinical progression, treatment-related AEs, or death.

Phase 3:

The sample size for this portion of study was calculated based on maintaining 90% power for the dual primary endpoint of PFS with an alpha of 0.02 and 88% power for the dual primary endpoint of OS with an alpha of 0.03. For PFS, 317 events from Arm 3A or 3B are required with 90% power to detect a hazard ratio of 0.67 (4.5 months median PFS in Arm 3B versus 6.75 months in Arm 3A) using a 2-sided log-rank test and alpha of 0.02. For OS, 354 events from Arm 3A or 3B are required with 88% power to detect a hazard ratio of 0.70 (10 months median OS in Arm 3B versus 14.3 months in Arm 3A) using a 2-sided log-rank test and alpha of 0.03. The 2 primary endpoints will be evaluated using parallel testing, with alpha recycling if only one of them meets statistical significance.

Approximately 500 subjects will be randomized in approximately an 8:8:1 ratio to Arm 3A, Arm 3B, or Arm 3C. Approximately 470 subjects are expected to be randomized to the formal comparison of Arm 3A and Arm 3B. Assuming an accrual period of 30 months and a 5% yearly drop-out rate, it is expected that 317 PFS events and 354 OS events out of the 470 subjects will be observed approximately 25 and 39 months after first subject randomized, respectively.

Interim Analyses

The SMC will undertake safety and PK analyses once the first 6 subjects evaluable for DLT in each dose level in the paclitaxel dose optimization stage have been followed for at least 1 cycle. The SMC will conduct additional analyses of safety and PK should a dose level be expanded to include a total of 9 subjects. If alternative paclitaxel dose levels/schedule are evaluated, the SMC will undertake similar assessments.

In the Phase 3, there is no formal interim analysis planned for PFS. An interim efficacy analysis for OS is planned at the time of final analysis for PFS. Approximately 61% of the total OS events are expected to have occurred by the time of the interim analysis. The stopping boundary will be determined using Lan-DeMets spending functions with O'Brien and Fleming boundaries.

Analysis Methods

For Phase 2, "treatment group" will designate each dose level evaluated in the Phase 2 for analyses done in the All-Treated analysis set. For analyses using the Recommended Dose analysis set, 2 treatment groups will be presented: 1) subjects with HER2+ disease according to blood-based NGS assay treated at the paclitaxel recommended dose in the dose optimization stage or Cohort 2A, and 2) subjects who have HER2-negative disease according to blood-based NGS but HER2+ disease according to IHC/ISH assay of a tumor tissue sample treated at the paclitaxel recommended dose in the dose optimization stage or Cohort 2B.

For Phase 3, Arms 3A and 3B will be compared in the ITT analysis set and the Safety Analysis set; Arm 3C will be separately evaluated in these analysis sets.

In the Phase 2, efficacy will be summarized by treatment group in the Recommended Dose analysis set; safety will be summarized by treatment group in the All-Treated analysis set. In the Phase 3, efficacy and PROs will be summarized by treatment group in the ITT analysis set; safety will be summarized by treatment group in the Safety Analysis set.

In the Phase 2, ORR, confirmed ORR, DOR, DCR and PFS per investigator will be summarized by treatment group. In the Phase 3, for the primary endpoints of PFS per investigator and OS, Arm 3A and Arm 3B will be compared using a 2-sided stratified log-rank test. Estimation of the hazard ratio will be based upon the stratified Cox regression model. PFS per investigator and OS will also be summarized using the Kaplan-Meier method, which will be used to estimate the time to event curves, including the median and milestone estimates. All subjects randomized to Arms 3A and 3B in the Phase 3 portion of the study will be included in the primary analysis of PFS and OS.

If only one of the two primary endpoints are statistically significant, the unused alpha can be passed to the other one. If both PFS per investigator and OS are statistically significant, then confirmed ORR per investigator among subjects with measurable disease in the Phase 3 portion will be formally compared between two treatment arms at the two-sided alpha level of 0.05, using a stratified Cochran-Mantel-Haenszel test.

The other secondary efficacy endpoints for the Phase 3 portion, including PFS, ORR per investigator, confirmed ORR per BICR, and DOR and DCR per BICR and per investigator, will be summarized by treatment arm. The PFS per investigator, OS, and confirmed ORR per investigator will be summarized separately for Arm 3C.

In the Phase 3, assessments based on the EORTC-QLQ-C30, EORTC QLQ OG25, EQ 5D 5L and HCRU data will summarized using descriptive statistics by treatment group for Arms 3A and 3B of the ITT set. PRO scores will be analyzed using longitudinal models. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment timepoint may be presented. Time to deterioration will be assessed in specific pre-specified single items from either the EORTC QLQ-C30 or EORTC QLQ OG25; deterioration is defined as a 10-point increase from baseline in the symptom scales and a 10-point decrease from baseline for overall HRQoL.

Safety will be assessed through summaries of AEs, changes in laboratory test results, 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 version 5.0 criteria. All collected AE data will be listed.

Worst post-baseline laboratory values (hematology, coagulation, chemistry, and liver enzyme tests) and change from baseline will be summarized. Abnormal laboratory values (relative to respective normal ranges) will be flagged in listings. The frequency and percentage of subjects with post-baseline clinically significant vital signs will be summarized. Cardiac ejection fraction data will be summarized for the all-treated subjects in Phase 2, by initial dose level, and for the Phase 3 by treatment group.

Extent of exposure for study drugs including frequency of dose holding, dose reductions, and dose discontinuations, as well as treatment compliance (percent of actual to planned dosing) will be summarized.

Statistical analysis methods for PK will include descriptive statistics on plasma concentrations and PK parameters, as well as exploratory analysis of the geometric mean ratios and 90% CIs of AUC_{last} and C_{max} for paclitaxel and its metabolites between Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1, and exploratory analysis of the geometric mean ratios and 90% CIs of tucatinib and ONT-993 between Cycle 1 Day 8 and Cycle 2 Day 1, and between subjects with and without gastrectomy.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 2
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 19
1 INTRODUCTION 22
1.1 HER2+ Gastroesophageal Cancers 22
1.2 Tucatinib 23
2 OBJECTIVES 24
3 INVESTIGATIONAL PLAN 27
3.1 Summary of Study Design 27
3.1.1 Phase 2 28
3.1.2 Phase 3 32
3.1.3 Dose-Limiting Toxicity 33
3.1.4 Safety Monitoring Committee 34
3.1.5 Independent Data Monitoring Committee 34
3.1.6 Stopping Criteria 34
3.1.7 End of Study 35
3.1.8 Method of Assigning Subjects to Treatment Groups 35
3.1.9 Blinding and Unblinding 35
3.2 Discussion and Rationale 36
3.2.1 Rationale for Study Design 36
3.2.2 Rationale for Combination of Tucatinib and Trastuzumab 37
3.2.3 Rationale for Selection of Doses 38
4 STUDY POPULATION 42
4.1 Inclusion Criteria 42
4.2 Exclusion Criteria 44
4.3 Childbearing Potential 47
4.4 Removal of Subjects from Therapy or Assessment 47
4.4.1 Discontinuation of Study Treatment 47
4.4.2 Subject Withdrawal from Study 48
5 TREATMENTS 48
5.1 Treatments Administered 48
5.1.1 Investigational Products 49
5.1.2 Standard of Care 52
5.2 Dose Modifications 54
5.2.1 Tucatinib/placebo Dose Modifications 55
5.2.2 Trastuzumab/placebo Dose Modifications 56
5.2.3 Ramucirumab Dose Modifications 58
5.2.4 Paclitaxel Dose Modifications 60
5.3 Required Premedication and Postmedication 62
5.4 Concomitant Therapy 62
5.4.1 Allowed Concomitant Therapy 62
5.4.2 Prohibited Concomitant Therapy 63
5.4.3 Management of Overdose 64
5.5 Treatment Compliance 64
6 STUDY ACTIVITIES 65
6.1 Schedule of Events 65
6.2 Screening Visit (Days –28 to -1) 65
6.2.1 Baseline Visit (Days –7 to 1) 66
6.3 Randomization (Days –5 to 1) 66
6.4 Treatment Period (28-day cycles) 66
6.4.1 Cycle 1 Day 1 66
6.4.2 Cycle 1 Day 8 (±1 day) 67

6.4.3 Cycle 1 Day 15 (±1 day) 68
6.4.4 Cycle 1 Day 22 (±1 day) 68
6.4.5 Cycles >1 Day 1 (-1 to +3 days) 68
6.4.6 Cycles >1 Day 8 (±1 day) 69
6.4.7 Cycles >1 Day 15 (±1 day) 69
6.4.8 Every 6 Weeks as Determined by Cycle 1 Day 1, through Week 36, then Every 9 Weeks (±7 days) 70
6.4.9 Every 12 Weeks (±14 days) 70
6.5 End of Treatment Visit (30 to 37 days after last dose of any study drug) 70
6.6 Follow-up 71
6.6.1 Follow-up Until Disease Progression (At Least Every 9 Weeks ±1 week) 71
6.6.2 Survival Follow-up (Every 12 Weeks After Disease Progression ±2 weeks) 72
6.7 End of Study/End of Follow-up 72
7 STUDY ASSESSMENTS 73
7.1 Screening/Baseline Assessments 73
7.1.1 Evaluation of HER2 Status at Screening 73
7.2 Response/Efficacy Assessments 74
7.3 Pharmacokinetic Assessments 75
7.4 Biomarker Studies 77
7.5 Biospecimen Repository 77
7.6 Healthcare Resource Utilization 77
7.7 Patient-Reported Outcomes 77
7.7.1 EORTC QLQ-C30 78
7.7.2 EORTC QLQ-OG25 78
7.7.3 EQ-5D-5L – Utility Measurement 78
7.8 Safety Assessments 79
7.8.1 Adverse Events 79
7.8.2 Vital Signs 85
7.8.3 Clinical Laboratory Tests 85
7.8.4 Physical Examination 86
7.8.5 Pregnancy Testing 86
7.8.6 Cardiac Function 86
7.9 Appropriateness of Measurements 87
8 DATA QUALITY CONTROL AND QUALITY ASSURANCE 88
8.1 Site Training and Monitoring Procedures 88
8.2 Data Management Procedures 88
8.3 Access to Source Data 89
8.4 Accuracy and Reliability of Data 89
8.5 Quality Assurance Procedures 89
8.6 Data Handling and Record Keeping 89
8.6.1 Data Handling 89
8.6.2 Investigator Record Retention 90
9 DATA ANALYSIS METHODS 91
9.1 Determination of Sample Size 91
9.1.1 Phase 2 91
9.1.2 Phase 3 91
9.2 Study Endpoint Definitions 92
9.2.1 PFS 92
9.2.2 Overall Survival 92
9.2.3 Objective Response Rate 92
9.2.4 Duration of Response 92
9.2.5 Disease Control Rate 93
9.2.6 Exploratory Endpoints 93
9.3 Statistical and Analytical Plans 93

9.3.1 General Considerations 94
9.3.2 Subject Disposition 97
9.3.3 Subject Characteristics 97
9.3.4 Concomitant, and Further Therapy 97
9.3.5 Exposure 97
9.3.6 Efficacy Analyses 98
9.3.7 Pharmacokinetic Analyses 99
9.3.8 Biomarker Analyses 99
9.3.9 Patient Reported Outcomes and HCRU Analyses 99
9.3.10 Safety Analyses 100
9.3.11 Interim Analyses 101
10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS 102
10.1 Informed Consent 102
10.2 Ethical Review 102
10.3 Regulatory Considerations 103
10.3.1 Investigator Information 103
10.3.2 Protocol Amendments and Study Termination 103
10.4 Study Documentation, Privacy and Records Retention 103
10.5 Clinical Trial Agreement 103
11 REFERENCES 104
APPENDIX A: SCHEDULE OF EVENTS 109
APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION 111
APPENDIX C: GUIDANCE ON CONTRACEPTION 112
APPENDIX D: CYP3A INDUCERS AND THEIR ELIMINATION HALF-LIVES 113
APPENDIX E: CYP2C8 INHIBITORS/INDUCERS AND THEIR ELIMINATION HALF-LIVES 114
APPENDIX F: CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM 115
APPENDIX G: EORTC QLQ-C30 116
APPENDIX H: EORTC QLQ-OG25 118
APPENDIX I: EQ-5D-5L 120
APPENDIX J: INVESTIGATOR SIGNATURE PAGE 123
APPENDIX K: DOCUMENT HISTORY 124
SUMMARY OF CHANGES IN AMENDMENT 1 125
SUMMARY OF CHANGES IN AMENDMENT 2 130

LIST OF IN-TEXT TABLES

Table 1: Objectives and corresponding endpoints (Phase 2) 24
Table 2: Objectives and corresponding endpoints (Phase 3) 25
Table 3: Treatment schedule 49
Table 4: Criteria for paclitaxel treatment on Day 1, 8, and 15 of each cycle 54
Table 5: Tucatinib/placebo: Recommended dose reduction schedule for adverse events 55
Table 6: Dose modifications for clinical adverse events related to tucatinib/placebo 56
Table 7: Dose modifications of tucatinib/placebo for liver enzyme abnormalities, regardless of relationship to tucatinib/placebo 56
Table 8: Trastuzumab and trastuzumab placebo dose modification guidelines for left ventricular dysfunction 57
Table 9: Ramucirumab: Recommended dose reduction schedule for adverse events 58
Table 10: Dose modifications for clinical adverse events 59
Table 11: Paclitaxel dose modifications for clinical adverse events related to paclitaxel 61
Table 12: Paclitaxel dose modifications for hematological abnormalities, regardless of relationship to paclitaxel 61
Table 13: Paclitaxel dose modification guidelines for liver enzyme abnormalities, regardless of relationship to paclitaxel 61
Table 14: Paclitaxel premedication 62
Table 15: PK and biomarker sample collection timepoints: All subjects in Phase 2 and Phase 3 76
Table 16: PK sample collection timepoints: Phase 2 paclitaxel dose optimization stage and first 6 subjects with a gastrectomy in Phase 2 dose expansion stage 76
Table 17: Expected 95% CI under different underlying true ORRs for a sample size of 30 91

LIST OF IN-TEXT FIGURES

Figure 1: Study visits and overall study design 28
Figure 2: Phase 2 design 31
Figure 3: Phase 3 design 32

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{last}	AUC to the time of the last quantifiable concentration
β-hCG	beta human chorionic gonadotropin
BAP	biomarker analysis plan
BICR	blinded independent central review
BID	twice daily
CAP	College of American Pathologists
CBC	complete blood count
CDX	cell line-derived xenograft
CHF	congestive heart failure
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
CR	complete response
mCRC	metastatic colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	trough concentration
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
GEC	gastric or gastroesophageal junction adenocarcinoma

GFR	glomerular filtration rate
HCRU	health care resource utilization
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB/IEC	Institutional review board/independent ethics committee
IRR	infusion-related reaction
ISH	in situ hybridization
ISO	International Organization for Standardization
ITT	intent-to-treat
IV	intravenous
LC	liquid chromatography
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	metabolic ratio based on AUC
MRI	magnetic resonance imaging
MS	mass spectrometry
MSI	microsatellite instability
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NGS	next generation sequencing
NSAID	nonsteroidal anti-inflammatory agents
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction

PD-1	programmed death receptor-1
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PPE	palmar-plantar erythrodysesthesia
PR	partial response
PRO	patient-reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
QLQ	quality of life questionnaire
RECIST	Response evaluation criteria in solid tumors
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatinine
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reactions
T-DM1	trastuzumab emtansine
T-DXd	trastuzumab deruxtecan
TGI	tumor growth inhibition
TKI	tyrosine kinase inhibitor
T_{max}	time of the maximum observed concentration
ToGA	Trastuzumab for Gastric Cancer
ULN	upper limit of normal
UPC	urine protein/creatinine
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VEGFR-2	vascular endothelial growth factor receptor-2

1 INTRODUCTION

1.1 HER2+ Gastroesophageal Cancers

Gastric cancer is the 6th most common cancer and the 2nd leading cause of cancer-related death worldwide (Bray 2018). Incidence rates for gastric cancer vary based on geographic region, with the highest rates reported in Eastern Asia, Eastern Europe, and South America, and lower rates reported in Northern Europe, North America, and Africa. The vast majority of gastric cancers are adenocarcinomas, and when combined with gastroesophageal junction adenocarcinomas, are often referred to as gastroesophageal cancers. The prognosis for early stage gastric or gastroesophageal junction adenocarcinomas (GEC) is favorable, with 5-year survival rates exceeding 90% following surgery and chemotherapy. Unfortunately, the majority of cases are diagnosed at an advanced stage, where the median overall survival (OS) is less than 12 months (Digklia 2016; Song 2017).

Approximately 12%-23% of GEC overexpresses the human epidermal growth factor receptor 2 (HER2) (Tanner 2005; Yan 2010; Chua 2012; Gomez-Martin 2012; Janjigian 2012; Kunz 2012). 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 pathways, 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).

While the prognostic value of HER2 status in GEC is not clear, patients with advanced stage disease who are HER2-positive (HER2+) may benefit from the addition of trastuzumab (a HER2-directed monoclonal antibody [mAb]) to chemotherapy as first-line treatment (Bang 2010). In the Phase 3 Trastuzumab for Gastric Cancer (ToGA) study, 594 subjects were randomized 1:1 to receive chemotherapy (cisplatin with either capecitabine or fluorouracil) alone or in combination with trastuzumab. A statistically significant improvement in median OS was observed in subjects who received trastuzumab with chemotherapy (13.8 months) versus chemotherapy alone (11.1 months) (hazard ratio [HR] 0.74; 95% CI 0.60-0.91, p=0.0046). Based on these results, the use of trastuzumab in combination with a platinum-agent and fluoropyrimidine is globally recognized as standard first-line therapy in patients with HER2+ advanced GEC.

In second-line GEC, the vascular endothelial growth factor (VEGF) receptor-2 (VEGFR-2) inhibitor ramucirumab in combination with paclitaxel has become a standard of care (Lopez 2018). The Phase 3 RAINBOW study evaluated ramucirumab plus paclitaxel versus paclitaxel in subjects progressing on or soon after first-line treatment with a platinum agent and a fluoropyrimidine, with or without an anthracycline (Wilke 2014). Significant benefits were reported for the combination therapy in terms of OS (median 9.6 months

[95% CI: 8.5-10.8 months] for the combination versus 7.4 months [95% CI: 6.3–8.4 months] for paclitaxel alone), progression-free survival (PFS; median 4.4 months [95% CI: 4.2-5.3 months] versus 2.9 months [95% CI: 2.8–3.0]), and objective response rate (ORR; 28% [95% CI: 23%–33%] versus 16% [95% CI: 13%–20%]). The programmed death receptor-1 (PD-1) inhibitor pembrolizumab (in microsatellite instability (MSI)-high or mismatch repair-deficient disease) and chemotherapy (either as single-agent [paclitaxel, docetaxel, or irinotecan], or combination therapy [fluorouracil and irinotecan (FOLFIRI)]) are also recognized treatment options in this line of therapy. Response rates for these treatments range from 20% to 30%, with median OS ranging from 6 to 9 months. (Wesolowski 2009; Shitara 2018).

While several randomized studies have evaluated targeted HER2 therapies in the second-line setting, none have demonstrated an OS benefit over standard-of-care chemotherapy (Satoh 2014; Thuss-Patience 2017; Makiyama 2020). A potential explanation for the failure of anti-HER2 therapies in this setting may lie with the higher incidence of intratumoral heterogeneity of HER2 in gastric cancer than in breast cancer (Ruschoff 2012; Zhao 2019). Of particular note is the high frequency (approximately 30 to 60%) of conversion from HER2+ to HER2-negative disease following trastuzumab-based first-line therapy (Janjigian 2015; Pietrantonio 2016; Kashiwada 2018). However, in the third-line setting, the DESTINY-Gastric01 study has demonstrated an OS benefit for trastuzumab deruxtecan (T-DXd) over physician's choice of paclitaxel or irinotecan monotherapy (Shitara 2020), leading to approval in trastuzumab-pretreated patients.

To improve clinical outcomes, newer strategies are needed for patients with advanced HER2+ GEC in the second-line setting.

1.2 Tucatinib

Tucatinib ((*N*^{4}-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-*N*^{6}-(4,4-dimethyl-4,5-dihydrooxazol-2-yl) quinazoline-4,6-diamine) (formerly known as ARRY-380 and ONT-380) is an orally administered, potent, highly selective, small-molecule tyrosine kinase inhibitor (TKI) of HER2. Tucatinib is a potent inhibitor of HER2 in vitro, and in cellular signaling assays is >1000-fold more selective for HER2 compared to the closely related kinase EGFR. The selectivity of tucatinib for HER2 reduces the potential for EGFR-related toxicities that can be seen with dual HER2/EGFR inhibitors. Tucatinib inhibits the HER2-driven mitogen-activated protein and PI3 kinase signaling pathways, resulting in inhibition of tumor cell proliferation, survival, and metastasis. The frequent overexpression of HER2 in breast, colorectal, and gastric cancer and the tumor dependence on HER2 supports the use of tucatinib in these diseases. Tucatinib is being developed as a treatment for patients with advanced cancers that demonstrate HER2 overexpression.

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

MOUNTAINEER-02 is an international, multicenter Phase 2/3 study in subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment

with a HER2-directed antibody, and have received at least 1 prior line of therapy in the advanced disease setting. See Section 3.2 for the rationale for the study design, treatment regimen, and selection of doses.

2 OBJECTIVES

The Phase 2 portion of this study will determine the recommended dose of paclitaxel when administered in combination with tucatinib, trastuzumab, and ramucirumab, evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel, and evaluate the activity, and pharmacokinetics (PK) of the regimen in subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment with a HER2-directed antibody in the locally-advanced unresectable or metastatic disease setting. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints (Phase 2)

Primary Objectives	**Corresponding Endpoints**
• To determine the recommended dose of paclitaxel when administered in combination with tucatinib, trastuzumab, and ramucirumab	• Frequency of dose-limiting toxicities (DLT) during the first cycle of treatment with tucatinib, trastuzumab, ramucirumab, and paclitaxel
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, paclitaxel, trastuzumab, and ramucirumab
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated locally-advanced unresectable or metastatic GEC that is HER2+ according to blood-based next generation sequencing (NGS) assay of circulating tumor DNA (ctDNA)	• ORR (complete response [CR] or partial response [PR]) per Response evaluation criteria in solid tumors (RECIST) version 1.1 according to investigator assessment • Confirmed ORR per RECIST version 1.1 according to investigator assessment • PFS per RECIST version 1.1 according to investigator assessment • Duration of response (DOR; CR or PR) per RECIST version 1.1 according to investigator assessment • Disease control rate (DCR; CR or PR or stable disease/non-CR, non-progressive disease as best objective response) per RECIST version 1.1 according to investigator assessment
• To evaluate the PK of tucatinib and the tucatinib metabolite ONT-993 • To evaluate the PK of paclitaxel and its metabolites in the presence and absence of tucatinib	• The PK parameters to be calculated for tucatinib, paclitaxel, and their respective metabolites (if applicable) may include but are not limited to: area under the plasma concentration-time curve (AUC) to the time of the last quantifiable concentration (AUC_{last}), maximum observed concentration (C_{max}), time of C_{max} (T_{max}), trough concentration (C_{trough}), and metabolic ratio based on AUC (MR_{AUC})

Exploratory Objectives	Corresponding Endpoints
• To evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with disease that is HER2-negative according to blood-based NGS assay but HER2+ according to IHC/ISH assay of a tumor tissue sample	• ORR per RECIST version 1.1 according to investigator assessment • Confirmed ORR per RECIST version 1.1 according to investigator assessment • PFS per RECIST version 1.1 according to investigator assessment • Duration of response per RECIST version 1.1 according to investigator assessment • Disease control rate per RECIST version 1.1 according to investigator assessment
• To evaluate the correlation between HER2 alterations as detected by blood-based NGS assays and standard tissue-based assays	• Frequency of HER2 alterations according to blood-based NGS assay and according to assays on tumor tissue samples obtained after progression on the most recent line of therapy
• To explore correlations between blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in blood
• To evaluate the PK of tucatinib and ONT-993 in subjects with and without gastrectomy	• The PK parameters of tucatinib and ONT-993 in subjects with and without a gastrectomy may include but are not limited to: AUC_{last}, C_{max}, T_{max}, $C_{trough,}$ and MR_{AUC}

The Phase 3 portion will compare the efficacy, safety, patient-reported outcomes (PRO), and health care resource utilization (HCRU) of tucatinib and trastuzumab versus placebo in combination with ramucirumab and paclitaxel. It will also evaluate the activity of tucatinib combined with ramucirumab and paclitaxel. Specific objectives and corresponding endpoints for the study are summarized below (Table 2).

Table 2: Objectives and corresponding endpoints (Phase 3)

Primary Objective	Corresponding Endpoints
To compare the efficacy of tucatinib and trastuzumab versus placebo, in combination with ramucirumab and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ GEC	*Dual primary endpoints* • OS • PFS per RECIST version 1.1 according to investigator assessment *Key secondary endpoints* • Confirmed ORR per RECIST version 1.1 according to investigator assessment *Other secondary endpoints* • PFS per RECIST version 1.1 according to blinded independent central review (BICR) assessment • Confirmed ORR per RECIST version 1.1 according to BICR assessment • ORR per RECIST version 1.1 according to investigator assessment • ORR per RECIST version 1.1 according to BICR assessment • DOR per RECIST version 1.1 according to investigator assessment • DOR per RECIST version 1.1 according to BICR assessment • DCR per RECIST version 1.1 according to investigator assessment • DCR per RECIST version 1.1 according to BICR assessment

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, trastuzumab, ramucirumab, and paclitaxel
• To evaluate the anti-tumor activity of tucatinib in combination with ramucirumab and paclitaxel	*Secondary Endpoints* • Confirmed ORR per RECIST version 1.1 according to investigator assessment • DOR per RECIST version 1.1 according to investigator assessment *Exploratory Endpoints* • OS • PFS per RECIST version 1.1 according to investigator assessment • PFS per RECIST version 1.1 according to BICR assessment • Confirmed ORR per RECIST version 1.1 according to BICR assessment • ORR per RECIST version 1.1 according to investigator assessment • ORR per RECIST version 1.1 according to BICR assessment • DOR per RECIST version 1.1 according to BICR assessment • DCR per RECIST version 1.1 according to investigator assessment • DCR per RECIST version 1.1 according to BICR assessment
• To assess PROs by treatment arm	• Time to deterioration of GEC symptoms as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and EORTC QLQ-OG25 questionnaires • Change from baseline in health-related quality of life (HRQoL) • Utility index values as assessed by the EQ-5D-5L
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the safety and tolerability of tucatinib in combination with ramucirumab, and paclitaxel	• Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities • Vital signs and other relevant safety variables • Frequency of dose holds, dose reductions, and discontinuations of tucatinib, ramucirumab, and paclitaxel
• To evaluate the PK of tucatinib	• The PK parameter to be calculated for tucatinib (if applicable) includes: C_{trough}
• To explore correlations between blood-based biomarkers and clinical outcomes	• Potential biomarkers of response, resistance, or toxicity may be evaluated in blood
• To assess HCRU by treatment arm	• Cumulative incidence of healthcare resource utilization, including length of stay, hospitalizations, and emergency department visits

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is an international, multicenter Phase 2/3 study in subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment with a HER2-directed antibody, and have received 1 prior line of therapy in the advanced disease setting.

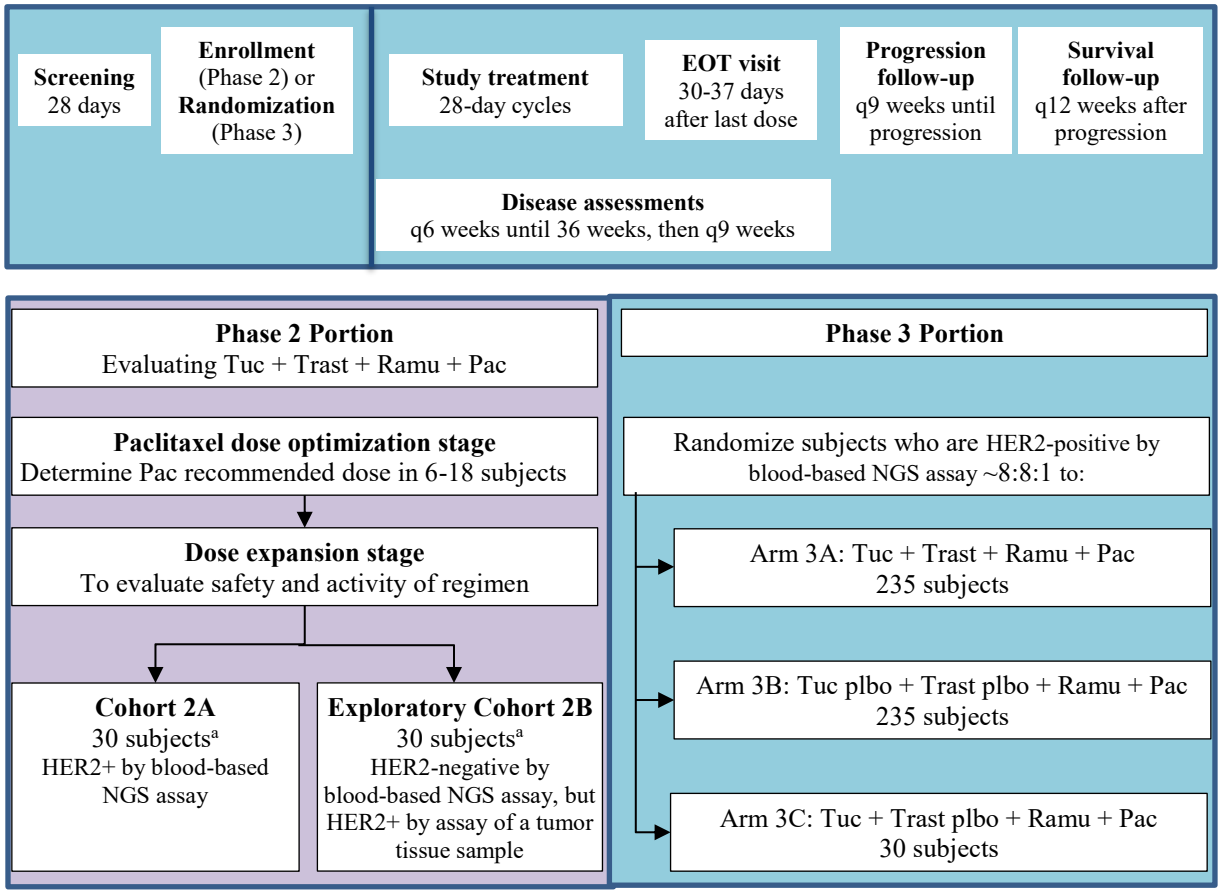
The study is composed of the following parts:

- Open-label Phase 2 portion:
  - Paclitaxel dose optimization stage: this single-arm stage will determine the recommended dose of paclitaxel when combined with tucatinib, trastuzumab, and ramucirumab (see Section 3.1.1.1 for details).
  - Dose expansion stage: this 2-cohort stage will enroll subjects to further evaluate the safety and activity of the regimen in a total of approximately 30 response-evaluable subjects in each cohort, once the recommended paclitaxel dose is determined (see Section 3.1.1.2 for details).
- Randomized, double-blind, placebo-controlled Phase 3 portion: will compare the efficacy and evaluate the safety of tucatinib and trastuzumab versus placebo, in combination with ramucirumab and paclitaxel, and evaluate the efficacy and safety of tucatinib combined with ramucirumab and paclitaxel (see Section 3.1.2 for details).

Dose reductions of tucatinib (or placebo), ramucirumab, and paclitaxel will be allowed. Dose reductions of trastuzumab (or placebo) will not be allowed; if trastuzumab cannot be restarted after being held for an AE, it must be discontinued. If any study drug is discontinued, the subject can continue to receive study treatment with the remaining agents. Study treatment (defined as the administration of any of the 4 study drugs, without initiation of new anti-cancer treatment) will continue until unacceptable toxicity, disease progression, withdrawal of consent, death, or study closure. Disease response and progression will be assessed using RECIST version 1.1.

While on study treatment, radiographic disease evaluations will be done every 6 weeks for the first 36 weeks, and every 9 weeks thereafter, irrespective of dose holds or interruptions (Figure 1). All efforts should be made to continue treatment until unequivocal evidence of radiologic progression occurs according to RECIST version 1.1. If study treatment is discontinued before documentation of disease progression, radiographic evaluations will be performed at least every 9 weeks until the occurrence of progression, withdrawal of consent, or study closure. After occurrence of disease progression, subjects will continue to be followed for survival every 12 weeks, until death, consent withdrawal, or study closure.

Figure 1: Study visits and overall study design



Pac=paclitaxel; plbo=placebo; Ramu=ramucirumab; Tuc=tucatinib; Trast=trastuzumab.
a Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.

3.1.1 Phase 2

3.1.1.1 Paclitaxel Dose Optimization Stage

In the paclitaxel dose optimization stage of the study, the initial paclitaxel dose will be 60 mg/m² intravenous (IV) on Days 1, 8, and 15 of each 28-day cycle, in combination with tucatinib 300 mg orally (PO) twice daily (BID), trastuzumab (6 mg/kg IV loading dose on Cycle 1 Day 1, 4 mg/kg IV on Cycle 1 Day 15 and Days 1 and 15 of each cycle thereafter), and ramucirumab (8 mg/kg IV on Days 1 and 15).

Six subjects will initially be enrolled and treated at paclitaxel 60 mg/m² (Figure 2). Subjects can have HER2+ disease according to a blood-based NGS assay of ctDNA done at screening or immunohistochemistry (IHC)/in situ hybridization (ISH) assay of a tumor tissue sample obtained after progression on the most recent line of systemic therapy. Once 6 subjects are evaluable for DLT, enrollment will be paused and the Safety Monitoring Committee (SMC) will undertake an evaluation of safety and PK (see Section 3.1.4 for details concerning the

SMC). If necessary, additional subjects will be enrolled to replace subjects who are not evaluable for DLT (see Section 3.1.3 for the definition of evaluable for DLT).

In the 6 DLT-evaluable subjects receiving 60 mg/m²:

- If ≤1 DLT are observed in 6 subjects, the paclitaxel dose will be escalated to 80 mg/m² and evaluated in a further 6 subjects.
- If 2 DLTs are observed in 6 subjects, an additional 3 subjects will be treated at 60 mg/m², for a total of 9 subjects:
    - If ≤2 DLT are observed in 9 subjects, the paclitaxel dose will be escalated to 80 mg/m² and evaluated in a further 6 subjects.
    - If >2 DLT are observed in 9 subjects, the evaluation of the regimen will be halted, or an alternative dose level/schedule may be recommended by the SMC.
- If >2 DLTs are observed in 6 subjects, the evaluation of the regimen will be halted, or an alternative dose level/schedule may be recommended by the SMC.

In the 6 DLT-evaluable subjects receiving 80 mg/m²:

- If ≤1 DLT are observed in 6 subjects, 80 mg/m² will be the recommended dose.
- If 2 DLTs are observed in 6 subjects, an additional 3 subjects will be treated at 80 mg/m², for a total of 9 subjects:
    - If ≤2 DLT are observed in 9 subjects, 80 mg/m² will be the recommended dose.
    - If >2 DLT are observed in 9 subjects, the 60 mg/m² paclitaxel dose will be declared the recommended dose, and evaluation of the regimen will continue in the Dose Expansion stage.
- If >2 DLTs are observed in 6 subjects, the 60 mg/m² paclitaxel dose will be declared the recommended dose, and evaluation of the regimen will continue in the Dose Expansion stage.

The SMC may also recommend the inclusion of additional subjects in any dose level or the evaluation of an alternative dose level/schedule, if necessary. The SMC will continuously monitor subjects for AEs, deaths, other serious adverse events (SAEs), dose modifications, and laboratory abnormalities, with a specific focus on DLTs (see Section 3.1.3).

3.1.1.2 Dose Expansion Stage

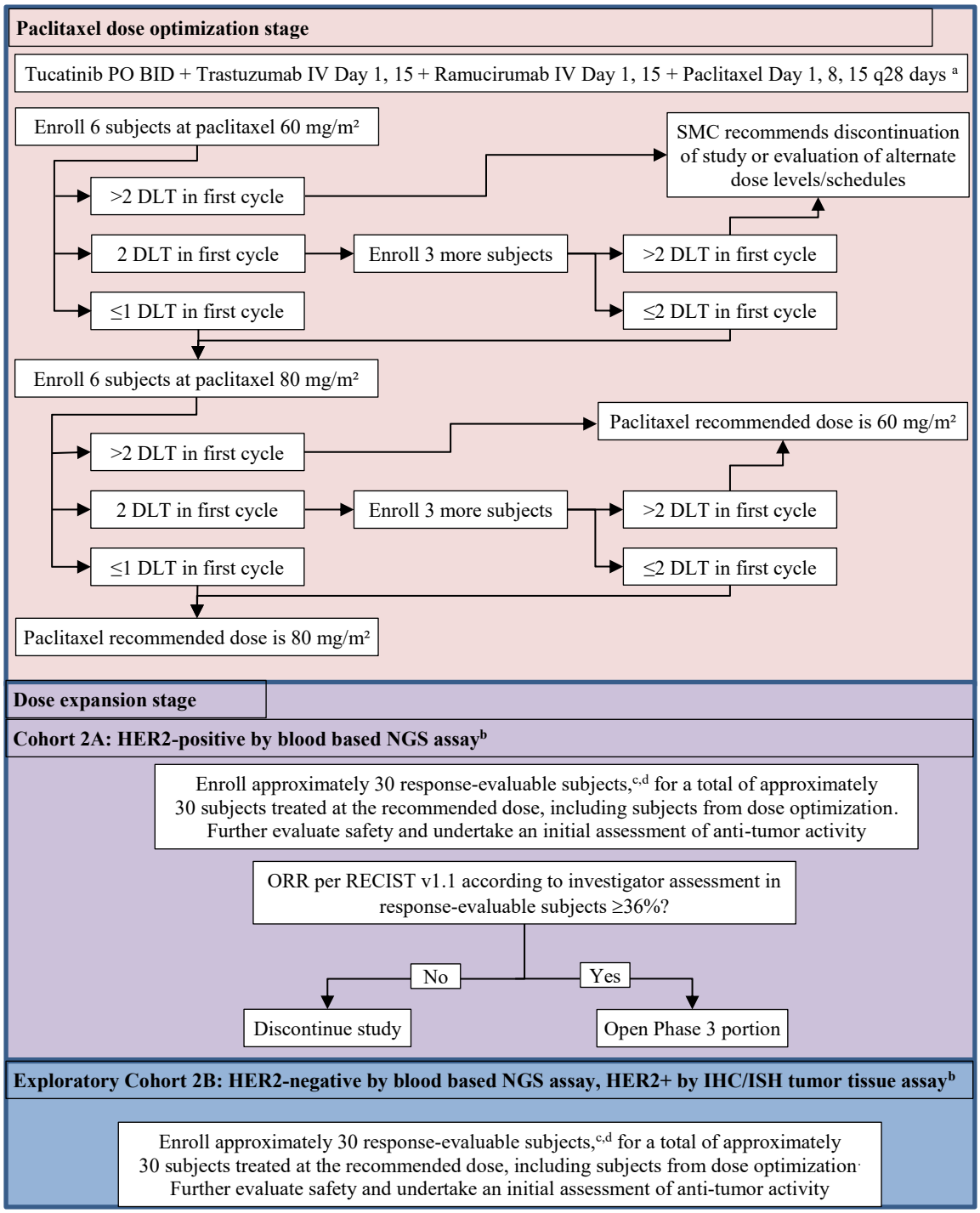
Following the paclitaxel dose optimization stage, two cohorts will be opened to enroll further subjects. Cohort 2A will enroll subjects with HER2+ disease as determined by HER2 amplification in a blood-based NGS assay of ctDNA performed at a central laboratory at screening. The exploratory Cohort 2B will enroll subjects whose disease did **not** show HER2 amplification in the blood-based NGS assay, but did show HER2 overexpression/amplification by IHC and ISH assay of a tumor tissue sample obtained after progression on the most recent line of systemic therapy, processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory, according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) 2016 guideline for gastroesophageal adenocarcinoma (IHC3+ or IHC2+/ISH+).

For each type of HER2 positivity evaluated (blood-based NGS assay or IHC/ISH assay of a tumor tissue sample), approximately 30 response-evaluable subjects who have been treated at the recommended paclitaxel dose will be included in Cohort 2A or 2B, in order to further evaluate the safety of the study regimen and undertake an initial assessment of anti-tumor activity. Subjects who are not evaluable for response will be replaced. See Section 7.2 for the definition of response-evaluable in the Phase 2. Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response evaluable.

The SMC will evaluate the safety of the study regimen throughout the remainder of the Phase 2, in the 2 cohorts. At least 6 subjects with a history of prior gastrectomy (without maintenance of the pylorus) will be enrolled in either cohort to evaluate the PK of tucatinib and ONT-993 in this population; alternative dose levels/schedules may be explored depending on the PK of tucatinib in subjects with gastrectomy.

A formal efficacy analysis will be undertaken when 30 subjects with HER2+ disease according to blood-based NGS assay from either Cohort 2A or the dose optimization stage have been treated at the recommended paclitaxel dose, are evaluable for response, and have been followed for at least 6 weeks. If the ORR per RECIST v1.1 according to investigator assessment is ≥36%, the SMC may recommend that the Phase 3 evaluation of the regimen be initiated in subjects with HER2 amplification in a blood-based NGS assay, given that it is safe and tolerable. See Section 9.1.1 for details concerning the formal end-of-Phase 2 analysis. Enrollment in Cohort 2B can continue after the initiation of the Phase 3.

Figure 2: Phase 2 design



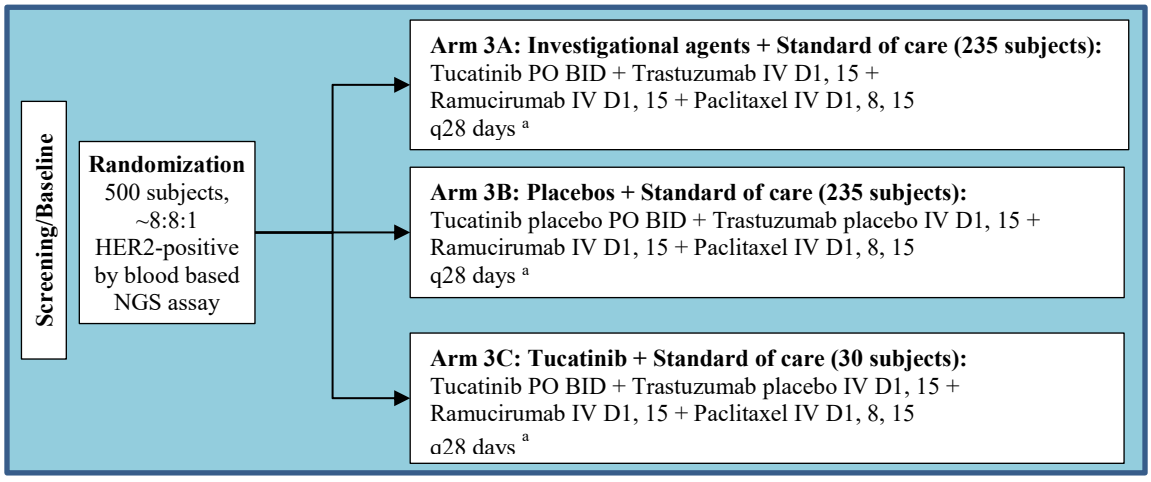
a. Tucatinib 300 mg BID PO; trastuzumab 6 mg/kg on Cycle 1 Day 1, then 4 mg/kg in subsequent infusions; ramucirumab 8 mg/kg per infusion; paclitaxel 60 or 80 mg/m² per infusion, or an alternate dose/schedule upon recommendation of the SMC.
b. HER2+ disease documented since progression of the most recent line of systemic therapy.
c. Subjects in the dose optimization stage will be counted towards the sample size for these cohorts, if they received the recommended dose and are response-evaluable.
d. Response-evaluable subjects will have a baseline disease assessment, receive study treatment, and have a post-baseline assessment or discontinue due to documented disease progression, clinical progression, treatment-related AEs, or death.

3.1.2 Phase 3

Approximately 500 subjects who have HER2 amplification in a blood-based NGS assay will be randomized in approximately an 8:8:1 ratio to either Arm 3A (tucatinib, trastuzumab, ramucirumab, and paclitaxel; 235 subjects), Arm 3B (tucatinib placebo, trastuzumab placebo, ramucirumab, and paclitaxel; 235 subjects), or Arm 3C (tucatinib, trastuzumab placebo, ramucirumab, and paclitaxel; 30 subjects) (Figure 3). Efficacy in Arms 3A and 3B will be formally compared to demonstrate the benefit of adding tucatinib plus trastuzumab to standard of care ramucirumab plus paclitaxel. Efficacy in Arm 3C will be analyzed separately. Randomization will be stratified by region (Asia vs Rest of World), time to progression on first-line therapy for locally-advanced unresectable or metastatic disease (<6 months vs ≥6 months), and history of prior gastrectomy (yes vs no). Subjects randomized to Arm 3B will receive a tucatinib placebo and a trastuzumab placebo; subject randomized to Arm 3C will receive a trastuzumab placebo. Subjects, investigators, and staff, and the sponsor study team will be blinded to study arm allocation. Subjects who are screened for the Phase 3 but are found to be HER2-negative according to the blood-based NGS assay, may be enrolled in Cohort 2B of the Phase 2 if it is still enrolling and the subject has HER2-positive disease according to assay of a tumor tissue sample obtained after progression on the most recent line of therapy.

In the Phase 3 portion of the study, an Independent Data Monitoring Committee (IDMC) will periodically review relevant aggregate safety data and will make recommendations to the sponsor on the conduct of the study (see Section 3.1.5 for details concerning the IDMC). Safety will also be monitored in an ongoing basis by the sponsor throughout the study.

Figure 3: Phase 3 design



a Tucatinib will be administered at 300 mg BID PO; trastuzumab 6 mg/kg will be administered on Cycle 1 Day 1, then 4 mg/kg in subsequent infusions; ramucirumab will be administered at a dose of 8 mg/kg per infusion; paclitaxel will be administered at the recommended dose and schedule determined in the Phase 2 in Arms 3A and 3C and at 80 mg/m² in Arm 3B.

3.1.3 Dose-Limiting Toxicity

DLTs will be AEs, laboratory abnormalities, or treatment modifications that occur during the first cycle of treatment in the Phase 2 paclitaxel dose optimization stage that are related to paclitaxel, to tucatinib, or to the combination of tucatinib, trastuzumab, ramucirumab and paclitaxel, and that meet any of the criteria listed below. AEs that are attributed only to trastuzumab and/or ramucirumab, but not tucatinib or paclitaxel will not be considered DLTs. Events for which there is an alternative clinical explanation (e.g., clearly related to an intercurrent illness or disease progression), will not be considered DLTs. The severity of AEs and laboratory abnormalities will be graded according to the NCI CTCAE Version 5.0. The relationship of AEs to study drugs will be determined by the investigator. Subjects who experience a DLT may continue on study treatment if treatment discontinuation is not required by protocol dose modification criteria (Section 5.2) and the investigator believes it to be in the subject's interest. Subjects may resume treatment at a lower dose (i.e., a reduced dose of tucatinib, ramucirumab, or paclitaxel) following recovery of the AE to ≤ Grade 1 or the baseline grade. Subjects will be considered evaluable for DLT if they received at least 75% of the planned administrations of each study drug and were followed for at least 1 cycle, or if they experienced a DLT during the first cycle. DLT is defined as any of the following:

Clinical AEs: any of the following AEs if considered related to tucatinib, paclitaxel, or the 4-drug combination:

- Any AE ≥ Grade 3 except:
  - Grade 3 fatigue ≤7 days
  - Grade 3 diarrhea, nausea, or vomiting without optimal use of anti-emetics or anti-diarrheals
  - Grade 3 rash without optimal use of corticosteroids or anti-infectives
- ≥ Grade 3 peripheral motor and or sensory neuropathy

Treatment modifications: any of the following due to AEs related to tucatinib, paclitaxel, or the 4-drug combination:

- >2 week delay in start of Cycle 2
- Dose delays of >5 days for Day 1, 8, 15
- Dose reduction/discontinuation of tucatinib, ramucirumab, or paclitaxel, or discontinuation of trastuzumab

Hematologic

- ≥ Grade 3 febrile neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L, with a single temperature >38.3°C or a sustained temperature ≥38°C for >1 hour)
- Grade 4 neutropenia (ANC $<0.5 \times 10^9$/L) for >7 days
- Grade 3 thrombocytopenia ($<50 \times 10^9$/L) with significant bleeding
- Grade 4 thrombocytopenia (platelet count $<25 \times 10^9$/L)
- Grade 4 anemia

Hepatic: any of the following not due to disease progression or intercurrent illness:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation >5.0 × ULN
- Bilirubin elevation (regardless of transaminases) >3.0 × ULN
- Any instance of AST/ALT elevations >3 × ULN AND total bilirubin elevation >2 × ULN

3.1.4 Safety Monitoring Committee

The SMC will be responsible for monitoring the safety of subjects in the Phase 2 at regular intervals. In particular, the SMC will evaluate DLTs, other safety data, and PK data in the paclitaxel dose optimization stage. The SMC will review data on AEs, deaths, other SAEs, treatment modifications, laboratory abnormalities, and PK data on a regular basis. The SMC will make recommendations to the sponsor regarding the conduct of the study, including changes to paclitaxel dose levels and administration schedules, and make recommendations concerning study continuation as planned, protocol amendment, or early discontinuation of the study for excessive toxicity. Once the Phase 3 is initiated, the SMC will be discontinued and the sponsor will be responsible for monitoring safety data in subjects still on-treatment in the Phase 2.

An SMC Charter will outline the committee's composition, members' roles and responsibilities, and describe SMC procedures. The sponsor will provide a copy of each SMC recommendation to the investigators.

3.1.5 Independent Data Monitoring Committee

The IDMC will be responsible for monitoring the safety of subjects in the Phase 3 at regular intervals. The IDMC will review unblinded data including deaths, study treatment and study drug discontinuations, dose reductions, AEs, SAEs, and laboratory abnormalities on a regular basis. The IDMC will make recommendations to the sponsor regarding the conduct of the study, including study continuation as planned or with protocol amendment, or early discontinuation of the study for excessive toxicity. An IDMC Charter will outline the committee's composition, members' roles and responsibilities, and describe IDMC procedures. The sponsor will provide a copy of each IDMC recommendation to the investigators.

3.1.6 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 the SMC, or an independent safety assessment by the IDMC.
- Subject enrollment is unsatisfactory.

3.1.7 End of Study

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

3.1.8 Method of Assigning Subjects to Treatment Groups

Phase 2

Following informed consent and screening assessments, eligible subjects will be assigned to the paclitaxel dose level currently enrolling during the paclitaxel dose optimization stage. Once the paclitaxel recommended dose is established, subjects will be assigned to either Cohort 2A or Cohort 2B based on the results of blood-based NGS assay or, if the former was negative, IHC/ISH assay of a tumor tissue sample obtained after progression on the most recent line of systemic therapy.

Phase 3

Following informed consent and screening assessments, eligible subjects will be randomly assigned to Arms 3A, 3B, and 3C in an approximately 8:8:1 ratio. Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment. Randomization procedures are detailed in the Study Manual.

Randomization will be stratified by:

- Region of inclusion: Asia versus Rest of World
- Time to progression on first-line therapy for locally-advanced unresectable or metastatic disease: <6 months versus ≥6 months
- History of prior gastrectomy: yes versus no

3.1.9 Blinding and Unblinding

Maintaining the blind of the study in the Phase 3 portion is crucial for achieving the study objectives. Unblinding an individual subject's treatment assignment may only occur when one of the following circumstances is applicable:

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

any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence.

Details regarding unblinding procedures are described in the Study Manual.

3.1.9.1 Unblinding for Safety Monitoring

Safety data in the Phase 3 portion is monitored by an IDMC. Unblinding of aggregate safety data for ongoing safety monitoring and risk/benefit assessment by the IDMC will be performed through an independent Data Coordinating Center to ensure the integrity of the study.

Suspected unexpected serious adverse reactions (SUSARs) will be unblinded in accordance with local regulatory reporting requirements. Pre-specified personnel from the sponsor Drug Safety Department will unblind the identity of study medication for any unexpected (as per the Investigator's Brochure) SAEs that are considered to be related to the blinded study drugs (tucatinib, trastuzumab, or placebo).

3.2 Discussion and Rationale

3.2.1 Rationale for Study Design

GEC which has progressed after first-line therapy is an area of significant unmet medical need, with only moderate increases in survival delivered by recent advances in therapy (Wilke 2014). In second-line HER2+ GEC, targeted anti-HER2 therapies have so far failed to yield benefit.

This study builds upon the standard of care for second-line treatment of advanced GEC, ramucirumab and paclitaxel, by adding the dual HER2 inhibition of tucatinib and trastuzumab. As discussed in Section 1.1, ramucirumab and paclitaxel is the current standard of treatment for subjects with GEC following failure of first line therapy. The combination of tucatinib and trastuzumab has proven efficacy in HER2+ metastatic breast cancer (mBC), when given with capecitabine. Additionally, the doublet of tucatinib and trastuzumab, without chemotherapy, has shown promising activity in HER2+ metastatic colorectal cancer (mCRC). See Section 3.2.2 for the detailed rationale for the evaluation of tucatinib and trastuzumab combined with ramucirumab and paclitaxel in this patient population.

The inclusion of an active, standard of care regimen as the comparator arm (Arm 3B) in this blinded, placebo-controlled study and the use of OS, the gold standard for anticancer therapies, as a dual primary endpoint will ensure a robust evaluation of the contribution of tucatinib and trastuzumab to the activity of the study regimen. The preclinical and clinical evidence for the significant contribution of tucatinib to HER2 blockade and treatment outcomes when combined with trastuzumab is presented in Section 3.2.2.

The HER2 status of subjects' disease will be established at screening using a central blood-based NGS assay of ctDNA. The evaluation of baseline HER2 status in second-line GEC is required, in order to assure that first-line anti-HER2 therapy has not resulted in loss of HER2-positivity, as discussed in Section 1.1. Given that the frequency of positive HER2

IHC/ISH assays of biopsies in subjects with negative HER2 assays in blood-based NGS is unknown in GEC, exploratory Cohort 2B of the Phase 2 dose expansion stage will enroll any such subjects identified, in order to determine the correlation between HER2-positivity in assays of ctDNA and tumor tissue, and evaluate the antitumor activity and safety of the study regimen in such subjects.

Evaluation of the safety of the study regimen will be undertaken in the Phase 2 portion of the study (see Figure 2) in the paclitaxel dose optimization and dose expansion stages. Once the safety and tolerability of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel are evaluated, and the regimen had been found to sufficiently active in the preliminary evaluation of efficacy in subjects with HER2+ disease by blood-based NGS assay in Phase 2, the Phase 3 portion of this study will compare the efficacy of tucatinib and trastuzumab versus placebo in 470 subjects with cancer. The activity of tucatinib combined with ramucirumab and paclitaxel will also be evaluated in 30 subjects, to establish the contribution of tucatinib to the standard of care therapy. All subjects enrolled on the Phase 3 will be HER2-positive according to the blood-based NGS assay. See Section 3.2.3 for a detailed rationale for the selection of doses in this study.

3.2.2 Rationale for Combination of Tucatinib and Trastuzumab

The combination of tucatinib and trastuzumab is being evaluated in this study based on preclinical data in GEC demonstrating superior activity of dual targeting of HER2 with tucatinib and trastuzumab compared with either single-agent alone. This is further supported by clinical data in other cancer types showing enhanced activity with tucatinib and trastuzumab.

Preclinical models examining single-agent tucatinib activity in HER2+ patient-derived xenograft (PDX) and cell line-derived xenograft (CDX) models have demonstrated activity of tucatinib in gastric, esophageal, colorectal, cholangiocarcinoma, and breast tumors. These models have also suggested a more robust anti-neoplastic response when tucatinib is administered in combination with trastuzumab, compared to monotherapy (Peterson 2017). Across 3 PDX models and a CDX model of gastric cancer, a nominal dose of tucatinib 50 mg/kg BID resulted in percent tumor growth inhibition (TGI) of 48% to 110%, while trastuzumab 20 mg/kg every 3 days resulted in TGIs of 38% to 93%. The combination of tucatinib and trastuzumab resulted in TGIs of 103% to 136%. Additionally, the frequency of PR and CR was higher for the combination than either single agent alone, indicating that the activity of the combined anti-HER2 agents was superior to either agent alone. Based on these data, several clinical studies are actively investigating the use of dual HER2 blockade with tucatinib and trastuzumab.

Clinical data from the pivotal HER2CLIMB study (ONT-380-206) clearly demonstrated the benefit of adding tucatinib to trastuzumab in HER2+ mBC (Murthy 2020). In this global, randomized, double-blind study, 612 subjects who had been treated with 3 prior HER2-directed agents (trastuzumab, pertuzumab, and trastuzumab emtansine [T-DM1]) were randomized in a 2:1 ratio to receive tucatinib (300 mg BID) or placebo in combination with

trastuzumab (8 mg/kg IV followed by 6 mg/kg every 3 weeks) and capecitabine (1000 mg/m² BID for 14 days of each 3 week cycle). The primary endpoint of PFS was positive and highly statistically significant in favor of the tucatinib combination, with an HR of 0.54 (95% CI: 0.42, 0.71; p<0.00001). Additionally, all multiplicity-adjusted secondary endpoints supported the primary endpoint and demonstrated benefit with tucatinib, including OS (HR 0.66; 95% CI: 0.50-0.88; P = 0.005), PFS in subjects with brain metastases (HR 0.48; 95% CI: 0.34 to 0.69; p<0.00001) and confirmed ORR (40.6% [95% CI: 35.3-46.0] in the tucatinib arm versus 22.8% [95% CI: 16.7-29.8] for placebo, p<0.001).

In addition to demonstrating benefit in HER2+ mBC, the combination of tucatinib and trastuzumab has shown promising activity in HER2+ mCRC, based on initial results reported from the single-arm, Phase 2 MOUNTAINEER trial (Strickler 2019). In this study, subjects with HER2+, RAS-wildtype mCRC who had been previously treated with fluorouracil, oxaliplatin, irinotecan, and an anti-VEGF antibody received tucatinib (300 mg BID) in combination with trastuzumab (8 mg/kg IV followed by 6 mg/kg every 3 weeks). The primary endpoint was ORR, with the study comparing an ORR of 20% (null hypothesis) versus 40% (alternative hypothesis). Among 23 evaluable subjects, an ORR of 52.2% was observed, with a median PFS of 8.1 months (95% CI: 3.8 months-not evaluable) and a median OS of 18.7 months (95% CI: 12.3 months-not evaluable).

The results from the HER2CLIMB and MOUNTAINEER studies demonstrate a clear benefit of dual targeted HER2 inhibition with tucatinib + trastuzumab in HER2+ malignancies. Following failure of first-line treatment with a trastuzumab-based regimen, patients with HER2+ GEC have limited treatment options. Both the preclinical and clinical data summarized above support the proposed comparison of tucatinib and trastuzumab versus placebo, in combination with ramucirumab and paclitaxel.

3.2.3 Rationale for Selection of Doses

3.2.3.1 Rationale for Tucatinib Dose

In the pivotal HER2CLIMB study (ONT-380-206) in subjects with HER2+ mBC, the combination of tucatinib 300 mg PO BID with trastuzumab and capecitabine was found to be well tolerated, with a manageable safety profile. The most frequent AEs included diarrhea (80.9% in the tucatinib, trastuzumab, and capecitabine arm versus 53.3% in the placebo, trastuzumab, and capecitabine arm), palmar-plantar erythrodysesthesia (PPE) syndrome (63.4% versus 52.8%), nausea (58.4% versus 43.7%), fatigue (45.0% versus 43.1%), and vomiting (35.9% versus 25.4%). Elevated liver enzyme test AEs were observed, with all grade AST, ALT and bilirubin elevations reported in 21.3%, 20.0% and 18.6% of subjects in the experimental arm, respectively, and 11.2%, 6.6%, and 10.2% in the control arm. Grade ≥3 AEs included PPE syndrome (13.1% versus 9.1%), diarrhea (12.9% versus 8.6%), increased AST (4.5% versus 0.5%), increased ALT (5.4% versus 0.5%), and increased bilirubin (0.7% versus 2.5%).

The Phase 1b studies ONT-380-004 and ONT-380-005 evaluated the safety of tucatinib 300 mg and 350 mg PO BID in combination with T-DM1 and trastuzumab/capecitabine, respectively, in subjects with HER2+ mBC. Both studies determined the recommended tucatinib clinical dose to be 300 mg PO BID.

In ONT-380-004, the most frequent AEs at the tucatinib 300 mg dose level combined with T-DM1 were nausea (72% of 50 subjects), diarrhea (60%), fatigue (58%), vomiting (46%). All grade AST, ALT, and bilirubin laboratory abnormalities were reported in 92%, 88%, and 36% of subjects, respectively. Grade ≥3 AEs included thrombocytopenia 28%, hypokalemia 16%, increased AST 16%, increased ALT 14%, and increased bilirubin 4%.

In ONT-380-005, the most frequent AEs in the tucatinib 300 mg plus trastuzumab and capecitabine cohort were diarrhea (74% of 27 subjects), nausea (78%), PPE syndrome (67%), vomiting (52%), and fatigue (44%). Grade ≥3 AEs occurring in >10% of subjects were fatigue (15%), and diarrhea and PPE syndrome (11% each). All grade AST, ALT and bilirubin laboratory abnormalities reported in 89%, 78%, and 52%, respectively. Grade ≥3 liver enzyme laboratory abnormalities were reported in 2 subjects (7%) each.

In the 18 subjects who received only tucatinib and trastuzumab the most frequent AEs were diarrhea (56% of 18 subjects), nausea (33%), constipation (28%), and arthralgia, vomiting, and dizziness (22% each). No Grade ≥3 AEs occurred in more than 1 subject. All grade AST, ALT and bilirubin laboratory abnormalities reported in 67%, 44%, and 22%, respectively. There were no Grade ≥3 liver enzyme laboratory abnormalities.

Interim data were reported from 26 subjects with HER2+ mCRC enrolled in the MOUNTAINEER study (SGNTUC-017) evaluating tucatinib 300 mg PO BID and trastuzumab (Strickler 2019). Combination treatment with tucatinib + trastuzumab appeared to be efficacious and well-tolerated. The most frequent AEs were AST increased (38.5%), ALT increased and diarrhea (23.1% each), fatigue (19.2%), and infusion-related reactions (IRR; 11.5%); only 2 Grade 3 AEs were reported, for diarrhea and hypertension (3.8% each).

Based on these studies, the proposed starting dose of tucatinib with trastuzumab, ramucirumab, and paclitaxel is 300 mg BID.

3.2.3.2 Rationale for Trastuzumab Dose and Schedule

Given the every 28 days schedule of the standard ramucirumab and paclitaxel regimen, trastuzumab will be administered on a biweekly schedule. The biweekly trastuzumab schedule has been evaluated in various Phase 2 studies and been found to be safe and tolerable (Orlando 2014; Qiu 2014; Mondaca 2019). Trastuzumab 4 mg/kg will be administered on Day 1 and 15 every 28 days (with a 6 mg/kg loading dose on Cycle 1 Day 1); this dose corresponds to the same dose intensity as weekly and every 3-week dosing. This will simplify the visits for subjects and investigators, and will preserve the rest week present in the paclitaxel Day 1, 8, 15 every 28 days schedule.

3.2.3.3 Rationale for Ramucirumab Dose and Schedule

Ramucirumab is being administered at the standard dose and schedule indicated for use in second-line treatment of advanced GEC (Wilke 2014).

3.2.3.4 Rationale for Paclitaxel Dose Levels and Schedule

To determine the tolerability of tucatinib and paclitaxel in combination, a safety and PK paclitaxel dose optimization stage is proposed, using a starting dose of paclitaxel reduced to 60 mg/m² (administered as a 1-hour IV infusion according to the standard schedule on Days 1, 8 and 15 every 28 days) for the combination with tucatinib, trastuzumab, and ramucirumab (see Section 3.1.1.1).

Paclitaxel is extensively metabolized, primarily via CYP2C8-mediated metabolism to 6α-hydroxypaclitaxel and via CYP3A4 to 3'-ρ-hydroxypaclitaxel and 6α-3'-ρ-dihydroxypaclitaxel (Taxol™ Prescribing Information, Bristol Myers Squibb Company, March 2015). Paclitaxel is also a substrate of P-gp. The US Prescribing Information for paclitaxel recommends use with caution when co-administering with known CYP2C8 or CYP3A4 substrates, inducers or inhibitors. Tucatinib is a strong, mechanism-based inhibitor of CYP3A4 and significantly increases the exposure of sensitive CYP3A4 substrates. In a clinical study of healthy volunteers (ONT-380-012), midazolam AUC_{inf} and C_{max} increased 5.7- and 3.0-fold, respectively, in the presence of tucatinib. In the same study, tucatinib was shown to be a weak CYP2C8 and weak P-gp inhibitor, with repaglinide and digoxin AUC_{inf} increasing 1.7- and 1.5-fold, respectively, in the presence of tucatinib (Tukysa™ Prescribing Information, Seagen Inc., March 2020). Given the potential for a drug-drug interaction (DDI) and/or overlapping toxicity between paclitaxel and tucatinib, the paclitaxel dose optimization stage with PK sampling is proposed to support a tolerability assessment of this combination.

Three studies have investigated the co-administration of paclitaxel (100 mg/m² every 2 weeks, 3-hour IV infusion) with strong CYP3A4 inhibitors (Nannan Panday 1999; Tulpule 2002; Cianfrocca 2011). These have shown paclitaxel in combination with strong CYP3A4 inhibitors to be well tolerated, even with an approximate doubling of paclitaxel AUC (and no statistically significant impact on C_{max}). Additionally, the combination of 50-80 mg/m² paclitaxel (1-hour IV infusion on Days 1, 8 and 15 every 28 days) with weak CYP3A4 inhibitors (lapatinib and/or pazopanib) resulted in a 26%-43% increase in paclitaxel AUC_{inf} (and up to a 62% increase in paclitaxel C_{max}) (Tan 2010; Satoh 2014; Tan 2014).

More recently, the I-SPY2 trial has evaluated the combination of tucatinib, with paclitaxel (80 mg/m^2 per week), trastuzumab and pertuzumab in the neoadjuvant breast cancer setting. Among the 20 chemotherapy-naïve subjects treated for up to 12 weeks, 35% (n=7) reported reversible Grade 3 (n=5) or Grade 4 (n=2) elevations of liver transaminases. All Grade 3/4 elevations of liver transaminases occurred within 4-6 weeks of treatment initiation and were resolved or resolving with dose hold or discontinuation of tucatinib and paclitaxel. There were no concurrent increases in total bilirubin or alkaline phosphatase, and no subject met criteria for Hy's law.

Increases in paclitaxel C_{max} and/or AUC at 60 mg/m² in the presence of tucatinib are predicted to be below exposures achieved when used at recommended doses (100 mg/m² administered as a 1-hour IV infusion weekly; 175 mg/m² administered as a 3-hour IV infusion every 3 weeks), where clinical safety is well established.

The proposed starting dose of 60 mg/m² was chosen as it is predicted to not exceed exposures seen at recommended clinical doses when administered in combination with a strong CYP3A4 inhibitor, it is a recommended dose level when dose reductions are made due to toxicity, and is expected to provide opportunity for clinical benefit with acceptable risk for adverse safety events. Should paclitaxel 60 mg/m^2 be found to be tolerable by the SMC, paclitaxel will be escalated to the standard dose of 80 mg/m^2(administered as a 1-hour IV infusion on Days 1, 8 and 15 every 28 days) and evaluated in the dose optimization stage (See Section 3.1.1.1).

4 STUDY POPULATION

This study will enroll subjects with locally-advanced unresectable or metastatic HER2+ GEC who have received prior treatment with a HER2-directed antibody. Subjects must meet all of the enrollment criteria specified in Section 4.1 and Section 4.2 to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma
2. HER2+ disease documented since progression of the most recent line of systemic therapy, as follows:
   a. Phase 2 paclitaxel dose optimization stage:
      - HER2 amplification in a blood-based NGS assay performed at a central laboratory, or
      - HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) assay of a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory

   b. Phase 2 dose expansion stage:
      i. Cohort 2A: HER2 amplification in a blood-based NGS assay performed at a central laboratory
      ii. Cohort 2B: No HER2 amplification by blood-based NGS assay, but HER2 overexpression/amplification by IHC and ISH (IHC3+ or IHC2+/ISH+) assay of a tumor tissue sample, processed in a CLIA- or ISO-accredited laboratory

   c. Phase 3: HER2 amplification in a blood-based NGS assay performed at a central laboratory
3. Can supply archival tumor tissue for central assay; if an archival sample is not available, the subject may be eligible, following approval by the medical monitor.
4. History of prior treatment with a HER2-directed antibody
5. Progressive disease during or after first-line therapy for locally-advanced unresectable or metastatic GEC
6. Phase 2: Measurable disease according to RECIST version 1.1
   Phase 3: Measurable or non-measurable disease according to RECIST version 1.1
7. Age ≥18 years, or considered an adult by local regulations, at time of consent
8. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (see APPENDIX B)
9. Life expectancy of at least 3 months, in the opinion of the investigator

10. Adequate hepatic function as defined by the following:

    a. Total bilirubin ≤1.5 × ULN, except for subjects with known Gilbert's disease, who may enroll if the conjugated bilirubin is ≤1.5 × ULN
    b. Transaminases (AST and ALT) ≤2.5 × ULN (≤5 × ULN if liver metastases are present)

11. Adequate baseline hematologic parameters as defined by:

    a. ANC ≥1.5 × 10^9/L
    b. Platelet count ≥100 × 10^9/L; subjects with a stable platelet count from 75-100 × 10^9/L may be included with approval from the medical monitor
    c. Hemoglobin ≥9 g/dL; subjects with hemoglobin ≥8-9 g/dL may be included with approval from the Medical Monitor
    d. In subjects transfused before study entry, transfusion must be ≥14 days prior to start of therapy to establish adequate hematologic parameters independent from transfusion support

12. Estimated glomerular filtration rate (GFR) ≥50 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation as applicable.

13. International normalized ratio (INR) ≤1.5, and prothrombin time (PT) and partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) ≤1.5 × ULN if not receiving anticoagulation therapy. Subjects on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin. If on warfarin, the subject must have an INR of ≤3 and have no active bleeding (within ≤14 days prior to enrollment or randomization, excluding trace hematuria) or pathological condition that carries a high risk of bleeding (i.e., tumor involving major vessels or known varices). See Section 5.4.2 for potential drug interactions with tucatinib and oral anticoagulants.

14. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram or multi-gated acquisition (MUGA) scan documented within 4 weeks prior to first dose of study treatment.

15. Urinary protein of ≤1+ on dipstick or routine urinalysis. If dipstick or routine analysis indicates proteinuria ≥2+, then either a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours or the urine protein/creatinine (UPC) ratio must be <1 to allow participation in study

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

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

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

17. 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 dose of any study drug
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

18. The subject must provide written informed consent

19. Subject must be willing and able to comply with study procedures, laboratory tests, and other requirements of the study

4.2 Exclusion Criteria

1. Subjects with squamous cell or undifferentiated GEC

2. Having received more than 1 line of prior systemic therapy for locally-advanced unresectable or metastatic disease

3. Having received taxanes ≤12 months prior to enrollment, prior treatment with ramucirumab, or prior treatment with tucatinib, lapatinib, neratinib, afatinib, or any other investigational anti-HER2 and/or anti-EGFR tyrosine kinase inhibitor, or with T-DM1, T-DXd, or any other HER2-directed antibody-drug conjugate

4. History of exposure to the following cumulative doses of anthracyclines:

a. Doxorubicin >360 mg/m²
b. Epirubicin >720 mg/m²
c. Mitoxantrone >120 mg/m²
d. Idarubicin >90 mg/m²
e. Liposomal doxorubicin (e.g. Doxil, Caelyx, Myocet) >550 mg/m²

5. History of allergic reactions to trastuzumab, ramucirumab, paclitaxel, or compounds chemically or biologically similar to tucatinib, except for Grade 1 or 2 IRR to trastuzumab or ramucirumab that were successfully managed, or known allergy to any of the excipients in the study drugs or placebos
6. Phase 2 paclitaxel dose optimization stage only: history of prior partial or total gastrectomy
7. Treatment with any systemic anticancer therapy (including hormonal and biologic therapy), radiation, or an experimental agent, or participation in another interventional clinical trial ≤3 weeks prior to first dose of study treatment.
8. Major surgery within 28 days prior to enrollment or randomization, central venous access device placement within 7 days prior to enrollment or randomization, or planned major surgery following initiation of study treatment
9. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    - Anemia
    - Alopecia
    - Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
10. Clinically significant cardiopulmonary disease such as:
    - Ventricular arrhythmia requiring therapy
    - Symptomatic hypertension or uncontrolled asymptomatic hypertension ≥150/≥90 mmHg despite standard medical management, as determined by the investigator
    - Any symptomatic history of CHF, left ventricular systolic dysfunction or decrease in ejection fraction
    - Severe dyspnea at rest (CTCAE Grade ≥3) due to complications of advanced malignancy or hypoxia requiring supplementary oxygen therapy, except when therapy is needed for obstructive sleep apnea
11. Known to be positive for hepatitis B by surface antigen expression. Known to be positive for hepatitis C infection (positive by polymerase chain reaction [PCR]). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks
12. Presence of known chronic liver disease

13. Phase 2: Known to be positive for human immunodeficiency virus (HIV)
    Phase 3: Subjects known to be positive for HIV are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/uL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks
14. Subjects who are pregnant, breastfeeding, or planning to become pregnant from time of informed consent until 7 months following the last dose of study drug
15. Unable to swallow pills
16. Have used a strong cytochrome P450 (CYP)2C8 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.
17. Other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
18. History of malignancy other than GEC within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS of ≥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.
19. History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism during the 3 months prior to enrollment or randomization.
20. Chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs; e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide). Aspirin use at doses up to 325 mg/day is permitted.
21. Significant bleeding disorders, vasculitis, or had a significant bleeding episode from the gastrointestinal tract within 3 months prior to study entry.
22. History of any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment or randomization.
23. History of gastrointestinal perforation and/or fistulae within 6 months prior to enrollment or randomization.
24. Serious non-healing wound or peptic ulcer or bone fracture within 28 days prior to enrollment or randomization

25. History of bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis or chronic diarrhea

26. Active or uncontrolled clinically serious infection

27. Known active central nervous system metastases. 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

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:

- Progressive disease
- AE
- Pregnancy or begins breast feeding while on study
- Investigator decision, due to clinical progression
- Investigator decision, other
- Subject decision, non-AE. Note: Ensure that subjects who decide to stop treatment **because of an AE** are not included in this rationale.
- Study termination by sponsor
- Other, non-AE

If a study drug (tucatinib/placebo, trastuzumab/placebo, ramucirumab, or paclitaxel) is discontinued, study treatment can continue with remaining study drug(s). Subjects who discontinue study treatment without documented radiologic disease progression will undergo follow-up disease assessments at least every 9 weeks until occurrence of disease progression per RECIST version 1.1. Following disease progression, subjects will be followed every 12 weeks until occurrence of a reason for withdrawal from the study (Section 4.4.2). No crossover will be allowed.

4.4.2 Subject Withdrawal from Study

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

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

5 TREATMENTS

5.1 Treatments Administered

Subjects in the Phase 2 portion of the study will receive combination therapy of the investigational medicinal products tucatinib and trastuzumab combined with standard-of-care ramucirumab and paclitaxel. In the Phase 3, subjects will receive either tucatinib and trastuzumab (Arm 3A), tucatinib placebo and trastuzumab placebo (Arm 3B), or tucatinib and trastuzumab placebo (Arm 3C), all combined with ramucirumab and paclitaxel. Study treatment will be given on a 28-day cycle, with tucatinib (or placebo) every day, trastuzumab (or placebo) and ramucirumab on Days 1 and 15, and paclitaxel on Days 1, 8, and 15 (Table 3). In subjects in the Phase 2 undergoing Cycle 1 PK assessments, the first tucatinib dose will be given in the evening on Day 1. In this study, subjects are considered to be on study treatment if they are receiving any of the study drugs (tucatinib/placebo, trastuzumab/placebo, ramucirumab, and/or paclitaxel). Cycles are defined by paclitaxel administration, with a new cycle starting whenever the Day 1 infusion of paclitaxel is administered. If paclitaxel is discontinued, cycles will be defined as occurring every 28 days from the last Day 1 administration of paclitaxel.

In the Phase 2, tucatinib should be dosed at approximately the same time as the start of the paclitaxel infusion on Cycle 1 Day 8 and Cycle 2 Day 1, when both tucatinib and paclitaxel PK are assessed (see Section 7.3). The administration order of the IV study drugs is paclitaxel first, then trastuzumab and ramucirumab, or according to institutional standard of care.

Table 3: Treatment schedule

Agent	Dose	Route	Cycle	Daily frequency	Cycle Day		
					Day 1	Day 8	Day 15
Phase 2							
Tucatinib	300 mg	PO	All	BID	Every day, from Cycle 1 Day 1[a]		
Trastuzumab[b]	4 mg/kg (6 mg/kg on Cycle 1 Day 1)	IV	All	Once	X		X
Ramucirumab	8 mg/kg	IV	All	Once	X		X
Paclitaxel	60 or 80 mg/m² [c]	IV	All	Once	X	X	X
Phase 3							
Arm 3A							
Tucatinib	300 mg	PO	All	BID	Every day, from Cycle 1 Day 1		
Trastuzumab[b]	4 mg/kg (6 mg/kg on Cycle 1 Day 1)	IV	All	Once	X		X
Ramucirumab	8 mg/kg	IV	All	Once	X		X
Paclitaxel	Phase 2 recommended dose	IV	All	Once	X	X	X
Arm 3B							
Tucatinib placebo	Not applicable	PO	All	BID	Every day, from Cycle 1 Day 1		
Trastuzumab placebo[b]	Not applicable	IV	All	Once	X		X
Ramucirumab	8 mg/kg	IV	All	Once	X		X
Paclitaxel	80 mg/m²	IV	All	Once	X	X	X
Arm 3C							
Tucatinib	300 mg	PO	All	BID	Every day, from Cycle 1 Day 1		
Trastuzumab placebo[b]	Not applicable	IV	All	Once	X		X
Ramucirumab	8 mg/kg	IV	All	Once	X		X
Paclitaxel	Phase 2 recommended dose	IV	All	Once	X	X	X

a In subjects in the Phase 2 undergoing Cycle 1 PK assessments, the first tucatinib dose will be given in the evening on Day 1.

b Trastuzumab may also be given on a weekly basis at 2 mg/kg IV, but only in circumstances where weekly infusions are required to resynchronize with the paclitaxel cycle.

c The paclitaxel dose optimization stage will initially evaluate 60 mg/m² and potentially escalate to 80 mg/m². Alternative dose levels/schedules may be evaluated as recommended by the SMC

5.1.1 Investigational Products

5.1.1.1 Tucatinib or Tucatinib Placebo

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

In the Phase 2, tucatinib will be supplied in an open-label manner, by the sponsor. In the Phase 3, treatment allocation to tucatinib or tucatinib placebo will be double-blinded.

Detailed information describing the preparation, administration, and storage of tucatinib is located in the Pharmacy Instructions.

Description

Tucatinib drug product is supplied as both a coated yellow oval-shaped tablet in a 150 mg dosage strength and a coated yellow round convex tablet in a 50 mg dosage strength. The tablets are manufactured from a drug product intermediate amorphous dispersion of tucatinib in polyvinylpyrrolidone-vinyl acetate copolymer, which is then combined with the

pharmaceutical excipients (microcrystalline cellulose, sodium chloride, potassium chloride, sodium bicarbonate, silicon dioxide, crospovidone, and magnesium stearate), and compressed into tablets.

Dose and Administration

Tucatinib will be administered according to the following:

- Route of administration: PO
- Dose: Tucatinib 300 mg will be administered PO BID from Cycle 1 Day 1 onwards.
- Dosing schedule: BID on each day of study treatment. Tucatinib or tucatinib placebo should be taken once in the morning and once in the evening, with approximately 8 to 12 hours between doses in the same calendar day. In subjects in the Phase 2 undergoing Cycle 1 Day 1 PK assessments, tucatinib will not be administered in the morning of Cycle 1 Day 1; the first dose will be in the evening, after all PK samples have been collected.

In the Phase 3, subjects in Arm 3B receive a tucatinib placebo PO BID.

Dose modifications of tucatinib or placebo are described in Section 5.2. Subjects will be instructed by the pharmacist or investigator as to the specific number of tablets required for each dose. At each visit during study treatment, subjects will be supplied with the appropriate number of tablets for the number of doses to be taken prior to the next scheduled visit.

It is recommended that if a subject misses a scheduled dose of tucatinib or placebo and less than 6 hours have passed since the scheduled dosing time, the dose should be immediately taken. It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose but should wait and take the next regularly scheduled dose. Tablets may be taken with or without food. Tablets must be swallowed whole and may not be crushed, chewed, or dissolved in liquid. On the day of dosing, the individual unit dose of the tucatinib or placebo 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 or pill count and study drug accountability.

Storage and Handling

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

The tablets are coated with a non-hazardous film to prevent any exposure to the active pharmaceutical ingredient during routine handling. Avoid breaking or crushing tablets. In the

event the tablets are broken or crushed, wash hands and exposed skin thoroughly with soap and water.

Refer to the Pharmacy Instructions for more information.

Packaging and Labeling

Each bottle of investigational study drug will be labeled in compliance with applicable regulatory requirements. Refer to the Pharmacy Instructions for more information.

Preparation

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.1.1.2 Trastuzumab or Trastuzumab Placebo

Description

Trastuzumab is a humanized immunoglobulin G1 (IgG1) kappa mAb which binds to the extracellular domain of HER2; it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which over express the HER2 protein. Trastuzumab is indicated for adjuvant treatment of HER2-overexpressing node positive or node negative breast cancer, in combination with paclitaxel for first-line treatment of HER2-overexpressing mBC, as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease, and in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic GEC who have not received prior treatment for metastatic disease.

Method of Procurement

In Phase 2, details regarding trastuzumab sourcing may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

In the Phase 3, treatment allocation to trastuzumab or trastuzumab placebo will be double-blinded, and will be supplied.

Dose and Administration

Trastuzumab will be administered on Day 1 and 15 of every 28-day cycle. A loading dose of 6 mg/kg IV will be administered on Cycle 1 Day 1 followed by 4 mg/kg with each subsequent dose. Trastuzumab placebo will be used in Arms 3B and 3C of the Phase 3. Trastuzumab may also be given on a weekly basis at 2 mg/kg IV once weekly, in order to resynchronize administration to Day 1 and 15 of the 28-day paclitaxel cycle, after discussion with the medical monitor. If dosing of trastuzumab has been held for >4 weeks and the medical monitor has agreed to restart trastuzumab, the IV loading dose of 6 mg/kg should be given per approved dosing instructions. Trastuzumab infusion rates will be per institutional guidelines.

To maintain the blind, subjects assigned to receive trastuzumab placebo will receive an IV infusion that does not contain trastuzumab. Refer to Pharmacy Manual for additional instructions.

Storage and Handling

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

Packaging and Labeling

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

Preparation

Trastuzumab is a lyophilized sterile powder for reconstitution and should be prepared and administered per instructions in the trastuzumab package insert for administration instructions. Trastuzumab will be administered IV under the direction of the investigator.

5.1.2 Standard of Care

5.1.2.1 Ramucirumab

Description

Ramucirumab (CYRAMZA®) is a recombinant human IgG1 mAb with an approximate molecular weight of 147 kDa, produced in genetically engineered mammalian NS0 cells. It is a VEGFR2 antagonist that specifically binds VEGFR2 and blocks binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. It is indicated for the treatment of subjects with advanced or metastatic GEC with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy as a single agent or in combination with paclitaxel. It is also indicated as first-line treatment in combination with erlotinib for metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 substitution mutations, treatment of previously-treated metastatic NSCLC in combination with docetaxel, treatment in subjects with previously treated mCRC in combination with FOLFIRI, and treatment in subjects with previously treated hepatocellular carcinoma.

Method of Procurement

Details regarding the sourcing of ramucirumab may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

Dose and Administration

Ramucirumab 8 mg/kg will be administered on Days 1 and 15 of each 28-day cycle. Ramucirumab will be administered IV per institutional guidelines, under the direction of the investigator. Ramucirumab is for IV infusion only. Do not administer as an IV push or bolus.

Calculate the UPC ratio on a urine sample taken within 1 day prior to each dose. If UPC ≥2, refer to the ramucirumab dose modification guidelines in Section 5.2.3.

IRRs related to ramucirumab have been observed. To reduce the risk of IRRs with Ramucirumab, subjects will receive premedication/postmedication as described in Section 5.3.

Storage and Handling

Ramucirumab should be stored according to the package insert.

Packaging and Labeling

Commercially available ramucirumab will be used.

Preparation

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

5.1.2.2 Paclitaxel

Description

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability inhibits the normal dynamic reorganization of the microtubule network, which is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Method of Procurement

Details regarding sourcing of paclitaxel may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

Dose and Administration

Paclitaxel will be administered on Days 1, 8, and 15 of each 28-day cycle. Paclitaxel will be administered IV per institutional guidelines, under the direction of the investigator. The initial paclitaxel dose to be evaluated in the Phase 2 dose optimization stage is 60 mg/m²; an 80 mg/m² dose level may be explored. Additional dose levels/schedules may be evaluated as recommended by the SMC. In the Phase 3, paclitaxel will be administered at the recommended dose identified in Phase 2 in Arms 3A and 3C, and at 80 mg/m² in Arm 3B.

Subjects with a history of severe hypersensitivity reactions to products containing polyoxyl 35 castor oil (e.g., cyclosporin for injection concentrate, teniposide for injection concentrate) are not to be treated with paclitaxel.

Injection site and hypersensitivity reactions related to paclitaxel are common. To reduce the risk of these reactions, subjects will receive premedication as described in Section 5.3. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Vital signs should be monitored frequently during the paclitaxel infusion.

Initiate concomitant G-CSF as clinically indicated.

Table 4 summarizes the conditions, in terms of AEs and laboratory test abnormalities, that must be met for before administering paclitaxel. If the conditions are not met on the planned Day 1 of a cycle, then the paclitaxel infusion should be delayed until the conditions are met. If the conditions are not met on the planned Day 8 or 15, then the paclitaxel infusion should be skipped.

Table 4: Criteria for paclitaxel treatment on Day 1, 8, and 15 of each cycle

AE/abnormality	Day 1	Day 8 and 15
ANC:	$\geq 1.5 \times 10^9$/L	$\geq 1.0 \times 10^9$/L
Platelets:	$\geq 75 \times 10^9$/L	
Bilirubin:	≤1.5 × ULN	
AST/ALT:	≤3 × ULN [a] (<5 × ULN if liver metastases present)	
Paclitaxel-related AEs:	Grade ≤1 or baseline (except for alopecia) Anemia Grade ≤2	

a On Cycle 1 Day 1, AST/ALT is to be ≤2.5 × ULN (≤5 × ULN if liver metastases present).

Storage and Handling

Paclitaxel should be stored according to the package insert.

Packaging and Labeling

Commercially available paclitaxel will be used.

Preparation

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

5.2 Dose Modifications

Dose modification recommendations (including dose holds, dose reduction, or discontinuation of drugs) in response to AEs are described in Section 5.2.1 for tucatinib/placebo, in Section 5.2.2 for trastuzumab/placebo, in Section 5.2.3 for ramucirumab, and in Section 5.2.4 for paclitaxel. Dose reductions or treatment interruption/discontinuation for reasons other than those described in the following sections may be made by the investigator if it is deemed in the best interest of subject safety. Whenever possible, these decisions should first be discussed with the study medical monitor.

All AEs and clinically significant laboratory abnormalities should be assessed by the investigator for relationship to tucatinib/placebo, trastuzumab/placebo, ramucirumab, and paclitaxel. An AE may be considered related to any single study drug, any combination of study drugs, or to none of them. In the event that the relationship is unclear, discussion should be held with the study medical monitor, to determine which study drug(s) should be held and/or modified.

The beginning of each cycle is defined by the administration of the Day 1 infusion of paclitaxel. During paclitaxel cycle delays, ramucirumab and trastuzumab administration should continue as planned. When the new paclitaxel cycle starts, ramucirumab should be administered on Day 1, even if it was administered the previous week. Trastuzumab should not be administered on Day 1 if trastuzumab 4 mg/kg was administrated the previous week; instead, to synchronize trastuzumab to a delayed paclitaxel cycle, trastuzumab 2 mg/kg should be given on Day 8 followed by trastuzumab 4 mg/kg on Day 15. If paclitaxel cannot be administered on Day 8 or Day 15 of a cycle, that day is skipped, ramucirumab and trastuzumab are administered as scheduled, and the paclitaxel schedule continues unchanged. If paclitaxel is discontinued, protocol-defined visits will proceed using a 28-day cycle starting from the last paclitaxel Day 1, regardless of dose holds or delays.

Doses held for toxicity will not be replaced. Once reduced, the dose of a study drug should not be re-escalated. Any study drug that requires a delay >4 weeks should be discontinued, unless a longer delay is approved by the study medical monitor. If one or more study drugs are discontinued, study treatment can continue with the remaining study drugs.

5.2.1 Tucatinib/placebo Dose Modifications

Up to 3 dose reductions of tucatinib/placebo are allowed (Table 5). Subjects who would require a dose reduction to below 150 mg BID should discontinue treatment with tucatinib/placebo. Dose reductions of larger intervals than those described in Table 5 may be made at the discretion of the investigator with approval by the medical monitor, but dose reductions to below 150 mg BID are not allowed.

Table 5: Tucatinib/placebo: Recommended dose reduction schedule for adverse events

Dose Reduction Schedule	Tucatinib/Placebo Dose Level
Starting dose	300 mg PO BID [a]
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 tucatinib

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

General dose modification guidelines for tucatinib/placebo are provided in Table 6 and Table 7. For subjects with documented Gilbert's disease, contact the medical monitor for guidance regarding dose modifications for liver enzyme abnormalities.

Table 6: Dose modifications for clinical adverse events related to tucatinib/placebo

Adverse Reactions	Tucatinib Dose Modification
Diarrhea	
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1 or baseline Resume tucatinib at same dose
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold tucatinib until recovery to ≤ Grade 1 or baseline Reduce tucatinib dose.
Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue tucatinib treatment.
Other adverse reactions	
Grade 3	Hold tucatinib until recovery to ≤ Grade 1 or baseline Reduce tucatinib dose
Grade 4	Permanently discontinue tucatinib.

Table 7: Dose modifications of tucatinib/placebo for liver enzyme abnormalities, regardless of relationship to tucatinib/placebo

Laboratory Abnormality	Tucatinib Dose Modification
Bilirubin elevation >1.5–3 × ULN	Hold tucatinib until recovery to ≤1.5 × ULN Resume tucatinib at same dose
Bilirubin elevation >3–10 × ULN	Hold tucatinib until recovery to ≤1.5 × ULN Reduce tucatinib dose.
Bilirubin elevation >10 × ULN	Permanently discontinue tucatinib.
ALT or AST elevation >5–20 × ULN	Hold tucatinib until recovery to ≤3 × ULN or return to baseline level in subjects with known liver metastasis Reduce tucatinib dose.
ALT or AST elevation >20 × ULN	Permanently discontinue tucatinib.
ALT or AST >3 × ULN AND bilirubin >2 × ULN	Permanently discontinue tucatinib.

5.2.2 Trastuzumab/placebo Dose Modifications

In the event of Grade ≥3 trastuzumab-related AEs, hold trastuzumab until the AE has resolved to Grade ≤1 or pretreatment levels and initiate or intensify applicable medical therapy, as appropriate. Resume trastuzumab at the same dose; the trastuzumab/placebo dose may not be reduced. If dosing of trastuzumab is held for >4 weeks and the medical monitor has agreed to restart trastuzumab, the IV loading dose of 6 mg/kg should be given per approved dosing instructions.

Trastuzumab dose modification guidelines for left ventricular dysfunction and cardiomyopathy are presented in Section 5.2.2.1, for IRR in Section 5.2.2.2, and for hypersensitivity reactions in Section 5.2.2.3.

5.2.2.1 Left Ventricular Dysfunction and Cardiomyopathy

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/placebo dose modification guidelines for left ventricular dysfunction, regardless of relationship to study drug, are provided in Table 8.

Table 8: Trastuzumab and trastuzumab placebo dose modification 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 <50%	
<10% decrease from baseline	Resume treatment with trastuzumab
≥10% decrease from baseline	Discontinue trastuzumab
- LVEF <45%	Discontinue trastuzumab

5.2.2.2 Infusion-related Reactions

Symptoms of IRR occurring after trastuzumab administration include fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. In severe cases, symptoms have included bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, usually reported during or immediately following the initial infusion. However, the onset and clinical course are variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious IRR.

Interrupt trastuzumab infusion in all subjects experiencing dyspnea or clinically significant hypotension, and administer supportive therapy (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms. In subsequent infusions, premedicate subjects with antihistamines and/or corticosteroids.

Discontinue trastuzumab in subjects with Grade 3 to 4 IRR.

5.2.2.3 Hypersensitivity Reactions

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE version 5.0). 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.

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 (Rosello 2017).

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

5.2.3 Ramucirumab Dose Modifications

Up to 2 dose reductions of ramucirumab will be allowed (Table 9). Subjects who would require a dose reduction to below 5 mg/kg should discontinue treatment with ramucirumab.

Table 9: Ramucirumab: Recommended dose reduction schedule for adverse events

Dose Reduction Schedule	Ramucirumab Dose Level
Starting dose	8 mg/kg
1st dose reduction	6 mg/kg
2nd dose reduction	5 mg/kg
Requirement for further dose reduction	Discontinue treatment

General dose modification guidelines for ramucirumab are provided in Table 10. Ramucirumab should be held for 28 days prior to any surgery, and resumed no sooner than 28 days after surgery, once the wound is fully healed and following discussion with the medical monitor.

Ramucirumab dose modification guidelines for hypertension are presented in Section 5.2.3.1, for IRR in Section 5.2.3.2, for proteinuria and nephrotic syndrome in Section 5.2.3.3, for impaired wound healing in Section 5.2.3.4, and for reversible posterior leukoencephalopathy syndrome (RPLS) in Section 5.2.3.5.

Table 10: Dose modifications for clinical adverse events

Clinical Adverse Event	Ramucirumab Dose Modification
Regardless of relationship to ramucirumab	
Grade 3-4 hemorrhage	Discontinue ramucirumab
Gastrointestinal perforation any grade	Discontinue ramucirumab
Wound healing complications of any grade that require medical intervention	Discontinue ramucirumab
Grade 3 or 4 arterial thromboembolic events or any pulmonary embolism or deep vein thrombosis occurring or worsening during anticoagulant therapy	Discontinue ramucirumab
Grade 3-4 hypertension	Hold until controlled by medical management
Grade 3-4 hypertension not controlled by antihypertensive therapy Hypertensive crisis or hypertensive encephalopathy	Discontinue ramucirumab
Proteinuria	
– >2+ by dipstick or routine urinalysis	Evaluate UPC ratio prior to next dose and continue ramucirumab if UPC ratio <2
– UPC ratio 2 to ≤3	Hold ramucirumab for up to 14 days until UPC ratio <2 Resume ramucirumab at reduced dose Discontinue ramucirumab if UPC remains ≥2 after 14 days Discontinue ramucirumab if reoccurrence of UPC ≥2
– UPC ratio >3 or nephrotic syndrome	Discontinue ramucirumab
RPLS confirmed by MRI	Discontinue ramucirumab
Spontaneous development of fistula	Discontinue ramucirumab
Hepatic encephalopathy or hepatorenal syndrome	Discontinue ramucirumab
Related to ramucirumab	
IRR	
– Grade 1-2	Reduce infusion rate by 50%
– Grade 3-4	Discontinue ramucirumab

5.2.3.1 Hypertension

Control hypertension prior to initiating treatment with ramucirumab. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold ramucirumab for severe hypertension until medically controlled.

Permanently discontinue ramucirumab for medically significant hypertension that cannot be controlled with antihypertensive therapy or in subjects with hypertensive crisis or hypertensive encephalopathy.

5.2.3.2 Infusion-related Reactions

Symptoms of IRR occurring after ramucirumab administration have included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

Premedicate prior to each ramucirumab infusion (see Section 5.3). Monitor subjects during the infusion for signs and symptoms of IRR in a setting with available resuscitation equipment.

Reduce the infusion rate by 50% for Grade 1 to 2 IRR. Permanently discontinue ramucirumab for Grade 3 to 4 IRRs.

5.2.3.3 Proteinuria and Nephrotic Syndrome

Monitor proteinuria by urine dipstick and/or UPC ratio. If the result of the urine dipstick is 2+ or greater, evaluate UPC ratio and withhold ramucirumab if UPC ratio is ≥2. Reinitiate ramucirumab at a reduced dose once UPC is <2. Permanently discontinue ramucirumab for UPC ratio >3, reoccurrence of UPC ratio >2, or in the setting of nephrotic syndrome.

5.2.3.4 Impaired Wound Healing

Withhold ramucirumab for 28 days prior to surgery. Do not administer ramucirumab for at least 28 days following a major surgical procedure, until the wound is fully healed, following discussion with the medical monitor. Discontinue ramucirumab in subjects who develop wound healing complications that require medical intervention.

5.2.3.5 Reversible Posterior Leukoencephalopathy Syndrome

In the event of RPLS, confirm the diagnosis of RPLS with magnetic resonance imaging (MRI) and permanently discontinue ramucirumab.

5.2.4 Paclitaxel Dose Modifications

The paclitaxel dose can be reduced by increments of 10 mg/m² (i.e., reductions to 70 mg/m² then to 60 mg/m² for a subject initially receiving 80 mg/m²); however, subjects who would require a dose reduction to below 60 mg/m² should discontinue treatment with paclitaxel. Dose reductions are implemented only at the start of a cycle, not on Day 8 or 15.

General dose modification guidelines for paclitaxel are provided in Table 11 and Table 12.

Paclitaxel dose modification guidelines for hepatotoxicity are presented in Section 5.2.4.1 and for hypersensitivity in Section 5.2.4.2.

Table 11: Paclitaxel dose modifications for clinical adverse events related to paclitaxel

Adverse Reaction	Paclitaxel Dose Modification
Paclitaxel-related non-hematological AEs	Delay Day 1 administration until recovery to Grade ≤1 or baseline or skip Day 8 or 15
– Grade ≥3	Reduce paclitaxel dose in next cycle
Grade 3-4 peripheral neuropathy	Delay Day 1 administration until recovery to Grade ≤1 or baseline or skip Day 8 or 15 Reduce paclitaxel dose in next cycle
Grade 3-4 hypersensitivity reaction	Discontinue paclitaxel

Table 12: Paclitaxel dose modifications for hematological abnormalities, regardless of relationship to paclitaxel

Hematological Abnormality	Paclitaxel Dose Modification
ANC $<1.5 \times 10^9$/L	Delay Day 1 administration until recovery to $\geq 1.5 \times 10^9$/L
ANC $<1.0 \times 10^9$/L	Delay Day 1 administration recovery to $\geq 1.5 \times 10^9$/L or skip Day 8 or 15 administration
Platelet count $<75 \times 10^9$/L	Delay Day 1 administration recovery to $\geq 75 \times 10^9$/L or skip Day 8 or 15 administration
Grade 4 hematological abnormalities	Reduce paclitaxel dose in next cycle

5.2.4.1 Hepatotoxicity

Dose modification for paclitaxel in the case of liver enzyme abnormalities, regardless of relationship to study drug, are summarized in Table 13. A rise in indirect bilirubin with a normal direct bilirubin believed to be attributable to Gilbert's disease does not require change in dose or a drug hold.

Table 13: Paclitaxel dose modification guidelines for liver enzyme abnormalities, regardless of relationship to paclitaxel

Liver enzyme abnormality	Action
Bilirubin elevation >1.5–3 × ULN	Delay Day 1 administration until recovery to ≤1.5 × ULN or skip Day 8 or 15 infusions
Bilirubin elevation >3-10 × ULN	Delay Day 1 administration until recovery to ≤1.5 × ULN or skip Day 8 or 15 infusions Reduce paclitaxel dose in next cycle
Bilirubin elevation >10 × ULN	Permanently discontinue paclitaxel.
AST or ALT elevation >5-20 × ULN	Delay Day 1 administration until recovery to ≤3 × ULN or return to baseline level in subjects with known liver metastasis or skip Day 8 or 15 infusions Reduce paclitaxel dose
AST or ALT elevation >20 × ULN	Permanently discontinue paclitaxel
ALT or AST >3 × ULN AND bilirubin >2 × ULN	Permanently discontinue paclitaxel

5.2.4.2 Hypersensitivity Reactions

Paclitaxel treatment interruption is not required for minor symptoms of hypersensitivity, such as flushing, skin reactions, dyspnea, hypotension, or tachycardia.

Paclitaxel should be discontinued and aggressive symptomatic therapy applied in the event of severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria.

5.3 Required Premedication and Postmedication

Suggested premedication to be administered prior to each paclitaxel infusion is presented in Table 14. Paclitaxel premedication can be adjusted according to standard institutional practice.

Table 14: Paclitaxel premedication

Pre-medication	Dose	Administration time prior to paclitaxel
Dexamethasone	8-10 mg PO or 8-10 mg IV	30 to 60 min
Diphenhydramine or equivalent	12.5-50 mg IV	30 to 60 min
Ranitidine	50 mg IV	30 to 60 min

Ramucirumab pre-medication with an IV histamine-1 receptor antagonist (e.g., diphenhydramine hydrochloride) may be given prior to each ramucirumab infusion at the discretion of the investigator. For subjects who have experienced a Grade 1 or 2 IRR considered at least possibly related to ramucirumab, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each ramucirumab infusion.

Subjects who have experienced dyspnea or clinically significant hypotension related to trastuzumab during or following the previous infusion should be premedicated with antihistamines and/or corticosteroids prior to subsequent trastuzumab infusions.

5.4 Concomitant Therapy

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

5.4.1 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. All blood products and concomitant medications received from the first day of study treatment administration until 30 days after the final dose of any study drug are to be recorded in the medical records

- During study treatment, subjects may receive supportive care, including bisphosphonates, hematologic and anti-infectious support, pain management, antacids, laxatives, and treatment of other newly diagnosed or concurrent medical conditions
- 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, following consultation with the medical monitor
- If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor). These concomitant procedures are permitted for non-target lesions only, in situations where other disease sites remain assessable per RECIST v1.1. These interventions should be avoided if clinically feasible until after the second response assessment. The medical monitor should be consulted prior to the intervention occurring.
- Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.
- Subjects stabilized on chronic oral anticoagulation therapy are eligible, provided that the coagulation parameters defined in the inclusion criteria are met.
- Routine prophylaxis with vaccines is permitted, if vaccines used do not contain live micro-organisms

5.4.2 Prohibited Concomitant Therapy

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

- Investigational drugs and devices
- Anticancer therapy, including but not limited to chemotherapy
- Radiation therapy, except for palliative radiotherapy at focal sites which are not considered target lesions per RECIST version 1.1, which may be given after consultation with the medical monitor. Radiation therapy directed at target lesions per RECIST version 1.1 requires prior approval by the medical monitor. Tucatinib and paclitaxel must be held 7 days prior to and 7 days after radiation therapy.
- Live vaccines
- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment (see APPENDIX D)
- Strong inhibitors or inducers of CYP2C8 are prohibited as concomitant medications during study treatment; Strong inhibitors of CYP2C8 are also prohibited within one week of discontinuation of tucatinib treatment (see APPENDIX E). Moderate inhibitors of CYP2C8 should be used with caution
- Use of sensitive CYP3A substrates should be avoided 1 week prior to first dose of study treatment and during study treatment (see APPENDIX F). Consider using an alternate medication which is not a sensitive CYP3A substrate. If unavoidable,

consider dose reduction of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.

- Concomitant use of tucatinib with digoxin, a P-glycoprotein (P-gp) substrate, increases digoxin concentrations, which may increase the risk for digoxin related adverse reactions. Concomitant use of tucatinib with digoxin or P-gp substrates with a narrow therapeutic index (such as, but not limited to, dabigatran, fexofenadine, and cyclosporine) should be used with caution. Refer to the prescribing information of digoxin or other P-gp substrates for dosage adjustment recommendations due to drug interactions.
- NSAIDs (e.g., indomethacin, ibuprofen, naproxen, or similar agents) or other anti-platelet agents (e.g., clopidogrel, ticlopidine, dipyridamole, anagrelide). Aspirin use at doses up to 325 mg/day is permitted. Ongoing aspirin therapy at doses exceeding 325 mg/day is not permitted.
- Subjects who develop venous thromboembolism during study treatment may continue study therapy and receive anticoagulation. Subjects who begin anticoagulation therapy during treatment on study must receive low molecular weight heparin (not oral anticoagulation).

5.4.3 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.

Refer to the package insert for overdose information for trastuzumab, ramucirumab, and paclitaxel.

5.5 Treatment Compliance

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

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

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

6 STUDY ACTIVITIES

6.1 Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related AE (defined in Section 7.8.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (blood chemistry panel, complete blood count [CBC] with differential, coagulation panel, and urinalysis [see Section 7.8.3]), vital signs, weight, physical exam, 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.

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 Visit (Days –28 to -1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Height
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight
- Blood sample for NGS assay of HER2 amplification for biomarker analysis
- Collection of archived tumor tissue sample (or freshly-cut slides following consultation with the medical monitor) sampled following progression during/after the most recent line of therapy, or performed prior to the first line therapy for advanced disease
- Blood sample for hepatitis B and C serology (see Section 7.8.3)
- Electrocardiogram (ECG)
- Echocardiogram or MUGA scan
- Radiographic disease assessments will evaluate all known sites of disease, preferably using high quality spiral contrast computed tomography (CT), and covering, at a minimum, the chest, abdomen, and pelvis. positron emission tomography (PET)-CT scans (if high quality CT scan is included) and/or MRI scans may also be used as appropriate, as well as additional imaging of any other known sites of disease (e.g., nuclear bone scan imaging for bone lesions). For each subject, the same imaging modality as used at baseline should be used throughout the study.

6.2.1 Baseline Visit (Days –7 to 1)

- Study eligibility per inclusion/exclusion criteria
- Serum or urine β-hCG pregnancy test for subjects of childbearing potential (see Section 4.3)
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight
- Physical exam
- ECOG performance status
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3):
  - CBC with differential
  - Blood chemistry panel
  - Coagulation panel
  - Urinalysis; if urinalysis indicates proteinuria ≥2+, then either a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours or the UPC ratio must be <1 to allow participation in study

6.3 Randomization (Days –5 to 1)

Randomization occurs in the Phase 3 portion after eligibility per inclusion/exclusion criteria is confirmed. Randomization MUST occur on or before Cycle 1 Day 1, such that dosing commences within 5 days after randomization. See Section 3.1.8 for a description of randomization and stratification procedures.

6.4 Treatment Period (28-day cycles)

6.4.1 Cycle 1 Day 1

- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Physical exam *
- ECOG performance status *
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3):
  - CBC with differential *
  - Blood chemistry panel *
  - Urinalysis *
- Serum or urine β-hCG pregnancy test for subjects of childbearing potential (see Section 4.3); to be done within 7 days prior to study drug dosing
- Paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with a gastrectomy: Paclitaxel PK samples (see Section 7.3)

- Phase 3 only: HRQoL questionnaires (Section 7.7; to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment):
  - EORTC QLQ-C30
  - EORTC QLQ-OG25
  - EQ-5D-3L
- Dispense tucatinib or placebo and provide dosing diary to subject. Administer the first dose of tucatinib/placebo. (Subject will self-administer the remainder of doses during the treatment cycle and document in the diary.).
  In subjects in the Phase 2 undergoing Cycle 1 paclitaxel PK assessment, do not administer the first dose of tucatinib until the evening, when all PK samples have been drawn.
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B
- Administer trastuzumab 6 mg/kg IV loading dose or trastuzumab placebo IV
- Administer ramucirumab 8 mg/kg IV

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

6.4.2 Cycle 1 Day 8 (±1 day)

- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Blood samples for laboratory testing (as listed in Section 7.8.3)
  - CBC with differential *
  - Blood chemistry panel *
- Paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with a gastrectomy: Tucatinib and paclitaxel PK samples (see Section 7.3). Record the date and time of the subject's last meal prior to tucatinib administration.
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B

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

6.4.3 Cycle 1 Day 15 (±1 day)

- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3:
  - CBC with differential *
  - Blood chemistry panel *
  - Urinalysis *
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B
- Administer trastuzumab 4 mg/kg IV or trastuzumab placebo IV
- Administer ramucirumab 8 mg/kg IV

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

6.4.4 Cycle 1 Day 22 (±1 day)

- Blood samples for laboratory testing (as listed in Section 7.8.3)
  - CBC with differential *
  - Blood chemistry panel *

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

6.4.5 Cycles >1 Day 1 (-1 to +3 days)

- Phase 3 only: HRQoL questionnaires (Section 7.7) and HCRU (Section 7.6); to be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment:
  - EORTC QLQ-C30
  - EORTC QLQ-OG25
  - EQ-5D-3L
  - Review HCRU since the last study visit
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Physical exam *
- ECOG performance status *
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3:
  - CBC with differential *
  - Blood chemistry panel *
  - Urinalysis *
  - Coagulation panel *
- Serum or urine β-hCG pregnancy test for subjects of childbearing potential (see Section 4.3); to be done within 7 days prior to study drug dosing

- PK samples (see Section 7.3):
  - Paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with a gastrectomy: Cycle 2: Tucatinib and paclitaxel PK samples
  - All other subjects: Cycles 2 to Cycle 6: Tucatinib predose sample
    Record the date and time of the subject's last meal prior to tucatinib administration.
- Review subject diary or pill count for tucatinib (or tucatinib placebo in Phase 3) drug compliance from previous cycle, dispense tucatinib (or tucatinib placebo in Phase 3), and administer the first dose. (Subject will self-administer the remainder of doses during the treatment cycle and may document self-administration in the diary.)
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B
- Administer trastuzumab 4 mg/kg IV or trastuzumab placebo IV
- Administer ramucirumab 8 mg/kg IV

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

6.4.6 Cycles >1 Day 8 (±1 day)

- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Blood samples for laboratory testing (as listed in Section 7.8.3
  - CBC with differential *
  - Blood chemistry panel *
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B

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

6.4.7 Cycles >1 Day 15 (±1 day)

- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight *
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3:
  - CBC with differential *
  - Blood chemistry panel *
  - Urinalysis *
- Administer paclitaxel IV at the current dose level in the Phase 2, the recommended dose in Arms 3A and 3C, and at 80 mg/m² in Arm 3B
- Administer trastuzumab 4 mg/kg IV or trastuzumab placebo IV
- Administer ramucirumab 8 mg/kg IV

* Predose assessments do not need to be repeated if performed within 1 day prior to dose administration

6.4.8 Every 6 Weeks as Determined by Cycle 1 Day 1, through Week 36, then Every 9 Weeks (±7 days)

- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or MRI scan, as appropriate (see Section 7.2). The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated
  If an interim unscheduled assessment is performed, scans should continue to be done on schedule, with scheduling determined by the date of Cycle 1 Day 1. In cases of medical contraindication for repeat scans, contact the medical monitor to discuss as, in some instances, assessments done at an unscheduled timepoint may not need to be repeated if medically contraindicated as approved by the medical monitor

6.4.9 Every 12 Weeks (±14 days)

- Echocardiogram or MUGA scan, using the same cardiac testing modality performed in Screening/Baseline. Scheduling is determined by date of most recent screening or on treatment echocardiogram/MUGA.

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

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

- Phase 3 only: HRQoL questionnaires (Section 7.7) and HCRU (Section 7.6); to be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment:
  - EORTC QLQ-C30
  - EORTC QLQ-OG25
  - EQ-5D-3L
  - Review HCRU since the last study visit
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiration rate) and weight
- Physical exam
- ECOG performance status
- Blood and urine samples for laboratory testing (as listed in Section 7.8.3:
  - CBC with differential
  - Blood chemistry panel
  - Coagulation panel
  - Urinalysis
- ECG

- Echocardiogram or MUGA scan, using the same cardiac testing modality performed in Screening/Baseline. Not required if an echocardiogram or MUGA scan was done within the previous 12 weeks (excluding the Screening/Baseline assessment).
- Serum or urine β-hCG pregnancy test for subjects of childbearing potential (see Section 4.3)
- Blood sample for biomarker analysis
- Only in subjects who discontinue study treatment for reasons other than radiographic disease progression per RECIST version 1.1: High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or MRI scan, as appropriate (see Section 7.2). The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated. Not required if imaging was performed within 30 days of discontinuing study treatment.
- Review subject diary or pill count for tucatinib (or tucatinib placebo in Phase 3) drug compliance from previous cycle, if tucatinib was administered in the last cycle
- For persons of childbearing potential: Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment. Testing may be performed at home. If performed at home, site staff will contact the subject monthly to confirm testing was performed and obtain pregnancy test results.

6.6 Follow-up

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

6.6.1 Follow-up Until Disease Progression (At Least Every 9 Weeks ±1 week)

For subjects who discontinue study treatment prior to disease progression (per RECIST version 1.1), the following assessments must be undertaken at least every 9 weeks (±1 week) starting from the date of the last imaging scan, until investigator-assessed disease progression (per RECIST version 1.1), death, withdrawal of consent, or study closure:

- Phase 3 only: HRQoL questionnaires (Section 7.7) and HCRU (Section 7.6); to be completed prior to evaluation by study personnel:
  - EORTC QLQ-C30
  - EORTC QLQ-OG25
  - EQ-5D-3L
  - Review HCRU since the last study visit
- High-quality spiral contrast CT (preferred); PET/CT (if high quality CT scan is included), and/or MRI scan, as appropriate (see Section 7.2). The same imaging modalities used in Screening/Baseline should be repeated, unless otherwise clinically indicated.

- Cardiac function should be assessed (echocardiogram or MUGA) every 6 months until 24 months from the last administration of trastuzumab
- For persons of childbearing potential (for 7 months after the last dose of study treatment):
  - Confirm with the subject that monthly pregnancy tests have been performed and review results
  - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment

6.6.2 Survival Follow-up (Every 12 Weeks After Disease Progression ±2 weeks)

Once subjects have experienced disease progression (per RECIST version 1.1) as assessed by the investigator during follow-up or discontinued study treatment after documentation of disease progression, they will undergo long-term survival follow-up every 12 weeks (±14 days) from the EOT visit or from the date of the last progression follow-up visit, whichever is later, until death, withdrawal of consent, or study closure. The following information is to be collected:

- Subject contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anticancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to contact the subject are unsuccessful.
- Cardiac function should be assessed (echocardiogram or MUGA) every 6 months until 24 months from the last administration of trastuzumab
- For persons of childbearing potential (for 7 months after the last dose of study treatment):
  - Confirm with the subject that monthly pregnancy tests have been performed and have been negative
  - Remind subject that monthly pregnancy tests should be performed for 7 months after the last dose of study treatment

More frequent long-term follow-up may be conducted as needed for OS event tracking

6.7 End of Study/End of Follow-up

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

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

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

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.

The following assessments are required for all subjects at screening and/or baseline as described in Section 6.2, and APPENDIX A: physical exam, height, vital signs, weight, ECOG performance status, CT with contrast/PET-CT/MRI scan for baseline disease assessment, CBC with differential, blood chemistry panel, coagulation panel, urinalysis, ECG, echocardiogram/MUGA, Hepatitis B and C screening, blood sample for biomarker assay, and serum or urine β-hCG pregnancy test (for females of childbearing potential).

7.1.1 Evaluation of HER2 Status at Screening

A blood sample will be drawn at screening to establish baseline HER2 amplification using an NGS assay, performed at a central laboratory.

Archival tumor blocks (or freshly-cut slides, following consultation with the medical monitor) sampled following progression during/after the most recent line of therapy, or other archival tumor tissue samples collected prior to the first line therapy for advanced disease, are to be collected at screening. Tissue samples obtained via resection, excision, punch (skin lesions only), or core needle from a tumor site are suitable for testing. Fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content; e.g., samples should contain a minimum of 100 tumor cells that preserve cellular context and tissue architecture, regardless of the needle gauge used to collect the sample or the retrieval method. See the Laboratory Manual for details concerning tissue samples.

HER2 expression in the tumor tissue sample will be evaluated using tissue-based NGS and according to the 2016 guideline of the ASCO/CAP "HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma", processed in a CLIA- or ISO-accredited laboratory.

See the Central Laboratory Manual for more details.

7.2 Response/Efficacy Assessments

Disease response to study treatment and the occurrence of disease progression will be determined according to RECIST version 1.1 (Eisenhauer 2009), as assessed by the investigator and by the BICR (Phase 3). Radiographic scans and additional imaging assessments (if applicable) will be performed at protocol-specified time points outlined in Section 6 and APPENDIX A. Clinical management decisions will be based on local investigator assessment to ensure that treatment decisions are made in a timely manner; results of centralized review will not be available to investigators for clinical decision making.

Disease assessments will be performed at screening, and every 6 weeks for the first 36 weeks then every 9 weeks, irrespective of dose holds or interruptions. Subjects that discontinue study treatment for reasons other than documented progressive disease will continue to have disease assessments at least every 9 weeks until the occurrence of documented progression per RECIST version 1.1, death, withdrawal of consent, or study closure.

All known sites of metastatic or locally-advanced unresectable disease should be assessed by radiographic imaging at Screening/Baseline to document sites of disease and tumor burden. Imaging, preferably by high quality spiral contrast CT scan (with oral and/or IV contrast), should include the chest, abdomen, and pelvis, at a minimum; PET/CT (if high quality CT scan is included) and/or MRI scan may also be done as appropriate. If a CT scan with contrast is contraindicated (i.e., in subjects with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed instead, with MRI scans of the abdomen and pelvis. At the investigator's discretion, other appropriate imaging (e.g., nuclear bone scan imaging for bone lesions) should be used to assess additional known sites of measurable disease. The same imaging modalities employed in Screening/Baseline should be used for all subsequent response assessments during study treatment and in the follow-up period, unless otherwise clinically indicated. If any other radiographic or assessment exam, including pathology from any on-study biopsies or procedures, is conducted per standard of care, the assessment information will be collected in the CRF. In the Phase 3, all imaging will be collected for retrospective BICR.

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

In the Phase 2, subjects will be considered evaluable for response if they meet the following 3 criteria: (1) had baseline disease assessment, (2) received study treatment, and (3) had post-baseline disease assessment or discontinued treatment due to documented disease progression, clinical progression, treatment-related AE(s), or death.

In the Phase 3, all randomized subjects with measurable disease at baseline will be considered evaluable for response.

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. In the Phase 3, all imaging will be submitted or uploaded for retrospective BICR as soon as reasonably possible (e.g., within approximately 2 weeks) following the date of assessment. Refer to the Study Manual for instructions on collecting and submitting tumor imaging studies to the third-party imaging core laboratory for BICR.

7.3 Pharmacokinetic Assessments

Blood samples for tucatinib, ONT-993, paclitaxel, and paclitaxel metabolites PK assessment will be collected at protocol-defined timepoints; Table 15 specifies tucatinib and ONT-993 PK and biomarker sample collection timepoints for all subjects in Phase 2 and Phase 3, while Table 16 specifies additional tucatinib, paclitaxel, and their metabolites PK collection timepoints for subjects in the paclitaxel dose optimization stage and the first 6 subjects with and without a gastrectomy (without maintenance of the pylorus).

In all subjects in the paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with a gastrectomy, tucatinib and ONT-993 concentrations will be sampled on Cycle 1 Day 8 and Cycle 2 Day 1; concentrations of paclitaxel and its metabolites will be sampled on Cycle 1 Days 1 and 8 and Cycle 2 Day 1. Subjects with a gastrectomy can come from Cohort 2A or Cohort 2B.

In all subjects in the Phase 2 and Phase 3, tucatinib trough drug concentrations will be sampled on Day 1 of Cycles 2 to 6 prior to administration of tucatinib or placebo.

The date and time of the subject's last meal prior to tucatinib administration must be recorded on all days when tucatinib PK draws are made.

Plasma concentrations of tucatinib, ONT 993, paclitaxel, and its metabolites will be determined using validated liquid chromatography (LC)-mass spectrometry (MS)/MS methods. PK parameters of tucatinib, paclitaxel, and their respective metabolites will be calculated using standard noncompartmental methods. PK parameters to be estimated may include, but are not limited to: AUC_{last}, C_{max}, C_{trough}, T_{max}, and MR_{AUC}.

Trough PK samples should continue to be collected on schedule regardless of dose holds or interruptions. The Cycle 1 and Cycle 2 post-dose samples should not be collected during dose hold or interruptions.

Table 15: PK and biomarker sample collection timepoints: All subjects in Phase 2 and Phase 3

Visit	Cycle day	Time	Window	Relative time	Tucatinib and ONT-993 PK	HER2 status and biomarkers
Screening			–28 days	Initiation of study treatment		Blood sample for NGS and biomarker assay Archival tumor tissue sample assay[a]
Cycles 2–6	1	Predose	–2 hours	Time of administration of tucatinib	X	
EOT			30 to 37 days	Last dose of any study drug		Blood sample for biomarker assay

a Archival tumor blocks (or freshly-cut slides, following consultation with the medical monitor) performed following progression during/after the most recent line of therapy, or other archival tumor tissue samples collected prior to the first line therapy for advanced disease, are to be collected.

Table 16: PK sample collection timepoints: Phase 2 paclitaxel dose optimization stage and first 6 subjects with a gastrectomy in Phase 2 dose expansion stage

	Cycle day	Time	Window	Relative time	Paclitaxel and metabolites PK	Tucatinib and ONT-993 PK
Cycle 1	1	Predose	-24 hours	START of paclitaxel infusion	X	
		EOI	Within 15 min after end of paclitaxel infusion		X	
		2 hours	±15 min		X	
		4 hours	±15 min		X	
		6 hours	±30 min		X	
		8 hours	±30 min		X	
	8 [a]	Predose	-2 hours	START of paclitaxel infusion	X	X[a]
		EOI	Within 15 min after end of paclitaxel infusion	(co-administer with tucatinib dose)	X	X
		2 hours	±15 min		X	X
		4 hours	±15 min		X	X
		6 hours	±30 min		X	X
		8 hours	±30 min		X	X
Cycle 2	1	Predose	-2 hours	START of paclitaxel infusion	X	X[a]
		EOI	Within 15 min after end of paclitaxel infusion	(co-administer with tucatinib dose)	X	X
		2 hours	±15 min		X	X
		4 hours	±15 min		X	X
		6 hours	±30 min		X	X
		8 hours	±30 min		X	X

EOI=end of infusion.
For assessment of PK in 6 subjects with a gastrectomy (without maintenance of the pylorus), subjects can come from Cohort 2A or Cohort 2B.
a Tucatinib should be dosed at approximately the same time as the start of the paclitaxel infusion on the PK day.

7.4 Biomarker Studies

HER2 status will be determined by blood-based NGS in samples taken at screening (unless previously determined by the Sponsor, since the end of prior therapy). A blood sample for biomarker assay will be drawn at EOT (Table 15). Archival tumor blocks (or freshly-cut slides, following consultation with the medical monitor) sampled following progression during/after the most recent line of therapy, or other tumor tissue samples collected prior to the first line therapy for advanced disease are to be collected at screening. HER2 expression in the tumor tissue sample will be evaluated following the ASCO/CAP 2016 guideline for HER2 testing in gastroesophageal adenocarcinoma, processed in a CLIA- or ISO-accredited laboratory. HER2 status by tissue-based NGS will also be evaluated. Blood samples for biomarker assay will be drawn at screening and at EOT.

Biomarker assessments may include an exploratory assessment of HER2 mutations or other mutations as potential biomarkers of response. Additional exploratory analyses including but not limited to IHC and NGS analysis may be performed to interrogate biomarkers that are associated with tumor growth, survival, and resistance to targeted therapeutics. This assessment may enable the correlation of additional biomarkers with treatment outcome and may ultimately guide or refine patient selection strategies to better match tucatinib regimens with tumor phenotype/genotype in the future.

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 and the identification of biomarkers. 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 Healthcare Resource Utilization

In the Phase 3, all healthcare encounters related to the subject's cancer, cancer treatment, or cancer-related assessments will be collected for all subjects until the EOT visit or the end of follow-up for progression, whichever is later. HCRU data include, but are not limited to, procedures that occur on study, such as length of stay, hospitalizations, emergency department visits, planned/unplanned provider visits, medication use, radiology, and other treatments and procedures. See APPENDIX A and Section 6 for timing of HCRU data collection, and see the Study Manual for detailed guidance.

7.7 Patient-Reported Outcomes

In the Phase 3, the EORTC QLQ-C30, EORTC QLQ-OG25, and EQ-5D-5L questionnaires will be administered according to the schedule specified in APPENDIX A and Section 6, until the EOT visit or the end of follow-up for progression, whichever is later. The objective

is to compare improvements, deteriorations, and stabilization in HRQoL between treatment arms. During study treatment, these questionnaires must be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment on treatment days.

7.7.1 EORTC QLQ-C30

The EORTC QLQ was developed to measure aspects of HRQoL pertinent to subjects with a broad range of cancers who are participating in international clinical trials (Aaronson 1993). The recall period is the past week. The core instrument, the QLQ-C30 (version 3.0), is a 30-item questionnaire consisting of the following:

- 5 functional domains (physical, role, cognitive, emotional, social)
- 3 symptom scales (fatigue, pain, nausea, and vomiting)
- Single items for symptoms (shortness of breath, loss of appetite, sleep disturbance, constipation, diarrhea) and financial impact of the disease
- 2 global items (health, overall HRQoL)

See APPENDIX G for a sample EORTC QLQ-C30 form.

7.7.2 EORTC QLQ-OG25

The EORTC questionnaires for assessing HRQoL for esophageal cancer (QLQ-OES18) and stomach cancer (QLQ-STO22) were combined into a single questionnaire for tumors of the esophagus, esophago-gastric junction or stomach (EORTC QLQ-OG25; APPENDIX H) (Lagergren 2007). The QLQ-OG25 is a 25-item questionnaire consisting of the following subscales: dysphagia, eating restrictions, reflux, odynophagia, pain, and anxiety. The recall period is the past week.

7.7.3 EQ-5D-5L – Utility Measurement

The European Quality of Life (EuroQol) 5-Dimension 5-Level (EQ-5D-5L) is a standardized instrument developed by the EuroQol Group for use as a generic, preference based measure of HRQoL outcomes that can be used in a wide range of health conditions and treatments (van Agt 1994). The EQ-5D-5L consists of a descriptive system questionnaire and the EuroQol (EQ) visual analog scale (VAS; APPENDIX I).

The descriptive system questionnaire assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preference compared to other health profiles. The EQ VAS records the subject's self-rated health status on a vertical VAS ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The recall period is the day in which the questionnaire is administered.

7.8 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, physical examination findings, vital signs including weight, ECGs, ECOG performance status, concomitant medication, pregnancy testing, and laboratory tests. Assessment of cardiac ejection fraction will be performed using MUGA scan or echocardiogram.

Safety will be monitored throughout the course of the study by the sponsor, and by the SMC during the Phase 2 and the IDMC during the Phase 3, as described in Section 9.3.11.

7.8.1 Adverse Events

7.8.1.1 Definitions

Adverse Event

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

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

- From the time of informed consent through the day prior to study Cycle 1 Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on Cycle 1 Day 1 that increase in CTCAE grade should be recorded.
- Medical conditions present or ongoing predose on study Cycle 1 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 Cycle 1 Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- 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, study treatment discontinuation, or dose modifications. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Events

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

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.8.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 5.0. 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).

Relationship of the Adverse Event to Study Treatment

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

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

7.8.1.2 Procedures for Eliciting and Recording Adverse Events

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

Eliciting Adverse Events

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

Recording Adverse Events

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

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

Diagnosis vs. Signs or Symptoms

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

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

Recording Serious Adverse Events

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

The following should be considered when recording SAEs:

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

Progression of Underlying Malignancy

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

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 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 7.8.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

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

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

Definition

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

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

AND

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

AND

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

Reporting Requirements

Any potential Hy's Law case should be handled as a SAE and reported 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 ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

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.

7.8.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

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

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

7.8.1.4 Serious Adverse Events Require Immediate Reporting

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

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

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator 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) unless otherwise instructed on the Sponsor's SAE form.

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

7.8.1.5 Adverse Events of Special Interest

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

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

AESIs for this study are:

- **Hepatotoxicity**: either of the following types of liver enzyme elevation:
  - AST or ALT elevations that are >3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin >2 × ULN, except in subjects with documented Gilbert's syndrome
  - AST or ALT elevations >20.0 × ULN
  - Bilirubin elevations >10.0 × ULN

    Measurement of conjugated and unconjugated bilirubin should be considered in cases of hyperbilirubinemia to assist in determination of its etiology. The sponsor will subsequently determine whether the elevations are associated with other possible causes of aminotransferase elevation and hyperbilirubinemia, such as viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.8.1.6 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.8.1.4). The sponsor will report all SAEs, including SUSARs to regulatory authorities as required per local legislation or regulatory reporting requirements.

7.8.2 Vital Signs

Vital signs measures are to include heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature.

7.8.3 Clinical Laboratory Tests

Local laboratory testing will include institutional standard tests for evaluating safety at scheduled timepoints (see APPENDIX A) during the course of the study and making clinical decisions:

- The blood chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, creatinine, chloride, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin (and direct bilirubin when total bilirubin is >ULN), and total protein
- The CBC with differential is to include, but not limited to, the following tests: CBC with white blood cell count, red blood cell count, platelet count, hemoglobin, and hematocrit, with differential (neutrophils, lymphocytes)

- The coagulation panel is to include the following tests: INR, PT, PTT, and aPTT
- The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL.
  GFR (mL/min/1.73 m²) = $175 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$
  Consider monitoring renal function with alternative markers, which are not based on creatinine to determine whether renal function is impaired.
- Urinalysis
  - Standard urinalysis (Note: specify ± reflexive microscopy if clinically indicated)
  - Urine protein and urine creatinine for UPC ratio
  - If dipstick or routine analysis indicates proteinuria ≥2+ during treatment, a urine collection should be done to calculate the UPC ratio
- Hepatitis screening: hepatitis B surface antigen, antibodies to hepatitis B core, and antibodies to hepatitis C; if hepatitis C serology is positive, hepatitis C virus RNA test by PCR is required to confirm
- A serum or urine β-hCG pregnancy test for subjects of childbearing potential

7.8.4 Physical Examination

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

7.8.5 Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline, within 7 days prior to Day 1 of each treatment cycle, and at the EOT visit. A negative pregnancy result is required before the subject may receive study drug. After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months. Subjects may do monthly home pregnancy tests and report interim results at long-term follow-up visits. Pregnancy tests may also be repeated as requested per Institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations.

7.8.6 Cardiac Function

7.8.6.1 MUGA or Echocardiogram

Assessment of cardiac ejection fraction will be performed by MUGA scan or echocardiogram at screening and at least once every 12 weeks thereafter until treatment discontinuation, and at the EOT visit (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). If there is an interim assessment, subsequent cardiac echocardiogram 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 (echocardiogram 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.

7.8.6.2 Electrocardiogram

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

7.9 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.

In the Phase 3 part, the efficacy of study treatment will be evaluated using OS, the gold standard for evaluation of anticancer therapies, and PFS according to RECIST version 1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in GEC. Given that the randomization and blinding of the Phase 3 portion of the study reduces the potential for investigator bias in disease assessments, investigator assessment, rather than BICR assessment, will be used to determine date of progression for the primary PFS endpoint. The intervals of evaluation in this protocol are considered appropriate for disease management.

The QLQ-C30 (version 3.0) is a validated questionnaire developed by the EORTC to assess the HRQoL of cancer subjects (Aaronson 1993; Sneeuw 1998). The QLQ-OG25 is a validated questionnaire developed by the EORTC to assess the HRQoL of subjects with esophagus, esophago-gastric junction, or stomach cancer (Lagergren 2007). The EQ-5D-5L is a validated instrument for use as a measure of HRQoL (Janssen 2013). These PROs have been incorporated into previous clinical trials that seek to quantify the HRQoL in subjects.

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

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the 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.

8.2 Data Management Procedures

Seagen will provide CRF Completion Guidelines for electronic CRF (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 collected is correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4 Accuracy and Reliability of Data

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

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

8.5 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

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.

Electronic patient-reported outcomes (ePRO) instruments, electronic patient diaries (eDiary), and electronic transfer of BICR review findings may be utilized. If any of these instruments are utilized, the data will be transmitted to the eCRF from those instruments.

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.

9 DATA ANALYSIS METHODS

9.1 Determination of Sample Size

9.1.1 Phase 2

Up to approximately 78 DLT-evaluable and/or response-evaluable subjects will be enrolled in the phase 2 portion: up to 18 DLT-evaluable subjects in the paclitaxel dose optimization stage and up to 30 response-evaluable subjects in each of Cohorts 2A and 2B. Up to 9 subjects enrolled in the dose optimization stage may count towards the 60 subjects in Cohorts 2A and 2B, if they are response-evaluable and receive the recommended paclitaxel dose.

The preliminary activity of the study regimen will be formally evaluated using ORR irrespective of confirmation per investigator in approximately 30 response evaluable subjects from the dose optimization stage or the dose expansion stage (Cohort 2A) who are HER2+ by the blood-based NGS assay and who were treated at the paclitaxel recommended dose.

The Phase 3 will be initiated if the observed ORR is ≥36%. With the sample size of 30, it is expected that at least 11 responders will be observed if the underlying ORR is ≥36%. Table 17 provides the point estimate and 95% CI for ORR under different underlying ORR for the sample size of 30.

Table 17: Expected 95% CI under different underlying true ORRs for a sample size of 30

ORR	Number of responses in 30 subjects	Lower bound of 95% CI	Upper bound of 95% CI
30%	9	14.7%	49.4%
36%	11	19.4%	55.5%
40%	12	22.7%	59.4%
47%	14	28.6%	66.0%
50%	15	31.3%	68.7%

9.1.2 Phase 3

The sample size for the Phase 3 was calculated based on maintaining 90% power for the dual primary endpoint of PFS with an alpha of 0.02 and 88% power for the dual primary endpoint of OS with an alpha of 0.03. For PFS, 317 events from Arm 3A or Arm 3B are required with 90% power to detect a HR of 0.67 (4.5 months median PFS in Arm 3B versus 6.75 months in Arm 3A) using a 2-sided log-rank test and alpha of 0.02. For OS, 354 events from Arm 3A or Arm 3B are required with 88% power to detect a HR of 0.70 (10 months median OS in Arm 3B versus 14.3 months in Arm 3A) using a 2-sided log-rank test and alpha of 0.03. The 2 primary endpoints will be evaluated using parallel testing, with alpha recycling if only one of them meets statistical significance. Approximately 470 subjects are needed with equal randomization to Arm 3A and Arm 3B.

Therefore, approximately 500 subjects will be randomized in an approximately 8:8:1 ratio to Arm 3A, Arm 3B, or Arm 3C, with approximately 30 subjects randomized to Arm 3C. Assuming an accrual period of 30 months and a 5% yearly drop-out rate, it is expected that 317 PFS events and 354 OS events from Arm 3A or Arm 3B will be observed approximately 25 and 39 months after first subject randomized, respectively.

9.2 Study Endpoint Definitions

9.2.1 PFS

PFS is defined as the time from the date of treatment initiation (Phase 2) or randomization (Phase 3) to the date of disease progression according to RECIST version 1.1 or death from any cause, whichever occurs first. Subjects without documentation of progression or death at the time of analysis will be censored at the date of the last disease assessment with an overall response of CR, PR, SD or non-CR/non-progressive disease. If there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of treatment initiation/randomization. PFS per investigator and per BICR are based on investigator response assessments and BICR response assessments, respectively.

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

9.2.2 Overall Survival

OS is defined as the time from treatment initiation (Phase 2) or randomization (Phase 3) to death due to any cause. For a subject who is not known to have died by the end of study follow-up, observation of OS is censored on the date the subject was last known to be alive (i.e., the date of last contact). Subjects lacking data beyond the day of treatment initiation/randomization will have their survival time censored on the date of treatment initiation/randomization (i.e., OS duration of 1 day).

9.2.3 Objective Response Rate

ORR is defined as the proportion of subjects with best overall response of CR or PR according to RECIST version 1.1. Only response assessments before first documented disease progression or new anticancer therapies will be considered. Confirmed ORR and ORR irrespective of confirmation will be evaluated. ORR per investigator and per BICR are based on investigator response assessments and BICR response assessments, respectively.

9.2.4 Duration of Response

DOR is defined as the time from first documentation of objective response of CR or PR to the first documentation of disease progression per RECIST version 1.1 or death from any cause, whichever occurs earlier. Only subjects with an objective response will be included in the analysis of DOR. DOR per investigator and per BICR are based on investigator response assessments and BICR response assessments, respectively.

9.2.5 Disease Control Rate

DCR is defined as the proportion of subjects with CR, PR, or stable disease (SD or non-CR/non-progressive disease) according to RECIST version 1.1. DCR per investigator and per BICR are based on investigator response assessments and BICR response assessments, respectively.

9.2.6 Exploratory Endpoints

9.2.6.1 Pharmacokinetic Analysis

PK parameters such as AUC_{last}, C_{max}, T_{max}, C_{trough}, and MR_{AUC} will be calculated using non-compartmental analysis for tucatinib, paclitaxel, and their metabolites in Phase 2 and tucatinib in Phase 3.

9.2.6.2 Biomarker Analysis

Biomarkers assessments in blood may include measurements of HER2 amplification, and genetic polymorphisms in order to assess potential response and resistance biomarkers. Methods of analysis may include, but are not limited to, NGS of RNA and DNA.

9.2.6.3 Healthcare Resource Utilization

HCRU data collected from the eCRF and will include procedures that occur on study, length of stay, hospitalizations, emergency department visits, planned/unplanned provider visits, medication use, radiology, and other treatments and procedures.

9.2.6.4 Patient-Reported Outcomes

PRO assessments will be analyzed to determine if treatment affects PRO scores. PRO scores will be analyzed using longitudinal models. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data at each scheduled assessment timepoint may be presented. Time to deterioration will be assessed in specific pre-specified single items from either the EORTC QLQ-C3, EORTC QLQ-OG250, or EQ-5D-5L.

Additional statistical modeling for PRO and HCRU measures may be performed separately in post hoc analyses.

9.3 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (e.g., adding baseline assessments to define a subgroup). 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

Hereafter, "treatment group" will be used to designate the following:

For analyses based on the All-Treated analysis set:

- Each dose level evaluated in the Phase 2,

For analyses based on the Phase 2 Recommended Dose analysis set,

- Subjects with HER2+ disease according to blood-based NGS assay treated at the paclitaxel recommended dose in the dose optimization stage or Cohort 2A
- Subjects with HER2-negative disease according to blood-based NGS but HER2+ disease according to IHC/ISH assay of a tumor tissue sample, treated at the paclitaxel recommended dose in the dose optimization stage or Cohort 2B

For Phase 3 analyses,

- Each randomization arm in the Phase 3.

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data, by treatment group.

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).

9.3.1.1 Randomization and Blinding

The Phase 2 portion has a 2-stage, 2-cohort, open-label design.

The randomized, double-blind, placebo-controlled, active comparator, international, multicenter Phase 3 portion of this study will enroll approximately 500 subjects. Subjects will be randomized in an approximately 8:8:1 ratio to receive tucatinib and trastuzumab, or tucatinib placebo and trastuzumab placebo, or tucatinib and trastuzumab placebo in combination with ramucirumab and paclitaxel. Randomization will be stratified using the stratification factors described in Section 3.1.9.

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

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

9.3.1.2 Adjustments for Covariates

There will be no adjustment for covariates in the Phase 2.

In the Phase 3, stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 3.1.9). If the sample size of one stratum by a stratification factor is too small, the statistical analysis will not include this randomization stratification factor in the statistical analysis, such as stratified log-rank test and stratified Cox regression model. This minimum sample size requirement will be specified in the SAP. Covariates may be considered for adjustment in exploratory analyses.

9.3.1.3 Handling of Dropouts and Missing Data

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

9.3.1.4 Multicenter Studies

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

9.3.1.5 Multiple Comparisons and Multiplicity

There are no formal comparisons in the Phase 2.

In the Phase 3, to maintain strong control of the family-wise type I error rate at 0.05, the dual primary endpoints of PFS per investigator assessment and OS will be evaluated in Arms 3A and 3B using parallel testing, at the two-sided type I error rate of 0.02 and 0.03, respectively. If only one of the primary endpoints is positive at the specified level, alpha recycling will be applied to evaluate the other endpoint at a level of 0.05. OS will be tested twice with an overall two-sided alpha of 0.03. The first test of OS will be performed at the same time as the primary PFS analysis when approximately 317 PFS events per investigator assessment from Arms 3A or 3B are observed. The final test of OS will occur when approximately 354 OS events from Arms 3A or 3B are observed. The Lan-DeMets spending functions with O'Brien and Fleming boundaries (Chen 2014) will be used for the calculation of the alpha level at the first and final tests of OS, based on the actual number of OS events observed at the interim. If both PFS and OS are statistically significant at either the first or the final analysis, a formal statistical test of ORR per investigator assessment will be performed. Detailed rejection boundaries of P-values will be specified in the SAP.

9.3.1.6 Data Transformations and Derivations

Time variables based on 2 dates (e.g., start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified in the planned analysis section.

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

9.3.1.7 Analysis Sets

Phase 2

The All-Treated set is defined as all subjects in the Phase 2 who received any amount of any study drug.

The Phase 2 Recommended Dose analysis set is defined as all subjects in the Phase 2 who started paclitaxel at the dose that was finally adopted following evaluation in the dose optimization stage.

Phase 3

The intent-to-treat (ITT) analysis set is defined as all randomized subjects. Subjects will be included in the treatment group assigned at randomization regardless of the actual treatment received. Subjects in Arm 3C will be analyzed separately from Arms 3A and 3B.

The Safety Analysis set will include all randomized subjects who receive any component of combination therapy (or placebo). Treatment groups will be determined using the actual treatment received, regardless of the randomization treatment assignment. Subjects in Arm 3C will be analyzed separately from Arms 3A and 3B.

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. The subgroups and detailed methodology will be provided in the SAP.

9.3.1.9 Timing of Analyses

Phase 2

In the Phase 2, safety analyses will be undertaken by the SMC when the first 6 DLT-evaluable subjects in each paclitaxel dose level have been followed for at least 1 cycle (paclitaxel dose optimization stage). The SMC will conduct additional analyses of safety and PK should a dose level be expanded to include a total of 9 subjects. The SMC will undertake similar analyses if alternative paclitaxel dose levels/schedules are evaluated. Once the paclitaxel dose optimization stage is completed, the SMC will evaluate the safety of the study regimen throughout the remainder of Phase 2.

Final efficacy analyses will be undertaken separately for subjects with HER2+ disease according to blood-based NGS assay (from the dose optimization stage and Cohort 2A) and subjects without HER2 amplification by blood-based NGS but with HER2+ disease according to IHC/ISH assay of a tumor tissue sample (from the dose optimization stage and Cohort 2B). The final analyses will occur when approximately 30 response-evaluable subjects have been treated at the recommended paclitaxel dose and have been followed for at least 6 weeks in each group.

Phase 3

There is only one formal analysis of the dual primary endpoint PFS per investigator assessment. The analysis cutoff date for this analysis will be determined once approximately 317 PFS events per investigator assessment have been observed in the ITT analysis set in Arms 3A and 3B and subject enrollment is complete. This is estimated to be approximately 25 months after randomization of the first subject.

The dual primary endpoint of OS may be analyzed twice. The first, interim, analysis will be performed at the same time as the primary analysis of PFS per investigator assessment (see Section 9.3.11.2 for details). If OS is not statistically significant at the interim analysis, the final analysis of OS will occur when approximately 354 OS events in the ITT analysis set Arms 3A and 3B have occurred. The final OS analysis is estimated to occur approximately 14 months after completion of the primary analysis of PFS. Confirmed ORR by investigator assessment in the response-evaluable subjects in Phase 3 for Arms 3A and 3B will be formally tested if both PFS and OS are statistically significant.

9.3.2 Subject Disposition

An accounting of study subjects by treatment group will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who are off the study will be summarized with reason for drug or study discontinuation.

9.3.3 Subject Characteristics

The following baseline characteristics will be summarized by treatment group:

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

Details will be provided in the SAP.

9.3.4 Concomitant, and Further Therapy

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

The frequency and types of further anticancer therapies started after study treatment discontinuation will be summarized.

9.3.5 Exposure

Treatment administration will be summarized by treatment. Summary statistics for duration of therapy (weeks) and the number of cycles per subject will be presented. The number of dose reductions, holds, cycle delays, and doses skipped and dose intensity for each study drug will be summarized. Details will be provided in the SAP.

9.3.6 Efficacy Analyses

9.3.6.1 Phase 2

ORR, confirmed ORR, DOR, and DCR per RECIST version 1.1 according to investigator assessment will be evaluated by treatment group in response-evaluable subjects in the Phase 2 Recommended Dose set (see Section 7.2 for the definition of response-evaluable). PFS will be evaluated by treatment group in all subjects in the Phase 2 Recommended Dose set. See Section 9.3.1 for the definition of treatment groups.

The point estimate of ORR, confirmed ORR, and DCR and their corresponding 95% CIs will be presented by treatment group.

PFS and DOR will be estimated using the using Kaplan-Meier methodology, and Kaplan-Meier plots will be provided. Medians and 95% CIs will be calculated by treatment group, as appropriate. Detailed methodology will be provided in the SAP.

9.3.6.2 Phase 3

Primary Efficacy Analyses

The stratified log-rank test will be used in the primary evaluation of differences in PFS according to investigator assessment and OS between Arms 3A and 3B in the ITT analysis set, using a two-sided significance level of 0.02 for PFS and 0.03 for OS. The multiplicity adjustment is described in Section 9.3.1.5.

Stratified Cox proportional-hazards (PH) models will be used to estimate the hazard ratios and their 95% CIs. Both stratified log-rank and Cox PH models will take into account the stratification factors for randomization. If the sample size of one stratum from a stratification factor is too small, statistical analysis may not include this stratification factor. The minimum sample size for a stratum to be included in the statistical model will be specified in the SAP.

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

Kaplan-Meier curves depicting PFS and OS in all treatment groups will be generated for Arms 3A and 3B and Arm 3C in the ITT set. Additionally, median PFS and OS and the 2-sided 95% CIs for the medians will be reported using the complementary log-log transformation method (Collett 1994). Detailed methodology is provided in the SAP.

Secondary Efficacy Analyses

Objective Response Rate

Data summaries for confirmed ORR (per investigator and per BICR) and ORR irrespective of confirmation (per investigator and per BICR) will be provided for response-evaluable subjects in Arms 3A and 3B and in Arm 3C. The 95% CIs of ORRs will be estimated for each treatment group. If both PFS per investigator and OS are statistically significant in the comparison of Arm 3A and Arm 3B, then confirmed ORR per investigator in

response-evaluable subjects will be formally compared between two treatment groups at the two-sided alpha level of 0.05, using a stratified Cochran-Mantel-Haenszel test.

Disease Control Rate

The point estimates and 95% CIs of DCR per investigator and per BICR will be provided for each treatment group in the ITT set.

Progression-free survival

The secondary endpoint of PFS according to BICR assessment in the Phase 3 will be analyzed using same methods used for the primary endpoints.

Duration of Response

Only subjects with an objective response will be included in the analysis of DOR per investigator and per BICR. DOR will be graphically described using Kaplan-Meier methodology. The median DOR and its 95% CI will be provided for all treatment groups.

9.3.7 Pharmacokinetic Analyses

Individual (subject) plasma concentrations at each sampling time will be listed for tucatinib, paclitaxel, and their metabolites in the Phase 2, and tucatinib and ONT-993 in the Phase 3; corresponding summary statistics at each sampling time will also be calculated.

The PK parameters to be calculated (if applicable) may include but are not limited to: AUC_{last}, C_{max}, T_{max}, C_{trough}, and MR_{AUC}. The PK parameters of tucatinib and ONT-993 in subjects with and without gastrectomy (without maintenance of the pylorus) will be evaluated.

Exploratory analyses investigating the relationship between tucatinib, paclitaxel, and/or their metabolites exposure and efficacy and safety endpoints may be conducted. Additional exploratory PK analyses may be conducted.

Details will be described separately in the SAP or Biomarker Analysis Plan (BAP).

9.3.8 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 BAP.

9.3.9 Patient Reported Outcomes and HCRU Analyses

In the Phase 3, assessments based on the EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D-5L and HCRU data will summarized using descriptive statistics by treatment group for Arms 3A and 3B of the ITT set.

PRO assessments will be analyzed to determine if treatment affects PRO scores. PRO scores will be analyzed using longitudinal models. All subscales and individual item scores will be

tabulated. Descriptive summaries of observed data at each scheduled assessment timepoint may be presented. Time to deterioration will be assessed in specific pre-specified single items from either the EORTC QLQ-C30 or EORTC QLQ-OG25 and deterioration is defined as a 10-point increase from baseline in the symptom scales and a 10-point decrease from baseline for overall HRQoL. Further investigation of missing patterns and details of imputation will be provided in the SAP.

Additional statistical modeling for PRO and HCRU measures may be performed separately in post hoc analyses.

9.3.10 Safety Analyses

Safety analyses will, in general, be conducted by treatment group using the All-Treated set in the Phase 2 and the Safety Analysis set in the Phase 3.

9.3.10.1 Adverse Events

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

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

All collected AE data will be listed with study phase, treatment group, study site, subject number, and cycle. Separately, all serious AEs and AESIs (see Section 7.8.1.5) will be analogously listed.

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

9.3.10.3 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 version 5.0 and flagged when values are outside the normal reference range.

Changes from baseline in laboratory values (hematology, coagulation, chemistry, and liver function) will be summarized by study phase, treatment group and scheduled visit. Laboratory shift tables will also be provided by treatment group and scheduled visit. Abnormal values (relative to respective normal ranges) will be flagged in listings.

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

9.3.10.4 Other Safety Analyses

Vital Signs and Physical Examinations

The frequency and percentage of subjects with post-baseline clinically significant vital signs will be summarized, by study phase and treatment arm. Abnormal physical examination findings may be collected as AEs.

ECOG Performance Status

ECOG performance status will be summarized by study phase and treatment arm 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 by study phase and treatment arm for each scheduled ECG, and shifts from baseline may be tabulated.

9.3.11 Interim Analyses

9.3.11.1 Phase 2

The SMC will undertake safety and PK analyses once the first 6 subjects evaluable for DLT in each dose level in the paclitaxel dose optimization stage have been followed for at least 1 cycle. The SMC will conduct additional analyses of safety and PK should a dose level be expanded to include a total of 9 subjects. If alternative paclitaxel dose levels/schedules are evaluated, the SMC will undertake similar assessments.

9.3.11.2 Phase 3

No formal interim analysis is planned for the dual primary endpoint of PFS. There is one planned interim analysis of the dual primary endpoint of OS, at the time of the final analysis of PFS. The final analysis of OS will be performed when approximately 354 OS events from Arms 3A and 3B of the ITT set have occurred. Approximately 61% of the total OS events are expected to have occurred by the time of the interim analysis. The Lan-DeMets O'Brien-Fleming approximation spending function (Chen 2014) will be used for calculation of the alpha level at the first and final tests of OS based on the actual number of OS events observed at the interim. Detailed rejection boundaries of p-values will be specified in the SAP.

The IDMC will periodically review relevant aggregate safety data from the Phase 3 portion, and will make recommendations to the sponsor on the conduct of the study (see IDMC charter).

10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

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

10.1 Informed Consent

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

For Phase 1 studies, it is preferable for a subject to provide consent themselves. If informed consent is obtained from a legally acceptable representative for a subject who is unable to provide informed consent at study entry (if applicable), but the subject is later able to provide informed consent, the investigator must obtain written informed consent from the subject.

10.2 Ethical Review

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

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

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

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

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

10.3 Regulatory Considerations

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

10.3.1 Investigator Information

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

10.3.2 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study 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.

10.4 Study Documentation, Privacy and Records Retention

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

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

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

10.5 Clinical Trial Agreement

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

11 REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

Chen LM, Ibrahim JG, Chu H. Flexible stopping boundaries when changing primary endpoints after unblinded interim analyses. J Biopharm Stat. 2014;24(4):817-33.

Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. Int J Cancer. 2012;130(12):2845-56.

Cianfrocca M, Lee S, Von Roenn J, et al. Pilot study evaluating the interaction between paclitaxel and protease inhibitors in patients with human immunodeficiency virus-associated Kaposi's sarcoma: an Eastern Cooperative Oncology Group (ECOG) and AIDS Malignancy Consortium (AMC) trial. Cancer Chemother Pharmacol. 2011;68(4):827-33.

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

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

Digklia A, Wagner AD. Advanced gastric cancer: current treatment landscape and future perspectives. World J Gastroenterol. 2016;22(8):2403-14.

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

Gomez-Martin C, Garralda E, Echarri MJ, et al. HER2/neu testing for anti-HER2-based therapies in patients with unresectable and/or metastatic gastric cancer. J Clin Pathol. 2012;65(8):751-7.

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

Holbro T, Hynes NE. ErbB receptors: directing key signaling networks throughout life. Annu Rev Pharmacol Toxicol. 2004;44:195-217.

Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005;5(5):341-54.

Janjigian YY, Riches JC, Ku GY, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in HER2-overexpressing esophagogastric (EG) tumors treated with trastuzumab. J Clin Oncol. 2015;33(3 Suppl):Abstract 63.

Janjigian YY, Werner D, Pauligk C, et al. Prognosis of metastatic gastric and gastroesophageal junction cancer by HER2 status: a European and USA International collaborative analysis. Ann Oncol. 2012;23(10):2656-62.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.

Kashiwada T, Saeki H, Uenosono Y, et al. Multicenter observational study on re-evaluation of HER2 status in patients with HER2-positive advanced or recurrent gastric cancer refractory to trastuzumab. J Clin Oncol. 2018;36(15 Suppl):Abstract 4038.

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

Kunz PL, Mojtahed A, Fisher GA, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. Appl Immunohistochem Mol Morphol. 2012;20(1):13-24.

Lagergren P, Fayers P, Conroy T, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-OG25, to assess health-related quality of life in patients with cancer of the oesophagus, the oesophago-gastric junction and the stomach. Eur J Cancer. 2007;43(14):2066-73.

Lopez A, Harada K, Mizrak Kaya D, Ajani JA. Current therapeutic landscape for advanced gastroesophageal cancers. Ann Transl Med. 2018;6(4):78.

Makiyama A, Sukawa Y, Kashiwada T, et al. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT Study). J Clin Oncol. 2020;38(17):1919-27.

Mondaca S, Margolis M, Sanchez-Vega F, et al. Phase II study of trastuzumab with modified docetaxel, cisplatin, and 5 fluorouracil in metastatic HER2-positive gastric cancer. Gastric Cancer. 2019;22(2):355-62.

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

Nannan Panday VR, Hoetelmans RM, van Heeswijk RP, et al. Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma--drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. Cancer Chemother Pharmacol. 1999;43(6):516-9.

Olayioye MA, Neve RM, Lane HA, Hynes NE. The ErbB signaling network: receptor heterodimerization in development and cancer. EMBO J. 2000;19(13):3159-67.

Orlando L, Giotta F, Lorusso V, et al. Biweekly combination of trastuzumab, docetaxel and gemcitabine for HER2-positive metastatic breast cancer: results of a phase II GOIM study. Future Oncol. 2014;10(5):725-33.

Peterson S, de Vries P, Piasecki J, Rosler R. Tucatinib, a HER2 selective kinase inhibitor, is active in patient derived xenograft (PDX) models of HER2-amplified colorectal, esophageal and gastric cancers. Ann Oncol. 2017;28(Suppl 5):576.

Pietrantonio F, Caporale M, Morano F, et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: implication for further clinical research. Int J Cancer. 2016;139(12):2859-64.

Qiu MZ, Li Q, Wang ZQ, et al. HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: a prospective cohort observation. Int J Cancer. 2014;134(10):2468-77.

Riese DJ, 2nd, Stern DF. Specificity within the EGF family/ErbB receptor family signaling network. Bioessays. 1998;20(1):41-8.

Rosello S, Blasco I, Garcia Fabregat L, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2017;28(Suppl 4):iv100-18.

Ruschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. Mod Pathol. 2012;25(5):637-50.

Satoh T, Xu RH, Chung HC, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol. 2014;32(19):2039-49.

Schlessinger J. Ligand-induced, receptor-mediated dimerization and activation of EGF receptor. Cell. 2002;110(6):669-72.

Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382(25):2419-30.

Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392(10142):123-33.

Sneeuw KC, Aaronson NK, Sprangers MA, et al. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. J Clin Epidemiol. 1998;51(7):617-31.

Song Z, Wu Y, Yang J, Yang D, Fang X. Progress in the treatment of advanced gastric cancer. Tumour Biol. 2017;39(7):1010428317714626.

Strickler JH, Zemla T, Ou FS, et al. Trastuzumab and tucatinib for the treatment of HER2 amplified metastatic colorectal cancer (mCRC): initial results from the MOUNTAINEER trial. Ann Oncol. 2019;30(Suppl 5):v200.

Tan AR, Dowlati A, Jones SF, et al. Phase I study of pazopanib in combination with weekly paclitaxel in patients with advanced solid tumors. Oncologist. 2010;15(12):1253-61.

Tan AR, Dowlati A, Stein MN, et al. Phase I study of weekly paclitaxel in combination with pazopanib and lapatinib in advanced solid malignancies. Br J Cancer. 2014;110(11):2647-54.

Tanner M, Hollmen M, Junttila TT, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol. 2005;16(2):273-8.

Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640-53.

Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer. 2002;95(1):147-54.

van Agt HME, Essink-Bot ML, Krabbe PFM, Bonsel GJ. Test-retest reliability of health state valuations collected with the EuroQol questionnaire. Soc Sci Med. 1994;39(11):1537-44.

Wesolowski R, Lee C, Kim R. Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol. 2009;10(9):903-12.

Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224-35.

Yan B, Yau EX, Bte Omar SS, et al. A study of HER2 gene amplification and protein expression in gastric cancer. J Clin Pathol. 2010;63(9):839-42.

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001;2(2):127-37.

Zhao D, Klempner SJ, Chao J. Progress and challenges in HER2-positive gastroesophageal adenocarcinoma. J Hematol Oncol. 2019;12(1):50.

APPENDIX A: SCHEDULE OF EVENTS

		Screening and Baseline		Treatment Period									EOT visit 30 days post last dose	Follow-up	
		D–28 to D–1	D–7 to D1	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 1 D22	Cycles >1 D1	Cycles >1 D8	Cycles >1 D15	Every 6 weeks [a]	Every 12 weeks		Every 9 weeks until progression[b]	Every 12 weeks after progression[c]
Visit window (days)					±1	±1	±1	-1, +3	±1	±1	±7	±14	+7	±7	±14
Screening/ Baseline	Informed consent [d]	X													
	Inclusion/exclusion criteria	X	X												
	Medical history	X													
	Height	X													
	Blood sample for NGS assay of HER2 amplification	X													
	Tumor specimen collection for HER2 status [e]	X													
	Serology for hepatitis B and C [f]	X													
Study treatment	Tucatinib (or placebo)[g]			BID every day, from Cycle 1 Day 1[h]											
	Paclitaxel			X	X	X		X	X	X					
	Trastuzumab (or placebo)			X		X		X		X					
	Ramucirumab			X		X		X		X					
Safety assessments	Vital signs[i], including weight [j]	X	X	X	X	X		X	X	X			X		
	Physical exam [j]		X	X				X					X		
	ECOG performance status [j]		X	X				X					X		
	CBC with differential [j]		X	X	X	X	X	X	X	X			X		
	Blood chemistry panel [j]		X	X	X	X	X	X	X	X			X		
	Coagulation panel [j]		X					X[k]					X		
	Urinalysis [j,l]		X	X		X		X		X			X		
	ECG	X											X		
	Echocardiogram or MUGA scan	X										X[m]	X[m]	X[n]	X[n]
	Serum or urine β-hCG pregnancy test (for FOCBP)		X	X[o]				X[o]					X[p]	X[p]	X[p]
	AEs and concomitant medication	Collected throughout study reporting period, from screening to EOT visit [q]													
Disease	CT-scan, PET-CT, and/or MRI assessments[r]	X									X		X	X	
	Survival and further therapy														X
PK	Blood samples for tucatinib and ONT-993 PK				X[t]			X[s,t]							
	Blood samples for paclitaxel and metabolites PK in Phase 2			X[t]	X[t]			X[t]							
	Blood sample for biomarker assay	X[u]											X		
PRO/ HCRU	EORTC QLQ-C30, EORTC QLQ-OG25, EQ-5D-5L (Phase 3 only)			X				X[v]					X	X	

FOCBP=females of childbearing potential.

a Scheduling determined by date of Cycle 1, Day 1 visit.

b Scheduling determined by date of the last imaging scan. To be performed every 9 weeks until the occurrence of documented disease progression, withdrawal of consent, death, or study closure.

c Every 12 weeks (±2 weeks) from the date of the last imaging scan, until withdrawal of consent, death, or study closure. May be either an in-person assessment, contact by telephone, or review of publicly available information (if reasonable efforts to contact the subject are unsuccessful).

d All subjects must sign informed consent for the study before Screening/ Baseline procedures are conducted.

e Archival tumor blocks (or freshly-cut slides, following consultation with the medical monitor) performed following progression during/after the most recent line of therapy, or other archival tumor tissue samples collected prior to the first line therapy for advanced disease, are to be collected.

f Hepatitis B surface antigen, antibodies to hepatitis B core, and antibodies to hepatitis C are to be assessed. If hepatitis C serology is positive, hepatitis C virus RNA test by PCR is required to confirm.

g On days when tucatinib PK blood draws are done, record the date and time of the subject's last meal prior to tucatinib administration.

h In subjects in the Phase 2 undergoing Cycle 1 paclitaxel PK assessment, the first tucatinib dose will be given in the evening on Day 1

i Vital signs to be collected are systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate

j Assessment to be done predose on days when study drug(s) are administered. Predose assessments can be done within 1 day prior to study visit. Confirm assessments results prior to administering any study drug.

k Coagulation panel should be assessed on Day 1 every 2 cycles, starting from Cycle 2.

l If the urine protein is ≥2+ on a dipstick, at baseline either a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours or the UPC ratio must be <1 to allow participation in the study. If the urine protein is ≥2+ during treatment, urine should be collected and the UPC ratio calculated.

m Scheduling is determined by date of most recent screening or on-treatment echocardiogram/MUGA. Not required at EOT visit if an echocardiogram or MUGA scan was done within the previous 12 weeks (excluding the Screening/Baseline assessment).

n Cardiac function should be assessed (echocardiogram or MUGA) every 6 months until 24 months from the last administration of trastuzumab.

o Pregnancy test must be performed within 7 days prior to Day 1 of each treatment cycle.

p FOCBP only: After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months. Subjects may do monthly home pregnancy tests and report interim results at long term follow up visits. Subjects will be asked to confirm that monthly pregnancy tests have been performed and have been negative.

q SAEs and non-serious AESIs will be followed until significant changes return to baseline, the event stabilizes or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All treatment-related SAEs that occur after the safety reporting period should be reported (see Section 7.8.1.3).

r At minimum, disease assessments, preferably using CT-scans, must include the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as bone imaging. Scans should be performed at screening, during treatment, and at the EOT visit. During treatment, scans will be performed every 6 weeks (based on Cycle 1 Day 1) through Week 36 then every 9 weeks through end of study treatment. If cycles are delayed for any reason or there is an interim unscheduled assessment, scans should continue to be performed according to the original schedule. After study treatment discontinuation, disease assessments should be undertaken 9 weeks until the occurrence of documented disease progression, withdrawal of consent, death, or study closure. Disease should be evaluated using the same modality as at screening/baseline. If bone imaging is collected, any RECIST-appropriate imaging modality may be used.

s In all subjects in Phase 2 and Phase 3: tucatinib predose trough concentration will be assessed in Cycles 2 to 6.

t In all subjects in the paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with gastrectomy (without maintenance of the pylorus): tucatinib and ONT-993 PK assessments will be done on Cycle 1 Day 8 and Cycle 2 Day 1, and PK assessments of paclitaxel and its metabolites will be done Cycle 1 Days 1 and 8 and Cycle 2 Day 1. Subjects with gastrectomy can come from either Cohort 2A or Cohort 2B.

u There is no need for a separate blood sample for biomarker analysis at screening, as is taken as part of the blood sample for NGS assay of HER2 amplification.

v Day 1 of every second cycle from Cycle 2

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

Karnofsky	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

ECOG	
Score	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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 any study drug).

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 (please see acceptable combinations below):

- 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 (male or female condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide)[b]

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.

b A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception).

Acceptable combinations of contraceptive methods:

- Hormonal method and vasectomy
- Hormonal method and barrier method
- Intrauterine device and vasectomy
- Intrauterine device and barrier method
- Tubal ligation and vasectomy
- Tubal ligation and barrier method

Contraception options for male subjects sexually active with a person who is pregnant or breast feeding

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
- Barrier methods alone, including double-barrier methods

APPENDIX D: CYP3A 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 inhibitors/inducers with continued research.

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

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

a. FDA. "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency)
b. EMA. "Guideline on the investigation of drug interactions" (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)
c. Drug package insert
d. (Kerb 1996)

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

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

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

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

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

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

c Drug package insert

APPENDIX F: CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

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

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

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

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

b Acid form is an organic anion transporting polypeptide 1B1 (OATP1B1) substrate.

c Listed based on pharmacogenetic studies.

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

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

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

APPENDIX G: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX H: EORTC QLQ-OG25

ENGLISH

EORTC QLQ - OG25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at all	A little	Quite a bit	Very much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had trouble enjoying your meals?	1	2	3	4
35. Have you felt full up too quickly after beginning to eat?	1	2	3	4
36. Has it taken you a long time to complete your meals?	1	2	3	4
37. Have you had difficulty eating?	1	2	3	4
38. Have you had acid indigestion or heartburn?	1	2	3	4
39. Has acid or bile coming into your mouth been a problem?	1	2	3	4
40. Have you had discomfort when eating?	1	2	3	4
41. Have you had pain when you eat?	1	2	3	4
42. Have you had pain in your stomach area?	1	2	3	4
43. Have you had discomfort in your stomach area?	1	2	3	4
44. Have you been thinking about your illness?	1	2	3	4
45. Have you worried about your health in the future?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you had a dry mouth?	1	2	3	4
48. Have you had problems with your sense of taste?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4

Please go on to the next page

During the past week:

		Not at all	A little	Quite a bit	Very much
50.	Have you had difficulty swallowing your saliva?	1	2	3	4
51.	Have you choked when swallowing?	1	2	3	4
52.	Have you coughed?	1	2	3	4
53.	Have you had difficulty talking?	1	2	3	4
54.	Have you worried about your weight being too low?	1	2	3	4
55.	Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

APPENDIX I: EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

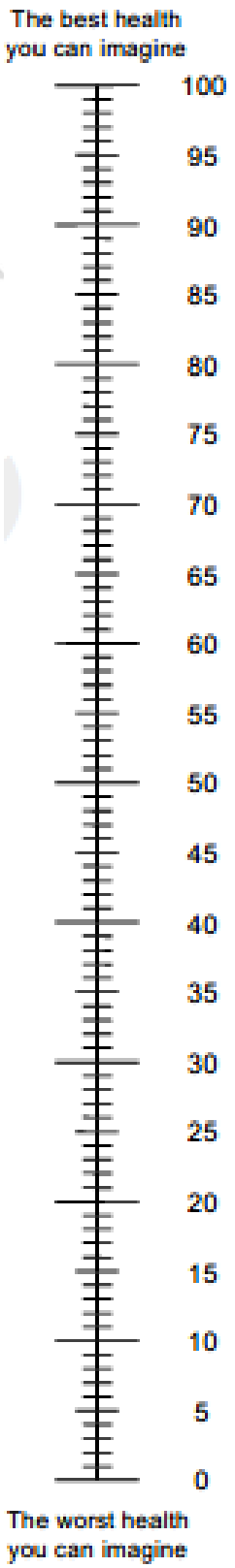
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

APPENDIX J: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled

MOUNTAINEER-02: A randomized, double-blind, placebo-controlled, active comparator Phase 2/3 study of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in subjects with previously treated, locally-advanced unresectable or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma (GEC)

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

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX K: DOCUMENT HISTORY

Version	Date
Original	08-Apr-2020
Amendment 1	26-Jun-2020
Amendment 2	02-Apr-2021

SUMMARY OF CHANGES IN AMENDMENT 1

Amendment A01

Section(s)	Change	Rationale
Throughout the protocol	Added identification of study as MOUNTAINEER-02	Study name newly designated
Throughout the protocol	Changed the Phase 2 safety lead-in stage, in which the tucatinib dose would potentially be de-escalated, to a paclitaxel dose optimization stage, to determine the recommended dose of paclitaxel administered with tucatinib, trastuzumab, and ramucirumab.	Concerns over a potential drug-drug interaction between tucatinib and paclitaxel led to the initial evaluation of a lower paclitaxel dose.
Throughout the protocol	Changed the Phase 2 Safety and activity assessments stage to Dose expansion stage.	To be consistent with paclitaxel dose optimization stage.
Throughout the protocol	Added Cohort 2B to the dose expansion stage of the Phase 2 to enroll subjects who are human epidermal growth factor receptor 2 (HER2)-negative according to blood-based next generation sequencing (NGS) assay of circulating tumor DNA (ctDNA) but HER2-positive (HER2+) according to tissue biopsy	In order to evaluate the study regimen in this subject population.
Throughout the protocol	Added the designations "Cohort 2A" and "Cohort 2B" in the Phase 2 dose expansion stage, changed the designations "Arm A" and "Arm B" to "Arm 3A" and "Arm 3B", and added the designation "Arm 3C" for the new arm in the Phase 3.	For the sake of clarity.
Throughout the protocol	Added an arm to Phase 3 to evaluate tucatinib, trastuzumab placebo, ramucirumab, and paclitaxel in 30 subjects	To establish the activity of tucatinib without trastuzumab when combined with ramucirumab and paclitaxel
Section 2, Synopsis	Added an objective and an endpoint to determine the recommended dose of paclitaxel.	To implement the paclitaxel dose optimization stage.
Section 2, Synopsis	Specified that the secondary objective to evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel applies to subjects that have HER2+ disease according to blood-based NGS assay.	Clarification required given the addition of Cohort 2B.
Section 2, Synopsis	Added objective response rate (ORR) irrespective of confirmation per Response evaluation criteria in solid tumors (RECIST) version 1.1 according to investigator assessment, and confirmed ORR per RECIST version 1.1 according to blinded independent central review (BICR) assessment to Phase 3 efficacy endpoints.	To expand sensitivity analyses of ORR.
Section 2, 9.2.3, 9.2.5, 9.3.6.1, Synopsis	Changed the first efficacy first endpoint in the Phase 2 to ORR irrespective of confirmation, added an endpoint for confirmed ORR, changed duration of response (DOR) and disease control rate (DCR) to use response irrespective of confirmation.	In order to be able to undertake the Phase 2 efficacy assessment once 30 subjects in Cohort 2A have been followed for 6 weeks rather than 12 weeks.

Amendment A01

Section(s)	Change	Rationale
Section 2, Synopsis	Added an exploratory objective to evaluate the preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel applies to subjects that have HER2-negative disease according to blood-based NGS assay but are HER2+ according to assay of biopsy.	As part of the addition of Cohort 2A.
Section 2, Synopsis	Added an exploratory objective to evaluate the correlation between HER2 blood-based amplification assay and HER2 overexpression/amplification in assays of biopsies	To evaluate the relative frequencies in the pretreated GEC population of the different types of HER2 positivity.
Section 2, 9.3.6.2, Synopsis	Added efficacy endpoints for ORR irrespective of confirmation per investigator and per BICR to the primary Phase 3 objective.	
Section 2, Synopsis	Added secondary and exploratory objectives, respectively, to evaluate the anti-tumor activity of tucatinib in combination with ramucirumab and paclitaxel, and to evaluate the safety and tolerability of tucatinib in combination with ramucirumab, and paclitaxel to the Phase 3.	To implement the addition of Arm 3C to the Phase 3.
Section 3.1.1.2, 3.1.2, 3.1.8, 3.2.1, 4.1, Synopsis	Changed the inclusion criteria for HER2+ disease, specifying that subjects need to have HER2+ according to assay of blood-based NGS or biopsy in the dose optimization stage, according to blood-based NGS for Cohort 2A and the Phase 3, and be HER2 negative according to blood-based NGS and HER2+ according to biopsy for Cohort 2B.	To implement the addition of Arm 3C to the Phase 3.
Section 4.1, Synopsis	Added an inclusion criteria to require that subjects have to supply archival tumor tissue for central assay; if an archival sample is not available, the subject may be eligible, following approval by the medical monitor.	In order to evaluate biomarker objectives.
Section 4.1, Synopsis	Added the specification that subjects with hemoglobin ≥8 and <9 g/dL may be included with approval from the Medical Monitor	According to feedback from investigators.
Section 4.1, Synopsis	In the inclusion criteria for subjects who can father children who are sexually active with a person who is pregnant or breastfeeding, changed the contraception requirements from 2 highly effective methods to 1 of 2 contraception options.	Update of Seattle Genetics standard contraception criteria.
Section 4.2, Synopsis	Added an exclusion criteria against having received more than 1 line of prior systemic therapy for locally-advanced unresectable or metastatic disease	Clarification of eligibility criteria.
Section 4.2, Synopsis	Changed exclusion criteria for having received prior taxanes to having received taxanes ≤12 months prior to enrollment	To allow use of taxanes in neoadjuvant therapy.

Amendment A01

Section(s)	Change	Rationale
Section 4.2, Synopsis	Added an exclusion criteria making subjects with gastrectomy ineligible for the Phase 2 dose optimization stage.	In order that potential tucatinib pharmacokinetic (PK) differences in subjects with gastrectomies will not affect the PK evaluation of the paclitaxel dose-finding stage.
Section 4.2, Synopsis	Added an exclusion criteria against subjects with major surgery planned for after treatment initiation.	To avoid treatment interruption and potential co-morbidities.
Sections 3.1, 3.1.1.1, 3.1.1.2, 3.1.2, 9.1.2, 9.3.1.1, Synopsis	Changed the planned number of Phase 2 subjects from 30 to 66, and the planned number of Phase 3 subjects from 470 to 500.	Phase 2: addition of Cohort 2B. Phase 3: addition of Arm 3C.
Sections 3.1.1.2, 5.2.1, Synopsis	Removed mentions of additional subjects possibly being enrolled if alternative tucatinib doses or administration schedules were evaluated.	The study design is now directed towards modification of the paclitaxel dose/schedule, rather than that of tucatinib.
Section 3.1.1.2, 9.3.1.9, Synopsis	Changed the follow-up required for a Phase 2 subject to be evaluable for response from 12 weeks to 6 weeks.	Only 6 weeks is required that the formal analysis of ORR in the dose expansion cohort is using ORR irrespective of confirmation, rather than confirmed ORR.
Sections 3.1.1.1, 3.1.3, 5.1, 5.1.2, 9.3.11.1, 9.3.11.1, Synopsis	Added that paclitaxel dose levels for assessment are 60 and 80 mg/m², that 6 subjects are to be evaluated in each paclitaxel dose level, that if ≤2 dose-limiting toxicities (DLT) are observed at 60 mg/m² the paclitaxel dose can be escalated, definition of evaluable for DLT, and added definitions of DLT.	To implement the paclitaxel dose optimization stage.
Sections 3.1.1.2, 9.1.1, Synopsis	Specified that 30 response-evaluable subjects are to be treated in each cohort of the dose expansion stage, and that they could have been enrolled in the dose optimization stage if treated at the recommended paclitaxel dose.	To implement the formal evaluation of activity in Phase 2.
Sections 3.1.1.2, 9.1.1, Synopsis	Added a formal efficacy gate to the Phase 2 (ORR ≥36%) to determine whether the Phase 3 can be initiated.	In order to have a more rigorous assessment of Phase 2 efficacy.
Sections 3.1.2, 3.1.8, 9.1.2, 9.3.1.1, Synopsis	Changed the randomization ratio from 1:1 to 8:8:1.	To adjust randomization to have approximately 235 subjects each in Arms 3A and 3B, and 30 subjects in Arm 3C.
Sections 3.1.1.1, 6.4.5, Synopsis	Added a full PK assessment for tucatinib and paclitaxel on Cycle 2 Day 1.	Given the potential drug-drug interaction (DDI) of tucatinib and paclitaxel, a more thorough evaluation of PK is required.
Sections 3.1.1.1, 3.1.1.2, 3.1.2, 5.1, 6.4.1, 6.4.2, 6.4.3, 6.4.5, 6.4.6, 6.4.7, Synopsis	Changed the paclitaxel dose from a uniform 80 mg/m² to 1) according to enrolling dose level in the Phase 2 dose optimization stage, 2) dose recommended by the dose optimization in the Phase 2 dose expansion stage and Arms 3A and 3C of the Phase 3, 3) 80 mg/m² in Arm 3B of the Phase 2.	Changes required by implementation of paclitaxel dose escalation, and by the need to use full dose paclitaxel in the standard of care comparator arm.

Amendment A01

Section(s)	Change	Rationale
Section 3.1.1, 5.1.1.1, Synopsis	Removed language pertaining to tucatinib dose de-escalation.	Tucatinib dose de-escalation replaced by paclitaxel dose escalation.
Sections 3.1.1.2, Synopsis	Specified that subjects with gastrectomy undergoing PK can come from Cohort 2A or 2B.	The evaluation of the effect of gastrectomies on tucatinib PK will not be affected by cohort.
Sections 3.1.1.1, 3.1.3, 3.1.4, 7.8, Synopsis	Removed mentions of clinically significant adverse events (AEs).	Assessment of clinically significant AEs is replaced by assessment of DLTs.
Sections 3.1.2, Synopsis	Specified that formal Phase 2 assessment of activity is to be done in all subjects treated at the recommended paclitaxel dose who were HER2+ according to the blood-based NGS assay.	Clarification given addition of Cohort 2B.
Sections 3.1.4, Synopsis	Added evaluation of PK data to SMC assessment of safety in paclitaxel dose levels.	PK data is important for the assessment of dose escalation given the potential DDI of tucatinib and paclitaxel.
Sections 5.1.1, 5.5, 6.4.5, 6.5	Added specification that tucatinib compliance may be evaluated by pill counts.	Either pill counts or patient diaries may be used in this study.
Section 5.1.2	Removed specification that subjects can receive paclitaxel with ongoing Grade 2 peripheral neurotoxicity, rather than Grade 1	Grade 2 peripheral neuropathy deemed too severe for paclitaxel administration.
Section 5.2.4	Updated paclitaxel dose reduction levels to take into account that subjects may not start at 80 mg/m².	To take into account subjects starting at 60 mg/m².
Section 5.2.4	Removed exception for Grade 2 peripheral neuropathy from paclitaxel dose modification table.	Changed because paclitaxel administration is now not allowed in the event of Grade 2 peripheral neurotoxicity.
Section 5.4.2	For inducers of CYP34A and CYP2C8, it is no longer required to avoid their administration with 2 weeks after tucatinib discontinuation. Strong inhibitors of CYP2C8 can be administered starting 1 week after discontinuation of tucatinib, rather than 2. Moderate inhibitors of CYP2C8 are now to be used with caution.	Re-evaluation of tucatinib DDI.
Sections 6.2, 7.1.1, 7.3, APPENDIX A	Changed tumor tissue collection specification to no longer require a fresh tissue biopsy to be performed at screening, Rather available tissue samples performed following progression during/after the most recent line of therapy, or performed prior to the first line therapy for advanced disease, are to be collected.	On-study biopsies are no longer mandated. Appropriate tissue samples will be analyzed only if available.
Section 6.4.1, 6.4.2, 6.4.3, 6.4.5, 7.3, APPENDIX A	Removed "without gastrectomy" from the specification that PK would be performed in the first 6 subjects in the Phase 2 with gastrectomy and without gastrectomy.	Not necessary to specifically call out 6 subjects without gastrectomy, as all subjects in the dose optimization stage will now be without gastrectomy.
Section 6.4.4, APPENDIX A	Added a complete blood count (CBC) with differential and a chemistry panel on Cycle 1 Day 22.	In order to fully evaluate laboratory abnormalities occurring during the first cycle.

Amendment A01

Section(s)	Change	Rationale
Section 7.8.1.2	Added a section specifying which event name and severity grading to use for events of left ventricular ejection fraction (LVEF) decreased.	In order to harmonize reporting of LVEF events.
Section 7.8.5, APPENDIX A	Specified that monthly pregnancy tests during follow-up can be done using home pregnancy test.	For subject convenience.
Section 9	Deleted tables showing objectives, endpoints, corresponding measurements, and time points.	No longer required per Seattle Genetics template.
Section 9.1.1, Synopsis	Updated table of 95% CIs according to number of responses observed for the case of 36% ORR.	Adjustment for efficacy gate.
Section 9.3.11.2, Synopsis	Added the information time (approximately 61% of the total OS events) for the OS interim analysis.	More completely specify the nature of the Phase 3 interim analysis.
APPENDIX E	Changed the list of strong CYP2C8 inhibitors, added a list of moderate inhibitors, and changed the list of strong inducers to moderate inducers.	Updates to referenced lists.
Throughout the protocol	Administrative changes.	

SUMMARY OF CHANGES IN AMENDMENT 2

Amendment A02

Section(s)	Change	Rationale
Synopsis	Revised the planned number of subjects from 66 to 78.	Due to each dose level in the paclitaxel dose optimization stage potentially enrolling 9 subjects, rather than 6.
Section 1.1	Added information regarding the approval of T-DXd in previously-treated gastric cancer, and revised the paragraph in consequence of this information.	Clarification.
Section 2, Synopsis	In the first exploratory phase 2 objective, added specification that HER2+ status is determined by IHC/ISH assay of a tumor tissue sample.	Clarification.
Section 3.1.1.1, 3.1.1.2, 4.1, Synopsis	Revised inclusion criterion #2 to remove the requirement for central confirmation of IHC/ISH assay of a tumor tissue sample.	Local assessment of a tumor tissue sample processed in a CLIA- or ISO-accredited laboratory is deemed sufficient to determine the presence of HER2+ disease.
Section 3.1.1.1, Figure 1, Figure 2, Synopsis	Revised the DLT evaluation in the Paclitaxel Dose Optimization stage to enroll 3 more subjects at a dose level if 2 DLT are observed, and to require ≤1 DLT in 6 subjects or ≤2 DLT in 9 subjects to escalate the dose or identify the recommended dose.	To more thoroughly evaluate a dose level if 2 DLT are observed in 6 subjects.
Section 3.1.1.2, Synopsis	Replaced statements that 24 to 30 subjects will be enrolled in the expansion cohorts with statements that 30 subjects will be enrolled in the expansion cohorts.	Clarified the manner in which subjects from the dose optimization stage may count towards the sample size of the expansion cohorts.
Section 3.1.1.2, 4.1, 7.1.1, 7.4, Synopsis	Revised the inclusion criterion #2 concerning determination of HER2+ status to specify that assays of tumor tissue should be processed in a CLIA- or ISO-accredited laboratory, rather than following the package insert of FDA-approved tests.	To ensure that appropriate tests are available in all countries.
Sections 3.1.3, 7.8.1.5	Changed the specification of hepatic DLTs and hepatotoxicity AESIs to elevations with respect to the ULN, rather than grades.	For consistency with other specifications of liver enzyme elevations.
Section 3.2.3.4	Added information regarding the evaluation of tucatinib, trastuzumab, paclitaxel, and pertuzumab in the I-SPY2 study.	Further information regarding the combination of tucatinib and paclitaxel.
Section 3.2.3	Subdivided the rationale for dose and schedule of trastuzumab, ramucirumab, and paclitaxel into separate subsections.	For the sake of clarity.
Section 3.2.3.4	Added information regarding the evaluation of tucatinib, trastuzumab, paclitaxel, and pertuzumab in the I-SPY2 study.	Further information regarding the combination of tucatinib and paclitaxel.

Amendment A02

Section(s)	Change	Rationale
Section 4.1, Synopsis	In inclusion criterion #2, changed "HER2+ disease at screening" to "HER2+ disease documented since progression of the most recent line of systemic therapy" and removed similar statements from #2.a and #2.b.ii.	This statement applies to all clauses of inclusion criterion #2.
Section 4.1, Synopsis	In inclusion criterion #2.b.ii, specified that subjects cannot have HER2 amplification by blood-based NGS assay in Cohort 2B.	Consistency.
Section 4.1, Synopsis	In inclusion criterion #13: Added the specification that subjects on full-dose anticoagulation must be on a stable dose of oral anticoagulant or low molecular weight heparin. If on warfarin, the subject must have an INR of ≤3 and have no active bleeding (within ≤14 days prior to enrollment or randomization, excluding trace hematuria) or pathological condition that carries a high risk of bleeding (i.e., tumor involving major vessels or known varices).	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Sections 4.1, 5.1.2.1, 6.2.1, Synopsis	In inclusion criterion #15: specified that a UPC ratio <1 is sufficient to allow enrollment in the event of proteinuria ≥2+, as an alternative to a 24-hour urine collection showing <1000 mg of protein.	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Section 4.2, Synopsis	Removed exclusion criterion #11, regarding myocardial infarction or unstable angina.	Already covered by exclusion criterion #22 (formerly #24).
Section 4.2, Synopsis	Removed prohibition on enteral feeding from exclusion criterion #15 (formerly #16).	Inability to swallow pills is an adequate restriction on the study population.
Section 4.2, Synopsis	Removed exclusion criterion #21, regarding therapeutic anti-coagulation.	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Section 5.1.1.2	Removed the specification of trastuzumab vial size.	Vial size of commercially available formulation may vary between countries.
Section 5.1.1.2	Changed trastuzumab storage and handling specifications to "should be prepared and administered per instructions in the package insert."	To ensure that applicable package insert is followed.
Section 5.1.2.1	Added that ramucirumab is also indicated as first-line treatment in combination with erlotinib for metastatic NSCLC with EGFR exon 19 deletions or exon 21 substitution mutations.	Update of ramucirumab indications.
Section 5.2.1	Added specifications concerning the resumption of tucatinib at the same dose, when applicable, to tucatinib dose modification tables.	Clarification.
Section 5.2.2.1	Revised trastuzumab dose modifications for left ventricular dysfunction.	Consistency with revised trastuzumab prescribing information.

Amendment A02

Section(s)	Change	Rationale
Section 5.2.3	In the ramucirumab dose modification table, specified that ramucirumab should be discontinued for Grade 3 or 4 arterial thromboembolic events, rather than any grade, and also for any pulmonary embolism or deep vein thrombosis occurring or worsening during anticoagulant therapy.	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Sections 5.2.3, 5.2.3.3	Modified the ramucirumab dose modification guidelines in the event of proteinuria, using UPC ratio rather than protein in a 24-hour urine collection to guide dose modifications.	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Section 5.4.1	Added specification that subjects stabilized on chronic oral anticoagulation therapy are eligible, provided that the coagulation parameters defined in the inclusion criteria are met	Revised ramucirumab treatment guidelines.
Section 5.4.2	Removed the prohibition of therapeutic anticoagulation with warfarin, low-molecular weight heparin or similar agents. Added that subjects who develop venous thromboembolism may continue study therapy and receive anticoagulation with low molecular weight heparin (not oral anticoagulation).	Revised ramucirumab treatment guidelines.
Section 5.4.2	Added specification that ongoing aspirin therapy at doses exceeding 325 mg/day is not permitted.	Revised ramucirumab treatment guidelines.
Sections 6.1, 6.2.1, 6.4, 6.5, 7.1, Schedule of Events	Changed "serum chemistry" to "blood chemistry".	To allow for plasma chemistry tests.
Sections 6.1, 7.4	Added specification that a blood sample for biomarker assay will be drawn at EOT.	Consistency with Schedule of Events.
Section 6.4.5	For PK assessment in the paclitaxel dose optimization stage and in the first 6 subjects in the Phase 2 dose expansion stage with a gastrectomy, specified that tucatinib PK is done as well as paclitaxel PK.	Consistency.
Sections 6.4.2, 6.4.5, 7.3, Schedule of Events	Added the specification that the date and time of the subject's last meal prior to tucatinib administration is to be recorded on days when tucatinib PK draws are made.	To evaluate the food effect on the potential tucatinib-paclitaxel DDI.
Sections 6.6.1, 6.6.2, 7.8.6.1, Schedule of Events	Added requirement that subjects undergo LVEF assessments every 6 months for 24 months after discontinuation of trastuzumab.	Harmonization with trastuzumab prescribing information.
Section 7.1.1	Removed forceps from the list of biopsy methods that are not acceptable for submitted tumor tissue samples.	Removed because primary tissue biopsy can be done endoscopically.
Section 7.4	Deleted the specification that tumor biopsies performed while the subject is on study should be made available to the Sponsor.	These biopsies will not be assayed.

Amendment A02

Section(s)	Change	Rationale
Section 7.8.1.1	Added the specification that laboratory values that result in dose modifications will be reported as AEs.	Previously, only treatment interruptions were mentioned.
Section 7.8.1.6	Added Sponsor Safety Reporting to Regulatory Authorities section	Change to protocol template.
Section 7.8.3, Schedule of Events	In the event that a dipstick or routine analysis indicates proteinuria ≥2+, specified that UPC ratio should be calculated, rather than evaluation of protein in a 24-hur urine collection.	Revised treatment guidelines from the ramucirumab marketing authorization holder.
Section 9.1.1	Added a paragraph detailing the planned phase 2 sample size. Also added the specification that ORR used in the evaluation of activity in the phase 2 will be ORR irrespective of confirmation.	Clarification.
Sections 9.3.1.9, 9.3.11.1, Synopsis	Added the specification that the SMC will conduct additional analyses of safety and PK should a dose level be expanded to include a total of 9 subjects.	To implement the modified DLT evaluation schema.
Throughout the document	Changed the Sponsor name, Seattle Genetics, to Seagen.	Company name change.
Throughout the protocol	Changed liver function tests to liver enzyme tests.	Liver enzyme tests refers more specifically to AST, ALT, and bilirubin.
Throughout the protocol	Changed "biopsy" to "tumor tissue sample" when not referring to the act of taking a biopsy.	To avoid confusion regarding the need to undertake on-study biopsies.
Throughout the protocol	Changed non-SI units to SI units.	Consistency.
Throughout the protocol	Administrative changes.	