Protocol Number:	SGNTUC-019
Version:	Amendment A05; 24-Apr-2024
Protocol Title:	A Phase 2 Basket Study of Tucatinib in Combination with Trastuzumab in Subjects with Previously Treated, Locally-Advanced Unresectable or Metastatic Solid Tumors Driven by HER2 Alterations
Investigational Product:	Tucatinib
Brief Title:	Basket study of tucatinib and trastuzumab in solid tumors with HER2 alterations
Phase:	2
IND Number:	152278
EudraCT Number:	2020-004873-29
EU Trial Number	2024-511481-37
Sponsor:	Seagen Inc*. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	PPD, DO Pfizer Inc. Tel: PPD E-mail: PPD
SAE Email or Fax:	See email or fax number specified on the SAE report form.

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

PROTOCOL SYNOPSIS

Protocol Number SGNTUC-019 **Version** Amendment A05; 24-Apr-2024 **Phase** 2	**Product Name** Tucatinib **Sponsor** Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A Phase 2 Basket Study of Tucatinib in Combination with Trastuzumab in Subjects with Previously Treated, Locally-Advanced Unresectable or Metastatic Solid Tumors Driven by HER2 Alterations

Study Objectives and Endpoints

Primary Objective To evaluate the antitumor activity of tucatinib given in combination with trastuzumab in subjects with previously treated, locally-advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) overexpressing/amplified or mutated solid tumors	**Corresponding Endpoints** **Primary Endpoint:** Confirmed objective response rate (ORR; confirmed complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment **Secondary Endpoints:** • Disease control rate (DCR; confirmed CR or PR, or stable disease) per investigator assessment • Duration of response (DOR; confirmed CR or PR) per investigator assessment • Progression-free survival (PFS) per investigator assessment • Overall survival (OS)
Secondary Objectives • To evaluate the safety and tolerability of tucatinib given in combination with trastuzumab with or without fulvestrant • To evaluate the pharmacokinetics (PK) of tucatinib	**Corresponding Endpoints** • Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs • Other relevant safety variables including AEs of special interest (AESIs) • Plasma concentrations of tucatinib
Exploratory Objectives • To determine the concordance of HER2 alterations as detected by tissue and blood-based HER2 testing methodologies • Identify tumor-specific alterations that are associated with resistance to tucatinib	**Corresponding Endpoints** • Concordance of HER2 alterations as detected by different testing methodologies • Identify tumor-specific alterations that are associated with resistance to tucatinib

• To evaluate patient-reported outcomes (PROs)	• Change from baseline in health-related quality of life (HRQoL), as assessed by the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)

Study Design

This multi-cohort, open label, multicenter, international Phase 2 clinical study is designed to assess the activity, safety, and tolerability of tucatinib in combination with trastuzumab for the treatment of selected solid tumors with HER2 alterations. Subjects will be enrolled into separate cohorts based on tumor histology and HER2 alteration status (see Table 1).

There are 5 tumor specific cohorts with HER2 overexpression/amplification (cervical cancer [Cohort 1], uterine cancer [Cohort 2], biliary tract cancer [Cohort 3], urothelial cancer [Cohort 4], and non-squamous non-small cell lung cancer [NSCLC] [Cohort 5]), 2 tumor specific cohorts with HER2 mutations (non-squamous NSCLC and [Cohort 7] breast cancer [Cohort 8]), and 2 cohorts which will enroll all other HER2 amplified/overexpressed solid tumor types (except breast, gastric or gastroesophageal junction adenocarcinoma [GEC], and colorectal cancer [CRC]) or HER2-mutated solid tumor types (Cohorts 6 and 9 respectively).

If a sufficient number of subjects with a particular tumor type are enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate cohort, drawn from optional Cohorts 10 to 15. If any optional cohort is opened, all subjects enrolled in Cohorts 6 or 9 with the applicable tumor type will be reassigned to the new tumor-specific cohort; these subjects will be replaced in Cohorts 6 and 9.

In Stage 1, up to approximately 12 response-evaluable subjects may be enrolled in each of Cohorts 1 to 5, and 7. If sufficient activity is observed in Stage 1 for a particular cohort (see Statistical Methods), up to a total of 30 response-evaluable subjects will be enrolled in the cohort (Stage 2 expansion) to further characterize the activity and safety of the study regimen in the given disease and HER2 alteration type. Cohorts 6, 8, and 9 will enroll up to 30 response-evaluable subjects without undergoing the Stage 1 assessment in 12 subjects. Subjects who are not response-evaluable will be replaced.

Table 1: Definition of cohorts according to disease type and HER2 alterations, and number of subjects

	HER2 alteration		N subjects per cohort	
	Overexpression/ amplification	Mutations	Stage 1	Stage 1 and Stage 2
Cervical cancer	Cohort 1		12	30
Uterine cancer	Cohort 2		12	30
Biliary tract cancer	Cohort 3		12	30
Urothelial cancer	Cohort 4		12	30
Non-squamous NSCLC	Cohort 5	Cohort 7	12	30
Other solid tumors (except breast cancer, GEC, and CRC)	Cohort 6		30	
Breast cancer		Cohort 8	30	
All solid tumors (except breast and non-squamous NSCLC)		Cohort 9	30	
Optional tumor specific Cohorts				
Cervical cancer		Cohort 10	12	30
Uterine cancer		Cohort 11	12	30
Biliary tract cancer		Cohort 12	12	30
Urothelial cancer		Cohort 13	12	30
Additional tumor specific	Cohort 14	Cohort 15	12	30

Study treatment is composed of tucatinib 300 mg BID PO combined with trastuzumab 8 mg/kg intravenously (IV) on Cycle 1 Day 1 and then 6 mg/kg every 21 days starting on Cycle 2 Day 1. Subjects with hormone receptor (HR) positive (HR+), HER2-mutated breast cancer will also receive, in combination with tucatinib and trastuzumab, fulvestrant 500 mg intramuscular (IM) once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15. A Safety Monitoring Committee (SMC) will be responsible for monitoring the safety of subjects in the study at regular intervals. Subjects will continue study treatment until the occurrence of

radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, death, or study closure. Following treatment discontinuation, disease progression (in subjects without progression at treatment discontinuation), further anti-cancer therapy, and survival status will be monitored from EOT until withdrawal of consent, death, or study closure.

As of Amendment 5, the objectives of the study have been achieved. Therefore, the decision has been made to close the study. For subjects in long-term follow-up, a last visit or contact will occur prior to the subject's discontinuation from participation in the study. Any subject on study treatment will transition to the long-term extension phase (LTEP) of the study. Once post-study access to study treatment is available, subjects will have a last visit or contact prior to discontinuation from the study. The Sponsor will provide continued access to study treatment for any subject who is still on treatment and receiving clinical benefit based on the investigator's assessment.

Study Population

Inclusion criteria

All subjects must meet the following eligibility criteria for enrollment:

1. Histologically or cytologically confirmed diagnosis of locally-advanced unresectable or metastatic solid tumor, including primary brain tumors
2. Prior therapy:
    a. Subjects with non-squamous NSCLC: Must have progressed during or after standard treatment or for which no standard treatment is available
    b. Subjects with other disease types: Must have progressed during or after ≥1 prior line of systemic therapy for locally-advanced unresectable or metastatic disease
        i. Subjects with metastatic HR+ HER2-mutated breast cancer must have received a prior CDK4/6 inhibitor in the metastatic setting
        ii. Subjects with metastatic cervical cancer must have received platinum-based chemotherapy with or without bevacizumab in the metastatic setting
3. Progression during or after, or intolerance of, the most recent line of systemic therapy
4. Disease demonstrating HER2 alterations (overexpression/amplification or HER2 activating mutations), as determined by local or central testing processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory, according to one of the following:
    a. HER2 overexpression/amplification from fresh or archival tumor tissue or blood utilizing one of the following tests, in subjects with tumor types other than breast cancer, GEC, or CRC:
        i. HER2 overexpression by immunohistochemistry (IHC): 3+ by breast or gastric algorithms
        ii. HER2 amplification by in situ hybridization (ISH) assay: fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) signal ratio ≥2.0 or gene copy number >6
        iii. HER2 amplification in tissue by next generation sequencing (NGS) assay
        iv. HER2 amplification in circulating tumor DNA (ctDNA) by blood-based NGS assay

b. Known activating HER2 mutations detected in fresh or archival tumor tissue or blood by NGS assay, including:
   - Extracellular domain: G309A/E; S310F/Y; C311R/S; C334S
   - Kinase domain: T733I; L755P/S; I767M; L768S; D769N/Y/H; Y772; A775; G776; V777L/M; G778; T798; L841V, V842I; N857S, T862A, L869R, H878Y, R896C, other exon 20 insertions
   - Transmembrane/juxtamembrane domain: S653C, I655V; V659E; G660D; R678Q; V697.
   - Subjects with HER2 activating mutations not listed above may be eligible, if supported by scientific literature and approved by the medical monitor

5. Have measurable disease per RECIST v1.1 criteria according to investigator assessment
6. Be at least 18 years of age at time of consent, or considered an adult by local regulations
7. Have Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
8. Have a life expectancy of at least 3 months, in the opinion of the investigator
9. Have adequate hepatic function as defined by the following:
   a. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × upper limit of normal (ULN) (≤5 × ULN if liver metastases are present)
   b. Total bilirubin ≤1.5 × ULN. Exception: subjects with known history of Gilbert's syndrome with direct bilirubin ≤1.5 × ULN and normal AST and ALT are eligible
10. Have adequate baseline hematologic parameters as defined by:
    a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L
    b. Platelet count ≥100 × 10^9/L; subjects with stable platelet count from 75 to 100 × 10^9/L may be included with approval from Medical Monitor
    c. Hemoglobin ≥9.0 g/dL; subjects with hemoglobin ≥8 and <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
11. Estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation
12. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram or multiple-gated acquisition scan (MUGA) documented within ≤28 days prior to first dose of study treatment

13. 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, and, if applicable, for at least 2 years after the final dose of fulvestrant.

    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through at least 7 months after the final dose of any study drug, and, if applicable, at least 2 years after the final dose of fulvestrant.

    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 B, 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, and, if applicable, for at least 2 years after the final dose of fulvestrant.

14. 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, and, if applicable, for at least 2 years after the final dose of fulvestrant.

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

    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 methods of birth control, as defined in Appendix B, 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, and, if applicable, for at least 2 years after the final dose of fulvestrant.

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

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

Exclusion criteria

1. Subjects with breast cancer, gastric or gastroesophageal junction adenocarcinoma, or CRC whose disease shows HER2 amplification/overexpression.

2. Previous treatment with HER2-directed therapy; subjects with uterine serous carcinoma or HER2-mutated gastric or gastroesophageal junction adenocarcinoma without HER2-overexpression/amplification may have received prior trastuzumab
3. Known hypersensitivity to any component of the drug formulation of tucatinib or trastuzumab (drug substance, excipients, murine proteins), or any component of the drug formulation of fulvestrant in subjects with HR+ HER2-mutated breast cancer
4. History of exposure to a >360 mg/m² doxorubicin-equivalent or >720 mg/m² epirubicin-equivalent cumulative dose of anthracyclines
5. Treatment with any systemic anti-cancer therapy, radiation therapy, major surgery, or experimental agent within ≤3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial.
6. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    a. Alopecia
    b. Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
    c. Anemia, which must have resolved to ≤ Grade 2
7. Have clinically significant cardiopulmonary disease such as:
    a. Ventricular arrhythmia requiring therapy
    b. Symptomatic hypertension or uncontrolled hypertension as determined by investigator
    c. Any history of symptomatic CHF
    d. Severe dyspnea at rest (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 or above) due to complications of advanced malignancy
    e. Hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea
8. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment
9. 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
10. Presence of known chronic liver disease

11. Subjects known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
    - CD4+ T-cell count of <350 cells/μL
    - Detectable HIV viral load
    - History of an opportunistic infection within the past 12 months
    - On stable antiretroviral therapy for <4 weeks
12. Are pregnant, breastfeeding, or planning a pregnancy from time of informed consent until 7 months after the final dose of any study drug, and, if applicable, for at least 2 years after the final dose of fulvestrant
13. Have inability to swallow pills
14. Have used a strong cytochrome P450 (CYP) 2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 days prior to start of treatment
15. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
16. History of another malignancy within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (eg, 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
17. Subjects with known central nervous system (CNS) lesions must not have any of the following:
    a. Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
    b. Ongoing use of systemic corticosteroids for control of symptoms of brain lesions at a total daily dose of >2 mg of dexamethasone (or equivalent). However, subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible, following approval by the medical monitor
    c. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to subject (eg, brain stem lesions). Subjects who undergo local treatment for such lesions identified by screening brain magnetic resonance imaging (MRI) may still be eligible for the study
    d. Known or suspected leptomeningeal disease as documented by the investigator
    e. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain lesions notwithstanding CNS-directed therapy

Number of Planned Subjects

Approximately 162 to 270 subjects may be enrolled in the study. This is comprised of up to approximately 12 to 30 subjects in each of Cohorts 1 to 5 and Cohort 7, and up to approximately 30 subjects in each of Cohorts 6, 8, and 9. Additional subjects may be enrolled if any of the optional Cohorts 10 to 15 are opened. Subjects initially enrolled in Cohorts 6 or 9 who are reassigned to an optional cohort will be replaced.

Investigational Product, Dose, and Mode of Administration

Tucatinib 300 mg will be administered PO BID continuously starting from Cycle 1 Day 1 onwards.

Trastuzumab 8 mg/kg will be administered IV on Cycle 1 Day 1 and then will be administered at 6 mg/kg every 21 days starting on Cycle 2 Day 1. However, if trastuzumab IV was administered within the 4 weeks prior to treatment initiation, trastuzumab 6 mg/kg IV should be administered on Cycle 1 Day 1.

Fulvestrant 500 mg will be administered IM once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15.

Duration of Treatment

Study treatment will continue until unacceptable toxicity, occurrence of radiographic progression or clinical progression, withdrawal of consent, death, or study closure. If a study drug (tucatinib, trastuzumab, or fulvestrant) is discontinued, study treatment can continue with remaining study drug(s).

Subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study drug during the LTEP. During this phase of the study, only pregnancies, SAEs, and adverse events of special interest (AESIs) will be collected by the Sponsor. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical ca**re.**

Efficacy Assessments

Disease response will be assessed by the investigator according to RECIST v1.1. 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) (with oral and/or IV contrast), and covering, at a minimum, the chest, abdomen, and pelvis. Positron emission tomography-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. In subjects with breast or lung cancer, a contrast MRI scan of the brain should be performed at screening. Subjects with known or suspected brain lesions should undergo brain MRIs during treatment and follow-up according to the same assessment schedule as for other disease assessments. If contrast is contraindicated (ie, 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 (if an MRI is not feasible, a non-contrast CT scan is acceptable). For each subject, the same imaging modality as used at screening/baseline should be used throughout the study, unless otherwise clinically indicated. In subjects with lung cancer, scans of the pelvis do not need to be undertaken after the screening assessment unless lesions were detected at screening, or as clinically indicated. Images will be collected by an independent central review (ICR) facility for possible future analysis. Disease assessments will be done at screening/baseline, and every 6 weeks for first 24 weeks then every 12 weeks, irrespective of dose interruptions.

Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (eg, CR at Week 6, confirmatory scans at Week 10–12, next assessment due at Week 12). Tumor imaging should also be performed whenever disease progression is suspected.

Subjects will be considered evaluable for response if they (1) had a baseline disease assessment with measurable disease (ie, at least one target lesion at baseline), (2) received study treatment, and (3) had a post-baseline disease assessment or discontinued treatment due to documented disease progression or clinical progression.

Subjects that discontinue study treatment for reasons other than documented progressive disease or death will continue to have disease assessments every 6 weeks (±1 week) until 24 weeks after treatment initiation, then every 12 weeks (±1 week), until the occurrence of documented disease progression per RECIST v1.1, death, withdrawal of consent, lost to follow-up, or study closure.

Follow-up for survival and subsequent anti-cancer therapy will occur approximately every 12 weeks (±14 days) from EOT and continue until death, withdrawal of consent, lost to follow-up, or study closure.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

Pharmacokinetic Assessments

Blood samples for PK assessment of trough tucatinib drug levels will be collected in all subjects on Day 1 of Cycles 2 to 6, prior to administration of tucatinib. On Day 1 of Cycle 3, PK assessments of peak levels of tucatinib will be performed 1 to 4 hours after administration of tucatinib. Plasma concentrations of tucatinib will be determined using validated liquid chromatography (LC)-mass spectrometry (MS)/MS methods. PK parameters will be summarized using descriptive statistics.

HER2 Testing for Eligibility and Biomarker Assessments

Study eligibility requirements for HER2 overexpressing/amplified disease and HER2-mutated disease are to be met by assays performed pre-study (assessments undertaken prior to any study-related activities) or in prescreening, as follows:

- Previously established HER2 alterations: HER2 eligibility can be demonstrated via HER2 overexpression or amplification in an IHC/ISH assay of tumor tissue or HER2 amplification or activating mutations in an NGS assay of ctDNA or tumor tissue, processed locally in a CLIA- or ISO-accredited laboratory before enrollment in the study.

- Pre-screening for HER2 alterations: if HER2 alterations have not been detected in pre-study assessments, HER2 eligibility may alternatively be established during pre-screening, up to 3 months prior to the Screening visit, via an NGS assay of ctDNA evaluating the presence of HER2 amplification or mutations.

Additional biomarker analyses: For the evaluation of the exploratory biomarker objectives, all subjects will provide a blood sample for NGS assay of ctDNA and archival tumor tissue or a fresh tumor biopsy, if available. The blood sample will be collected during pre-screening or on Cycle 1 Day 1, if not collected during pre-screening. However, the blood sample does not need to be drawn if a pre-study NGS assay of ctDNA has previously been performed by the sponsor since the end of prior therapy. The tumor tissue sample will be collected during screening, once the subject has been approved for enrollment by the medical monitor.

The list of acceptable known activating mutations are detailed in the inclusion criteria. As specified, subjects with HER2 exon 20 insertions are eligible. Subjects with HER2 activating mutations not listed in the inclusion criteria may be eligible, if supported by scientific literature and approved by the medical monitor. Archival tumor tissue samples should be the most recent tissue sample available. If an archival sample is not available, a fresh biopsy will be undertaken during screening, if the subject has an available tumor lesion and consents to the biopsy. Subjects with no archival tissue and whose tumors are considered not accessible or appropriate for biopsy are eligible for enrollment, following approval by the medical monitor.

Safety Assessments

Safety assessments will include the surveillance and recording of AEs, including serious adverse events (SAEs) and AESI, physical examination findings, vital signs, 12-lead electrocardiograms, concomitant medications, pregnancy testing, and laboratory tests. Assessment of cardiac ejection fraction will be performed using multigated acquisition scan (MUGA) scan or echocardiogram. An ongoing, real-time review of subject safety and SAEs will be conducted by the sponsor's Drug Safety Department. The SMC will be responsible for monitoring the safety of subjects in the study at regular intervals. AE and laboratory abnormality severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.

Only pregnancies, SAEs, and AESIs will be collected by the Sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.

Patient-Reported Outcomes Assessments

The EQ-5D-5L questionnaire will be administered to assess subject HRQoL. Administration will occur at Cycle 1 Day 1 prior to the start of study drug treatment and then on Day 1 of every second cycle, starting from Cycle 2. Additionally, a post-treatment assessment will be undertaken at the EOT visit.

Statistical Methods

Safety and efficacy will be assessed using descriptive statistics, including the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables. Confirmed ORR per investigator is defined as the proportion of subjects with confirmed CR or PR, per RECIST v1.1. The 2-sided 90% exact confidence interval (CI) using Clopper-Pearson method will be calculated for the response rates.

The primary analysis of the study will be performed when 30 response-evaluable subjects in each cohort have been followed for at least 12 weeks or have documented disease progression. The primary efficacy endpoint of confirmed ORR per RECIST v1.1 will be estimated for each cohort based on the response-evaluable set, comprising all subjects who received any amount of study treatment who are considered evaluable for response. The 90% exact CIs using the Clopper-Pearson method will be provided. The confirmed ORR may also be summarized combining cohorts with same disease type.

Interim futility analyses will be performed separately for Cohorts 1 to 5 and 7 after approximately 12 subjects of a given cohort (Stage 1) have been treated and had at least two response assessments post-baseline or had disease progression.

The Bayesian predictive probability approach will be used to determine the futility criteria. At the time of each interim analysis, the predictive probability of success (PPoS) will be calculated. A PPoS <20% indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the study given the interim result. Based on activity and safety data, together with the PPoS, a cohort may be stopped early by the sponsor. Cohorts that successfully pass the interim analysis for futility may, at the sponsor's decision, continue to enroll up to an additional 18 response-evaluable subjects, totaling up to 30 response-evaluable subjects for each tumor cohort. A cohort may be expanded to Stage 2 earlier if the futility rule is cleared before 12 subjects, in other words, if the minimal required responses are observed in fewer than 12 subjects.

Safety measurements will be summarized by descriptive statistics based on the safety analysis set. The safety analysis set will include all subjects who received any amount of study treatment.

For those cohorts that are expanded to Stage 2, a total of 30 subjects (combining two stages) will be treated in each cohort. For a sample size of 30 subjects, assuming confirmed ORR is between 10% and 30%, the 2-sided 90% exact CIs are summarized below:

Confirmed ORR	90% Exact CI (N=30)
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)

SCHEDULE OF EVENTS

		Pre-screening	Screening/ Baseline		Treatment						EOT	Follow-up		LTEP
					Cycles 1 and 2		Cycles >1	Every 4 weeks	Every 6 weeks[A]	Every 12 weeks	Within 30–37 days of last dose[B]	Until disease progression[C]	Every 12 weeks from EOT[D]	-
		up to 3 months prior to Screening	Days –28 to 1	Days –7 to 1	Predose Day 1	Day 12	Predose Day 1							
	Visit window (days)					-1,+3	-1,+3	±3	±7	±14		±7	±14	
HER2 alterations testing	HER2 testing informed consent	X												
	Blood sample for NGS assay of ctDNA	X			X[E]									
	Submission of archived tumor specimen [F]		X											
Screening/ Baseline Assessments	Study informed consent [G]		X											
	Inclusion/Exclusion		X	X										
	Medical history		X											
	Serology for hepatitis B and C [H]		X											
Study Drug Treatment	Tucatinib [I]				BID, from Cycle 1 Day 1									X
	Trastuzumab [J]				X		X							X
	Fulvestrant [K]				X	Cycle 1 Day 15		X						X
Safety Assessments	Physical exam [L]			X	X		X				X			X[AA]
	Vital signs and weight [L,M]			X	X		X				X			X[AA]
	ECOG performance status [L]			X	X		X				X			X[AA]
	CBC with differential [N,L]			X	X	X	X				X			X[AA]
	Serum or plasma chemistry panel [O L]			X	X	X	X				X			X[AA]
	12-lead ECG		X								X			X[AA]
	Echocardiogram or MUGA scan		X							X[P]	X[P]		X[Q]	X[AA]
	Serum or urine β-hCG pregnancy test for FOCBP			X	X[R]		X[R]				X[S]		X[S]	X
	Concomitant medications		Related to study procedures		Collect from Day 1 predose through safety reporting period of study drug(s)[T]									X[AA]
	Adverse event collection													X[AA, BB]
Disease Evaluation	CT scan, PET-CT, MRI [U]		X						X[V]	X[V]	X	X[W]		X[AA]
	Brain MRI		X[X]						X[V,Y]	X[V,Y]	X	X[W]		X[AA]
	Survival and further therapy												X	X[AA]
PK and Biomarker	Blood/tissue sample collection				See **Pharmacokinetic and biomarker sample collection time points,** Table 10									
PRO	EQ-5D-5L				X		X[Z]				X			

FOCBP=females of child-bearing potential.; LTEP=long-term extension phase

A. Scheduling determined by date of Cycle 1, Day 1 visit, irrespective of dose holds or interruptions.
B. EOT evaluations should be obtained before the initiation of non-protocol therapy. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30-37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred. For subjects who have received fulvestrant, the EOT visit should be undertaken no sooner than 8 weeks after the last dose of fulvestrant.
C. Scheduling determined by date of the last imaging scan. To be performed every 6 weeks until 24 weeks after treatment initiation, then every 12 weeks until the occurrence of documented disease progression, withdrawal of consent, death, or study closure
D. Every 12 weeks (±2 weeks) from the EOT visit, 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).
E. Blood sample for NGS assay of ctDNA to be drawn predose on Cycle 1 Day 1, if not already done in pre-screening. However, the blood sample does not need to be drawn if a pre-study NGS assay of ctDNA has previously been performed by the sponsor since the end of prior therapy.
F. Tumor tissue samples are to be collected once the subject has been approved for enrollment by the medical monitor. The archival sample should be the most recent tissue sample available. If an archival sample is not available, a fresh biopsy will be undertaken at screening, if the subject has an available tumor lesion and consents to the biopsy. Subjects with no archival tissue and whose tumors are considered not accessible or appropriate for biopsy are eligible for enrollment, following approval by the medical monitor.
G. All subjects must sign informed consent for the study before Screening/Baseline procedures are conducted.
H. 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 polymerase chain reaction is required to confirm. If hepatitis B core antibody is positive, and there is no evidence of long-term immunity, a hepatitis B virus DNA test by polymerase chain reaction is required to confirm.
I. Tucatinib is administered PO BID, on a 21-day cycle. On Day 1 of each cycle, review compliance from previous cycle and dispense tucatinib for next cycle.
J. Trastuzumab is administered IV, once every 21 days
K. For subjects with HR+ HER2-mutated breast cancer, administer fulvestrant 500 mg IM once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15.
L. 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.
M. Vital signs to be collected are heart rate, systolic and diastolic blood pressure, respiratory rate, and temperature.
N. Hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (lymphocytes, and neutrophils).
O. ALT, AST, alkaline phosphatase, total bilirubin (and direct bilirubin when total bilirubin is > ULN), albumin, bicarbonate (if available), blood urea nitrogen, magnesium, phosphorus, calcium, chloride, glucose, potassium, sodium, total protein, creatinine, calculated GFR using the MDRD equation (at baseline and as clinically indicated). In subjects with baseline GFR <50 mL/min/1.73 m^2, cystatin C will be evaluated at baseline and whenever serum or plasma creatinine is evaluated.
P. 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).
Q. Echocardiogram/MUGA assessments should be undertaken every 6 months for at least 2 years following trastuzumab discontinuation.
R. FOCBP only: Pregnancy test must be performed at baseline, at Cycle 1 Day 1 (within 24 hours predose for urine pregnancy tests or 72 hours for serum tests), within 7 days prior to Day 1 of each treatment cycle starting from Cycle 2, and at the EOT visit.
S. FOCBP only: After the last dose of study treatment, pregnancy tests will be performed once a month for 7 months, and for 2 years after the last dose of fulvestrant, if applicable. 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.
T. 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 7.6.1.2).
U. At minimum, disease assessments, preferably using CT-scans (with oral and/or IV contrast), must include the chest, abdomen, and pelvis, as well as appropriate imaging of any other known sites of disease such as bone imaging. If bone imaging is collected, any RECIST-appropriate imaging modality may be used. If contrast is contraindicated (ie, 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 (if an MRI is not feasible, a non-contrast CT scan is acceptable).
V. During treatment, scans will be performed every 6 weeks (based on Cycle 1 Day 1) through Week 24 then every 12 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. The same imaging modality as used at screening/baseline should be used throughout the study. In subjects with lung cancer, scans of the pelvis do not need to be undertaken after the screening assessment unless lesions were detected at screening, or as clinically indicated. Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan. Tumor imaging should also be performed whenever disease progression is suspected.
W. In subjects without disease progression at study treatment discontinuation, disease assessments should be undertaken every 6 weeks through Week 24 from treatment initiation then every 12 weeks until the occurrence of documented disease progression, withdrawal of consent, death, or study closure.
X. Contrast brain MRIs are to be performed at screening in all subjects with breast or lung cancer.
Y. Subjects with known or suspected brain lesions should undergo contrast brain MRIs during treatment and follow-up according to the same assessment schedule as for other disease assessments.
Z. Day 1 of every second cycle from Cycle 2.
AA. During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue every 3 weeks for subjects of child-bearing potential.
BB. Only SAEs, AESIs, and pregnancy collected by the Sponsor.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

%TGI	percent tumor growth inhibition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BID	twice daily
CAP	College of American Pathologists
CBC	complete blood count
CDX	cell line-derived xenograft
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
ER	estrogen receptor
FISH	fluorescence in situ hybridization
GDPR	General Data Protection Regulation
GEC	gastric or gastroesophageal junction adenocarcinoma
GFR	glomerular filtration rate
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive

HIV	human immunodeficiency virus
HR	hormone receptor
HR+	hormone receptor positive
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ICR	independent central review
IEC	independent ethics committee
IgG1	immunoglobulin G1
IHC	Immunohistochemistry
IM	Intramuscular
IND	investigational new drug
IRB	institutional review board
IRR	infusion-related reaction
ISO	International Organization for Standardization
IV	Intravenous
LC	liquid chromatography
LFT	liver function test
LTEP	long-term extension phase
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MDRD	Modification of Diet in Renal Disease [study]
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MS	mass spectrometry
MUGA	multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PO	Orally
PPE	palmar-plantar erythrodysesthesia
PPoS	predictive probability of success
PR	partial response
PRO	patient-reported outcomes

QTc	corrected QT intervals
RECIST	Response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
T-DM1	Trastuzumab emtansine
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VEGF	vascular endothelial growth factor

1 INTRODUCTION

1.1 HER2 in Cancer

Encoded by the ERBB2 gene, human epidermal growth factor receptor 2 (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. When overexpressed in tumors, HER2 forms ligand-independent homodimeric complexes that autophosphorylate. HER2 homo- or heterodimerization results in the activation of multiple signaling cascades, including the Ras/Raf/MEK/MAPK, PI3K/AKT, Src, and STAT pathways. These signaling pathways lead to cell proliferation, inhibition of apoptosis, and metastasis (Riese 1998; Olayioye 2000; Yarden 2001; Schlessinger 2002; Holbro 2004; Hynes 2005).

HER2 is a validated target in multiple solid tumors, with anti-HER2 biologics and small molecule-drugs approved for patients with HER2 overexpressing/amplified (hereafter HER2+) breast and gastric cancers. Amplification of the HER2 gene or overexpression of its protein occurs in approximately 15% to 20% of breast cancers (Haque 2012; American Cancer Society (ACS) 2018) and 6% to 30% of gastric and esophageal cancers (Kelly 2016). Recently, interest has grown in HER2-targeting strategies for patients with refractory metastatic colorectal cancer (CRC), where overexpression of HER2 has been found to occur in approximately 3% to 5% of patients (Valtorta 2015; Takegawa 2017). HER2 can also be overexpressed in other gastrointestinal cancers, such as cholangiocarcinoma and gallbladder carcinoma, where studies suggest ERBB2 amplification ranges from 1% to 6% (Weinberg 2019; Albrecht 2020).

Increasing attention has been given to the impact of oncogenic HER2 activation through somatic gene mutation. The majority of these HER2-mutant cancers have not been associated with concurrent HER2 gene amplification (Connell 2017), with the result that an important subgroup of HER2-altered cancers are not detected by immunohistochemistry (IHC) or in situ hybridization (ISH) methods. The role of HER2-directed therapy in these HER2-mutated cancers is the subject of active exploration.

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) (TUKYSA®; formerly known as ARRY-380 and ONT-380) is an orally (PO) 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.

Tucatinib, combined with trastuzumab and capecitabine, is approved for use in previously treated patients with advanced unresectable or metastatic HER2+ breast cancer in multiple regions of the world. It is being developed as a treatment for patients with advanced cancers that demonstrate HER2 overexpression, and is currently being evaluated in other breast cancer indications and in other combinations, and in CRC, gastric or gastroesophageal junction adenocarcinoma (GEC), cholangiocarcinoma, and gallbladder cancer.

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.

1.3 Trastuzumab

Trastuzumab, a humanized anti-HER2 antibody that binds to the HER2 extracellular domain, is approved for use in the treatment of HER2+ breast cancer and remains the backbone of treatment in the perioperative and metastatic setting, usually in combination with a taxane (Slamon 2001; Vogel 2002). Trastuzumab is also approved for the treatment of HER2+ metastatic GEC and is being evaluated in a variety of disease types, as a single agent and in combination therapy (Oh 2020).

1.4 Fulvestrant

Fulvestrant is an estrogen receptor (ER) antagonist approved for use in treatment of hormone receptor (HR) positive (HR+) metastatic breast cancer (mBC) in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant is administered via intramuscular (IM) injection.

For patients with tumors simultaneously expressing HR and HER2, guidelines support the combination of anti-HER2-targeted agents and endocrine therapy based on superior efficacy demonstrated in clinical studies (Rimawi 2018). Administration of fulvestrant will be required in subjects with HR+ HER2-mutant breast cancer.

2 OBJECTIVES

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of tucatinib in combination with trastuzumab in subjects with solid tumors displaying HER2 alterations. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1: Objectives and corresponding endpoints

Primary Objective	Corresponding Endpoints:
To evaluate the antitumor activity of tucatinib given in combination with trastuzumab in subjects with previously treated, locally-advanced unresectable or metastatic HER2 overexpressing/amplified or mutated solid tumors	*Primary endpoint:* Confirmed objective response rate (ORR; confirmed complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator assessment *Secondary endpoints:* • Disease control rate (DCR; confirmed CR or PR, or stable disease) per investigator assessment • Duration of response (DOR; confirmed CR or PR) per investigator assessment • Progression-free survival (PFS) per investigator assessment • Overall survival (OS)
Secondary Objectives	Corresponding Endpoints
• To evaluate the safety and tolerability of tucatinib given in combination with trastuzumab with or without fulvestrant	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs • Other relevant safety variables including AEs of special interest (AESIs)
• To evaluate the PK of tucatinib	• Plasma concentrations of tucatinib
Exploratory Objectives	Corresponding Endpoints
• To determine the concordance of HER2 alterations as detected by tissue and blood-based HER2 testing methodologies	• Concordance of HER2 alterations as detected by different testing methodologies
• Identify tumor-specific alterations that are associated with resistance to tucatinib	• Identify tumor-specific alterations that are associated with resistance to tucatinib
• To evaluate patient-reported outcomes (PROs)	• Change from baseline in health-related quality of life (HRQoL), as assessed by the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

SGNTUC-019 is a multi-cohort, multicenter, international, open-label Phase 2 study designed to assess the activity, safety, and tolerability of tucatinib in combination with trastuzumab for the treatment of subjects with previously treated solid tumors whose disease displays HER2 overexpression/amplification or activating mutations.

Subjects will be enrolled into separate cohorts based on tumor histology and HER2 alteration status (see Table 2, Figure 1). There are 5 tumor specific cohorts with HER2 overexpression/amplification (cervical cancer [Cohort 1], uterine cancer [Cohort 2], biliary tract cancer [Cohort 3], urothelial cancer [Cohort 4], and non-squamous non-small cell lung cancer [NSCLC] [Cohort 5]), 2 tumor specific cohorts with HER2 mutations (non-squamous NSCLC [Cohort 7] and breast cancer [Cohort 8]), and 2 cohorts which will enroll all other HER2 amplified/overexpressed solid tumor types (except breast cancer, GEC, and CRC) or HER2-mutated solid tumor types (Cohorts 6 and 9, respectively). If a subject has both HER2 overexpressed/amplified and HER2-mutated disease, and thus qualifies for enrollment in 2 different cohorts, the subject will be enrolled in the HER2 overexpressed/amplified cohort.

If a sufficient number of subjects with a particular tumor type are enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate cohort, drawn from optional Cohorts 10 to 15 (Table 2). If any optional cohort is opened, all subjects enrolled in Cohorts 6 or 9 with the applicable tumor type will be reassigned to the new tumor-specific cohort; these subjects will be replaced in Cohorts 6 and 9.

Table 2: Definition of cohorts according to disease type and HER2 alterations, and number of subjects

	HER2 alteration		N subjects per cohort	
	Overexpression/ amplification	Mutations	Stage 1	Stage 1 and Stage 2
Cervical cancer	Cohort 1		12	30
Uterine cancer	Cohort 2		12	30
Biliary tract cancer	Cohort 3		12	30
Urothelial cancer	Cohort 4		12	30
Non-squamous NSCLC	Cohort 5	Cohort 7	12	30
Other solid tumors (except breast cancer, GEC, and CRC)	Cohort 6		30	
Breast cancer		Cohort 8	30	
All solid tumors (except breast cancer and non-squamous NSCLC)		Cohort 9	30	
Optional tumor-specific cohorts				
Cervical cancer		Cohort 10	12	30
Uterine cancer		Cohort 11	12	30
Biliary tract cancer		Cohort 12	12	30
Urothelial cancer		Cohort 13	12	30
Additional tumor specific	Cohort 14	Cohort 15	12	30

Once up to approximately 12 response-evaluable subjects have been enrolled in Stage 1 of each of Cohorts 1 to 5 and Cohort 7, enrollment to the cohort will be halted for an interim analysis of activity (see Section 9.3.11). If sufficient activity is observed in Stage 1 for a particular cohort, up to a total of 30 response-evaluable subjects will be enrolled in the cohort (Stage 2 expansion) in order to further characterize the activity and safety of the study regimen in the given disease and HER2 alteration type. Cohorts 6, 8, and 9 will each enroll up to 30 response-evaluable subjects without an interim analysis. Subjects who are not response-evaluable (see Section 9.3.1.7) will be replaced. Approximately 162 to 270 response-evaluable subjects may be enrolled in the study. Additional subjects may be enrolled if optional cohorts are opened.

Adult subjects with any type of locally-advanced unresectable or metastatic solid tumor that shows HER2 overexpression/amplification or activating mutations will be enrolled (except subjects with HER2 overexpressing/amplified breast cancer, CRC, or GEC). In general, subjects will have progressed during or after ≥1 prior line of systemic therapy for locally-advanced unresectable or metastatic disease and will have progressed on or after, or be intolerant of, the most recent line of systemic therapy. Subjects must have measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, and adequate baseline hepatic, renal, and hematologic function. Subjects must not have received prior HER2-directed therapy (except for subjects with uterine serous carcinoma or HER2-mutated GEC without HER2-overexpression/amplification, who may have received prior trastuzumab), or have clinically significant cardiopulmonary disease, chronic liver disease, or uncontrolled central nervous system (CNS) metastases.

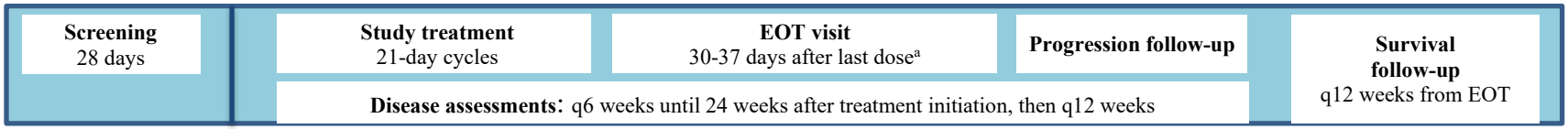
Study treatment is composed of tucatinib 300 mg twice daily (BID) PO combined with trastuzumab 8 mg/kg intravenously (IV) on Cycle 1 Day 1 and then 6 mg/kg every 21 days starting on Cycle 2 Day 1. Subjects with HR+ HER2-mutant breast cancer will also receive, in combination with tucatinib and trastuzumab, fulvestrant 500 mg IM once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15.

A Safety Monitoring Committee (SMC) will be responsible for monitoring the safety of subjects in the study at regular intervals. Subjects will continue study treatment until the occurrence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, death, or study closure. Following treatment discontinuation, disease progression (in subjects without progression at treatment discontinuation), further anti-cancer therapy, and survival status will be monitored from EOT until withdrawal of consent, death, or study closure.

As of Amendment 5, the objectives of the study have been achieved. Therefore, the decision has been made to close the study. For subjects in long term follow-up, a last visit or contact will occur prior to the subject's discontinuation from participation in the study. Any subject on study treatment will transition to the long-term extension phase (LTEP) of the study. Once post-study access to study treatment is available, subjects will have a last visit or contact prior to discontinuation from the study. The Sponsor will provide continued access to

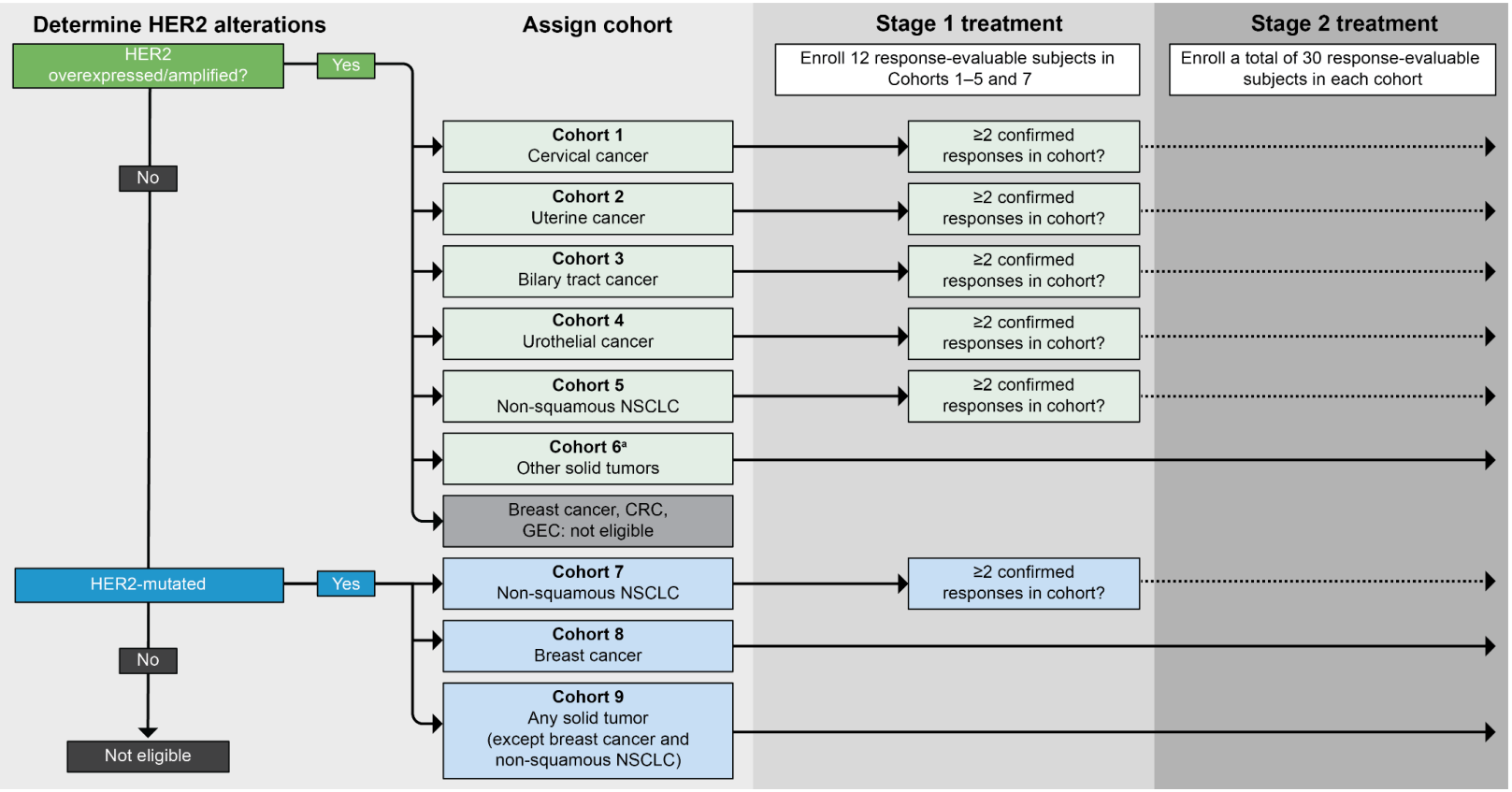
study treatment for any subject who is still on treatment and receiving clinical benefit based on the investigator's assessment.

Figure 1: Study visits



a For subjects who have received fulvestrant, the EOT visit should be undertaken no sooner than 8 weeks after the last dose of fulvestrant.

Figure 2: Study design



a If a sufficient number of subjects with a particular tumor type are enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate cohort, drawn from optional Cohorts 10 to 15 (See Section 3.1).

3.1.1 Safety Monitoring Committee

The SMC will be responsible for monitoring the safety of subjects in the study at regular intervals. The SMC will review data on deaths, study treatment and study drug discontinuations, dose reductions, AEs, serious adverse events (SAEs), 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 dosing and administration schedule, and make recommendations concerning cohort or study continuation as planned, protocol amendment, or early discontinuation of a cohort or the study for excessive toxicity. 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.

3.1.2 Stopping Criteria

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

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

3.1.3 End of Study

As of Amendment 5, all subjects still on study who are not entering the LTEP will have a last visit/contact. The study will end when the last LTEP subject has had their last visit/contact. The sponsor will provide continued access to study treatment for any subject who is still on treatment receiving clinical benefit based on the investigator's assessment.

3.1.4 Retreatment

Retreatment with study treatment is not permitted during the duration of the subject's participation in the study.

3.1.5 Method of Assigning Subjects to Treatment Groups

Following informed consent and screening assessments, eligible subjects will be assigned to currently enrolling cohorts on the basis of the subjects' disease type and the observed HER2 alterations (overexpression/amplification or mutation). If any disease-specific optional cohort is opened, all subjects enrolled in Cohorts 6 or 9 with the applicable tumor type will be reassigned to the new tumor-specific cohort.

3.2 Discussion and Rationale for Study Design

3.2.1 Rationale for Combination of Tucatinib and Trastuzumab

Trastuzumab binds to the extracellular domain of HER2, resulting in the inhibition of HER2 homodimerization and heterodimerization, inhibition of downstream signaling through the PI3K–AKT pathway, and suppression of tumor cell proliferation. Tucatinib prevents phosphorylation of the tyrosine kinase domain of the HER2 receptor, preventing activation of

MAPK and PI3K-AKT signal transduction pathways, thereby inhibiting tumor cell proliferation, survival, and metastasis.

The combination of tucatinib and trastuzumab is being evaluated in this study based on preclinical data in various tumor types that demonstrates 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 breast cancer and CRC 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 tucatinib activity 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 (Table 3) (Peterson 2017). Across 12 PDX models and 2 CDX models of breast, gastric, colorectal, and esophageal cancers and cholangiocarcinoma, a nominal dose of tucatinib 50 mg/kg BID resulted in percent tumor growth inhibition (%TGI) of 48% to 117%, while trastuzumab 20 mg/kg every 3 days resulted in %TGIs of -34% to 109%. The combination of tucatinib and trastuzumab resulted in %TGIs of 85% to 137%. 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.

Table 3: In vivo efficacy of tucatinib as monotherapy or in combination with trastuzumab in various tumor models

Tumor name	Cancer type	%TGI			Response rate (CR or PR) (%)		
		Tuc	Tras	Tuc+tras	Tuc	Tras	Tuc+tras
BT-474	Breast carcinoma CDX	86	68	133	0	0	92
CTG-0708	Breast carcinoma PDX	88	66	98	0	0	0
CTG-0717	Breast carcinoma PDX	79	21	99	13	0	38
CTG-0807	Breast carcinoma PDX	98	63	120	25	0	75
NCI-N87	Gastric carcinoma CDX	101	87	130	40	0	90
GXA-3038	Gastric carcinoma PDX	110	50	116	90	0	100
GXA-3039	Gastric carcinoma PDX	48	38	103	0	0	43
GXA-3054	Gastric carcinoma PDX	65	93	136	10	70	100
CTG-0121	Colorectal carcinoma PDX	104	109	124	60	80	100
CTG-0383	Colorectal carcinoma PDX	117	80	137	60	40	100
CTG-0784	Colorectal carcinoma PDX	50	36	103	10	0	0
CTG-0137	Esophageal carcinoma PDX	49	55	85	0	0	0
CTG-0138	Esophageal carcinoma PDX	69	−34	120	20	0	90
CTG-0927	Cholangiocarcinoma PDX	48	63	86	0	0	10

Tras=trastuzumab; Tuc=tucatinib.

Clinical data from the pivotal HER2CLIMB study (ONT-380-206) clearly demonstrated the benefit of adding tucatinib to trastuzumab and capecitabine in HER2+ mBC (Murthy 2020). In this global, randomized, double-blind study, 612 subjects who were required to have been treated with 3 prior HER2-directed agents (trastuzumab, pertuzumab, and trastuzumab emtansine) 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, PFS, was statistically significant and clinically meaningful in favor of the tucatinib combination, with a hazard ratio of 0.54 (95% confidence interval |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 (hazard ratio 0.66; 95% CI: 0.50-0.88; P= 0.005), PFS in subjects with brain metastases (hazard ratio 0.48; 95% CI: 0.34-0.69; P<0.00001) and confirmed ORR (40.6% [95% CI: 35.3-46.0] in the tucatinib arm vs 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+ metastatic CRC, based on initial results reported from the single-arm, Phase 2 MOUNTAINEER trial (Strickler 2019). In this study, subjects with HER2+, RAS-wildtype metastatic CRC who had been previously treated with fluorouracil, oxaliplatin, irinotecan, and an anti-vascular endothelial growth factor (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 is ORR, with the study comparing an ORR of 20% (null hypothesis) vs 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. Both the preclinical and clinical data summarized above support the proposed evaluation of tucatinib and trastuzumab in solid tumors showing HER2 alterations.

3.2.2 Rationale for Evaluation of Tucatinib and Trastuzumab in Solid Tumors

This "basket" study will provide the opportunity to evaluate the activity of targeted therapy with tucatinib and trastuzumab across a wide variety of solid tumors, in populations defined according to HER2 alterations, and, for a selected group of tumor types that display higher rates of HER2 alterations or that represent larger patient populations, in disease-specific cohorts. In this study, tucatinib combined with trastuzumab will be explored in solid tumors with HER2 overexpression/amplification or HER2 activating mutations. It has been found that most tumors have either HER2 amplification/overexpression or mutations, rather than both (Arcila 2012; Mazieres 2013), supporting the need to explore both within a clinical study to understand the impact of the type of HER2 alteration and disease on efficacy.

HER2 overexpressing/amplified solid tumors

While various HER2-directed agents have been evaluated in HER2-amplified and HER2-overexpressing tumors, there are no approved HER2 therapies outside of breast and gastric cancers, despite HER2 overexpression/amplification being present in >10% of patients for various disease types, and rising to >50% in certain types (Table 4). Current National Comprehensive Cancer Network (NCCN) guidelines recommend pertuzumab or lapatinib combined with trastuzumab in patients with HER2+ CRC unable to receive intensive therapy or following chemotherapy (NCCN, Colon Cancer, 15 June 2020). NCCN guidelines also recommend HER2 testing in uterine cancer, pancreatic cancer, and salivary gland cancer.

Based on the preclinical evidence for the activity of tucatinib across a variety of HER2 overexpressing/amplified xenograft models (Section 3.2.1), in particular when combined with trastuzumab, the proven efficacy of tucatinib in combination with trastuzumab and capecitabine in metastatic HER2 overexpressing/amplified breast cancer, and the preliminary activity observed for dual HER2 inhibition with tucatinib and trastuzumab in metastatic HER2 overexpressing/amplified CRC, this study will evaluate tucatinib and trastuzumab in disease-specific cohorts of HER2 overexpressing/amplified cervical cancer, uterine cancer, biliary tract cancer, urothelial cancer, and non-squamous NSCLC, and in a cohort of all other solid tumors.

Table 4: Reported frequency of HER2 amplification, overexpression, and mutation, by disease type

	HER2 amplification (%)	HER2 overexpression (%)	HER2 mutation (%)
Salivary	12-52	17-44	1
Breast	20	15-20	2
Stomach	11-16	20	3
Ovary	7	27	1
Uterus	4-59	18-80	2
Cervix	0.5-14	21	3
Lung	2-3	2.5	1-3
Biliary tract	5-15	20	2
Pancreas	2	26	<1
Colorectum	5.8	5	2
Bladder	8.6	12.4	9
Prostate	5.8-6	10	<1

Source: (Oh 2020)

HER2-mutant solid tumors

Mutations are found across all exons of ERBB2, the gene encoding for HER2, with significant heterogeneity both between and within human cancer types (Connell 2017). Mutations typically occur in the absence of gene amplification, can lead to enhanced HER2 kinase activity or receptor dimerization, and, unlike other mutant oncogenes, no single mutant allele predominates (Hyman 2018). The proportion of subjects with disease showing HER2 mutations varies with tumor type, not exceeding 10% in any type, and the distribution of mutations varies by tumor type.

HER2-directed agents are being evaluated in patients with HER2-mutated NSCLC, breast cancer, CRC, urothelial tract carcinoma, and solid tumors (Cocco 2019), and promising initial assessments of activity have been reported. Current NCCN guidelines recommend trastuzumab emtansine (T-DM1) for HER2-mutant lung cancer (NCCN, NSCLC, 15 June 2020). In HER2-mutated NSCLC, single agent trastuzumab deruxtecan achieved an ORR of 56% to 62% but only 5% ORR in HER2-mutated CRC (Smit 2020; Tsurutani 2020). Single agent pyrotinib achieved an ORR of 32% in patients with NSCLC showing HER2 exon 20 mutations (Gao 2019). In the SUMMIT basket study of neratinib in HER2-mutated solid tumors, an ORR of 24% was reported in breast cancer for single agent neratinib, with responses also observed in lung and cervical cancers (Hyman 2018). In HR+ HER2-mutated breast cancer, ORR was 30% for neratinib plus fulvestrant and 53% when trastuzumab was added (Smyth 2019; Wildiers 2020).

Tucatinib is a potent inhibitor of mutant HER2 signaling in vitro. In cell signaling assays, tucatinib exhibits potent inhibition of HER2 phosphorylation in exon20 insertion mutants without measurable effects on EGFR phosphorylation. In the exon 20 G776 InsV_G/C mutation background, tucatinib potently blocked downstream signal transduction and inhibited cell proliferation in vitro. In the HER2 L755S and V777L mutants tucatinib potently blocked HER2 phosphorylation (Peterson 2020).

Tucatinib is active in multiple HER2-mutant driven tumor models, including models containing the L755S mutation which has been associated with lapatinib resistance preclinically and trastuzumab resistance clinically. Tucatinib significantly inhibited tumor growth in 5 of 6 HER2 point mutant PDX models, compared to 1 of 6 for trastuzumab alone. The combination of the 2 drugs was significantly active in all HER2 mutant models (Peterson 2020).

Tucatinib has demonstrated selective inhibition of HER2-mutants, resulting in the regression or inhibition of tumor growth in patient derived xenograft models and supporting the evaluation of tucatinib in clinical studies in HER2-mutant driven cancers. Tucatinib's HER2 selective inhibition could potentially provide clinical benefit in patients with cancers with activating HER2 mutations by blocking oncogenic signaling elicited by mutant HER2.

3.2.3 Rationale for Evaluation of Tucatinib, Trastuzumab and Fulvestrant in HR+ HER2-mutant breast cancer

Somatic HER2 mutations occur in 7-8% of HR+ mBC (Bose 2013). Preclinical data suggests that resistance to anti-HER2-targeted therapies via upregulation of ER pathways can be suppressed by the addition of endocrine therapy (Giuliano 2013). For patients with tumors simultaneously expressing HR and HER2, guidelines support the combination of anti-HER2-targeted agents and endocrine therapy based on superior efficacy demonstrated in clinical trials (Rimawi 2018). It is hypothesized that if ER signaling is left uninhibited, it can become an alternative driver of cell growth and survival in ER+/HER2+ tumors in the presence of HER2 inhibition (Giuliano 2015).

Fulvestrant is an injectable pure steroidal ER antagonist and has a high ER-binding affinity to produce complete receptor blockade. Fulvestrant's lack of estrogen agonist activity is associated with reduced risk of endometrial abnormalities seen with tamoxifen (Bissett 1994; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005). Furthermore, fulvestrant uniquely impairs dimerization and the bound receptor is rapidly degraded (Steger 2005), blocking the nuclear ER as well as cytoplasmic and membrane-bound ER, which may limit the potential for cross-talk between EGFR/HER2-mediated pathways and delay the time to development of resistance to endocrine therapy (Wright 1992; Pietras 1995; Rusz 2018). Fulvestrant has clinical activity in patients previously treated with antiestrogen therapies, including aromatase inhibitors (Ingle 2006; Perey 2007) and in patients with ER+/HER2+ breast cancer (Steger 2005; Robertson 2010).

The results from the SUMMIT trial demonstrated that dual HER2-targeted therapy (neratinib and trastuzumab) with fulvestrant improved clinical benefit in patients with HR+ HER2-mutated mBC compared to neratinib combined with fulvestrant or neratinib monotherapy. The cohort who received neratinib + fulvestrant + trastuzumab demonstrated an ORR of 53% and median PFS of 9.8 months (Wildiers 2020) versus ORR of 30% in cohorts who received neratinib combined with fulvestrant (Smyth 2019) or neratinib monotherapy (Hyman 2018).

3.2.4 Rationale for Selection of Doses

3.2.4.1 Tucatinib

The tucatinib 300 mg PO BID dose regimen is approved in multiple regions of the world.

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 function test (LFT) AEs were observed, with all grade aspartate aminotransferase (AST), alanine aminotransferase (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 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 the 18 subjects in ONT-380-005 who received tucatinib 300 mg plus 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 LFT laboratory abnormalities.

In the tucatinib plus trastuzumab and capecitabine cohort, the most frequent AEs 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 LFT laboratory abnormalities were reported in 2 subjects (7%) each.

Interim data were reported from 26 subjects with HER2+ metastatic CRC 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 (IRRs; 11.5%); only 2 Grade 3 AEs were reported, for diarrhea and hypertension (3.8% each).

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%.

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

3.2.4.2 Trastuzumab

Trastuzumab will be administered IV in accordance with the every 3-week dosing schedule specified in the trastuzumab label for neoadjuvant treatment of subjects with breast cancer and for subjects with metastatic gastric cancer. The combination of this trastuzumab regimen with tucatinib 300 mg BID PO was found to be safe and tolerable in the HER2CLIMB, MOUNTAINEER, and ONT-380-005 studies described above.

3.2.4.3 Fulvestrant

Fulvestrant will be administered in accordance with the dosing schedule specified in the fulvestrant label for treatment of subjects with HR+ mBC. Fulvestrant 500 mg IM will be administered once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15.

3.2.5 Blinding and Unblinding

Not applicable, as this is an open-label study.

4 STUDY POPULATION

This study will enroll adult subjects with any type of locally-advanced unresectable or metastatic solid tumor that shows HER2 overexpression/amplification or mutations (except subjects with HER2 overexpressing/amplified breast cancer, CRC, or GEC).

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

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of locally-advanced unresectable or metastatic solid tumor, including primary brain tumors
2. Prior therapy:
    a. Subjects with non-squamous NSCLC: Must have progressed during or after standard treatment or for which no standard treatment is available
    b. Subjects with other disease types: Must have progressed during or after ≥1 prior line of systemic therapy for locally-advanced unresectable or metastatic disease
        i. Subjects with metastatic HR+ HER2-mutated breast cancer must have received a prior CDK4/6 inhibitor in the metastatic setting
        ii. Subjects with metastatic cervical cancer must have received platinum-based chemotherapy with or without bevacizumab in the metastatic setting
3. Progression during or after, or intolerance of, the most recent line of systemic therapy
4. Disease demonstrating HER2 alterations (overexpression/amplification or HER2 activating mutations), as determined by local or central testing processed in a Clinical Laboratory Improvement Amendments (CLIA)- or International Organization for Standardization (ISO)-accredited laboratory, according to one of the following:
    a. HER2 overexpression/amplification from fresh or archival tumor tissue or blood utilizing one of the following tests, in subjects with tumor types other than breast cancer, GEC, or CRC:
        i. HER2 overexpression (3+ IHC) (breast or gastric algorithms)
        ii. HER2 amplification by in situ hybridization assay (fluorescence in situ hybridization [FISH] or chromogenic in situ hybridization [CISH] signal ratio ≥2.0 or gene copy number >6)
        iii. HER2 amplification in tissue by next generation sequencing (NGS) assay
        iv. HER2 amplification in circulating tumor DNA (ctDNA) by blood-based NGS assay

b. Known activating HER2 mutations detected in fresh or archival tumor tissue or blood by NGS assay, including:

- Extracellular domain: G309A/E; S310F/Y; C311R/S; C334S
- Kinase domain: T733I; L755P/S; I767M; L768S; D769N/Y/H; Y772; A775; G776; V777L/M; G778; T798; L841V, V842I; N857S, T862A, L869R, H878Y, R896C, other exon 20 insertions
- Transmembrane/juxtamembrane domain: S653C, I655V; V659E; G660D; R678Q; V697.
- Subjects with HER2 activating mutations not listed above may be eligible, if supported by scientific literature and approved by the medical monitor.

5. Have measurable disease per RECIST v1.1 criteria according to investigator assessment
6. Be at least 18 years of age at time of consent, or considered an adult by local regulations
7. Have ECOG performance status 0 or 1
8. Have a life expectancy of at least 3 months, in the opinion of the investigator
9. Have adequate hepatic function as defined by the following:
   a. AST and ALT ≤3 × upper limit of normal (ULN) (≤5 × ULN if liver metastases are present)
   b. Total bilirubin ≤1.5 × ULN. Exception: subjects with known history of Gilbert's syndrome with direct bilirubin ≤1.5 × ULN and normal AST and ALT are eligible
10. Have adequate baseline hematologic parameters as defined by:
    a. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L
    b. Platelet count ≥100 × 10^9/L; subjects with stable platelet count from 75 to 100 × 10^9/L may be included with approval from Medical Monitor
    c. Hemoglobin ≥9.0 g/dL; subjects with hemoglobin ≥8 and <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
11. Estimated glomerular filtration rate (GFR) ≥30 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) study equation
12. Left ventricular ejection fraction (LVEF) ≥50% as assessed by echocardiogram or multigated acquisition scan (MUGA) documented within ≤28 days prior to first dose of study treatment

13. 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, and, if applicable, for at least 2 years after the final dose of fulvestrant

    c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through at least 7 months after the final dose of any study drug, and, if applicable, at least 2 years after the final dose of fulvestrant

    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 B, 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, and, if applicable, for at least 2 years after the final dose of fulvestrant

14. 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, and, if applicable, for at least 2 years after the final dose of fulvestrant

    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 B, 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, and, if applicable, for at least 2 years after the final dose of fulvestrant

    c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of 2 highly effective methods of birth control, as defined in Appendix B, 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, and, if applicable, for at least 2 years after the final dose of fulvestrant

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

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

4.2 Exclusion Criteria

1. Subjects with breast cancer, gastric or gastroesophageal junction adenocarcinoma, or CRC whose disease shows HER2 amplification/overexpression.
2. Previous treatment with HER2-directed therapy; subjects with uterine serous carcinoma or HER2-mutated gastric or gastroesophageal junction adenocarcinoma without HER2-overexpression/amplification may have received prior trastuzumab
3. Known hypersensitivity to any component of the drug formulation of tucatinib or trastuzumab (drug substance, excipients, murine proteins), or any component of the drug formulation of fulvestrant in subjects with HR+ HER2-mutated breast cancer
4. History of exposure to a >360 mg/m² doxorubicin-equivalent or >720 mg/m² epirubicin-equivalent cumulative dose of anthracyclines
5. Treatment with any systemic anti-cancer therapy, radiation therapy, major surgery, or experimental agent within ≤3 weeks of first dose of study treatment or are currently participating in another interventional clinical trial.
6. Have any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    a. Alopecia
    b. Congestive heart failure (CHF), which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
    c. Anemia, which must have resolved to ≤ Grade 2
7. Have clinically significant cardiopulmonary disease such as:
    a. Ventricular arrhythmia requiring therapy
    b. Symptomatic hypertension or uncontrolled hypertension as determined by investigator
    c. Any history of symptomatic CHF
    d. Severe dyspnea at rest (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3 or above) due to complications of advanced malignancy
    e. Hypoxia requiring supplementary oxygen therapy except when oxygen therapy is needed only for obstructive sleep apnea
8. Have known myocardial infarction or unstable angina within 6 months prior to first dose of study treatment

9. 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
10. Presence of known chronic liver disease
11. Subjects known to be positive for human immunodeficiency virus (HIV) are excluded if they meet any of the following criteria:
    a. CD4+ T-cell count of <350 cells/μL
    b. Detectable HIV viral load
    c. History of an opportunistic infection within the past 12 months
    d. On stable antiretroviral therapy for <4 weeks
12. Are pregnant, breastfeeding, or planning a pregnancy from time of informed consent until 7 months following the last dose of study drug and, if applicable, until 2 years after the final dose of fulvestrant
13. Have inability to swallow pills
14. Have used a strong cytochrome P450 (CYP) 2C8 inhibitor within 5 half-lives of the inhibitor, or have used a strong CYP3A4 or CYP2C8 inducer within 5 days prior to start of treatment
15. Have any other medical, social, or psychosocial factors that, in the opinion of the investigator, could impact safety or compliance with study procedures
16. History of another malignancy within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (eg, 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
17. Subjects with known CNS lesions must not have any of the following:
    a. Any untreated brain lesions >2.0 cm in size, unless approved by the medical monitor
    b. Ongoing use of systemic corticosteroids for control of symptoms of brain lesions at a total daily dose of >2 mg of dexamethasone (or equivalent). However, subjects on a chronic stable dose of ≤2 mg total daily of dexamethasone (or equivalent) may be eligible, following approval by the medical monitor
    c. Any brain lesion thought to require immediate local therapy, including (but not limited to) a lesion in an anatomic site where increase in size or possible treatment-related edema may pose risk to subject (eg, brain stem lesions). Subjects who undergo local treatment for such lesions identified by screening brain magnetic resonance imaging (MRI) may still be eligible for the study
    d. Known or suspected leptomeningeal disease as documented by the investigator
    e. Have poorly controlled (>1/week) generalized or complex partial seizures, or manifest neurologic progression due to brain lesions notwithstanding CNS-directed therapy

4.3 Childbearing Potential

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

A person who can father children is anyone born male who has testes and who has not undergone surgical sterilization (eg, 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). For subjects continuing to LTEP, data will only be documented in the subject's medical record.

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 breastfeeding 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, trastuzumab, or fulvestrant) is discontinued, study treatment can continue with remaining study drug(s). Subjects who discontinue study treatment for reasons other than documented progressive disease or death will continue to have disease assessments every 6 weeks (±1 week) until 24 weeks after treatment initiation, then every 12 weeks (±1 week), until the occurrence of disease progression per RECIST v1.1, death, withdrawal of consent, lost to follow-up, or study closure.

Follow-up for survival and subsequent anti-cancer therapy will occur approximately every 12 weeks (±14 days) from EOT and continue until death, withdrawal of consent, lost to follow-up, or study closure. (Section 4.4.2).

Every effort should be made to confirm disease progression (per RECIST v1.1) whenever possible. However, in instances where subjects appear to have progressive symptoms for

whom it is not possible or feasible to undergo radiologic assessment, investigators may remove the subject from study treatment due to "physician decision due to clinical progression." Use of this reason for removing such subjects from study treatment should be restricted to those cases in which it is not clinically appropriate for the subject to undergo further radiologic assessment and where there is clinical confidence for cancer progression in the absence of radiographic confirmation. Special consideration should be given to ensure that other possible reasons, particularly AEs, are not a more accurate description of the reason for study drug discontinuation in these cases.

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

4.4.3 Tucatinib Treatment After Study Closure

The sponsor commits to continue providing tucatinib in accordance with local regulations to subjects on tucatinib who are continuing to demonstrate clinical benefit upon study closure.

5 TREATMENTS

5.1 Treatments Administered

Subjects will receive combination therapy of the investigational medicinal products tucatinib and trastuzumab. Study treatment will be given on a 21-day cycle, with tucatinib every day and trastuzumab on Day 1 (Table 5). Subjects who have HR+ HER2-mutant breast cancer will also receive fulvestrant once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15. In this study, subjects are considered to be on study treatment if they are receiving any of the study drugs (tucatinib, trastuzumab, or fulvestrant). Cycles are defined by trastuzumab administration, with a new cycle starting whenever the Day 1 infusion of trastuzumab is administered. If trastuzumab is discontinued, cycles will be defined as occurring every 21 days from the last Day 1 administration of trastuzumab.

Table 5: Treatment schedule

Agent	Dose	Route	Period	Daily frequency	Dosing Schedule
Tucatinib	300 mg	PO	All cycles	BID	Every day, from Cycle 1 Day 1
Trastuzumab	8 mg/kg	IV	Cycle 1	Once	Day 1
	6 mg/kg	IV	Cycles >1	Once	Day 1
Fulvestrant	500 mg	IM	Every 4 weeks	Once	Starting from Cycle 1 Day 1
(if applicable)			Cycle 1	Once	Day 15

5.2 Investigational Products

5.2.1 Tucatinib

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.

Tucatinib will be supplied in an open-label manner, by the sponsor.

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

5.2.1.1 Description

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

5.2.1.2 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 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.

Dose modifications of tucatinib are described in Section 5.3.1. 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 and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. 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, cut or dissolved in liquid.

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 instructions will be assessed with the use of subject diaries and confirmed with pill counts. Study drug accountability will be assessed using pill counts.

5.2.1.3 Storage and Handling

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

5.2.1.4 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.

5.2.1.5 Preparation

Detailed drug preparation instructions are provided in the Pharmacy Binder.

5.2.2 Trastuzumab

5.2.2.1 Description

Trastuzumab is a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody 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 or docetaxel for first-line treatment of HER2-overexpressing mBC and in combination with an aromatase inhibitor for HR+ 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 a platinum agent and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic GEC who have not received prior treatment for metastatic disease.

5.2.2.2 Method of Procurement

Trastuzumab will be supplied in an open-label manner, by the sponsor.

5.2.2.3 Dose and Administration

Trastuzumab will be administered on Day 1 of every 21-day cycle. A loading dose of 8 mg/kg in a 90-minute IV infusion will be administered on Cycle 1 Day 1 followed by 6 mg/kg in a 30-minute IV infusion for each subsequent dose. However, if trastuzumab IV was administered within the 4 weeks prior to treatment initiation, trastuzumab 6 mg/kg IV should be administered on Cycle 1 Day 1. If the Day 1 dosing of trastuzumab is delayed by >1 week, the IV loading dose of 8 mg/kg should be given per approved dosing instructions. If dosing of trastuzumab is held for >6 weeks due to treatment-related AEs, medical monitor approval is required before restarting trastuzumab.

It is recommended to observe subjects from the start of the infusion for fever, chills and other infusion-related symptoms. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. All infusion-related symptoms must have resolved before the subject is discharged unless deemed clinically not significant by the investigator. See Section 5.3.2.2 for recommended treatment of IRRs and premedication for subsequent administrations.

5.2.2.4 Storage and Handling

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

5.2.2.5 Packaging and Labeling

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

5.2.2.6 Preparation

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

5.2.3 Fulvestrant

5.2.3.1 Description

Fulvestrant is an ER antagonist approved for use in treatment of HR+ mBC in postmenopausal women with disease progression following antiestrogen therapy.

Administration of fulvestrant will be required in subjects with HR+ HER2-mutant breast cancer.

5.2.3.2 Method of Procurement

Fulvestrant is commercially available. Details regarding its sourcing may vary by site and/or region as outlined in other documents such as Clinical Trial Agreements.

5.2.3.3 Dose and Administration

Fulvestrant will be administered once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15. The recommended dose is 500 mg to be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections; one in each buttock.

Because fulvestrant is administered intramuscularly, it should be used with caution in subjects with bleeding diatheses, thrombocytopenia, or anticoagulant use.

Injection site related events including sciatica, neuralgia, neuropathic pain, and peripheral neuropathy have been reported with fulvestrant injections. Caution should be taken while administering fulvestrant at the dorsogluteal injection site due to the proximity of the underlying sciatic nerve.

5.2.3.4 Storage and Handling

Consult the package insert for storage and handling.

5.2.3.5 Packaging and Labeling

Each syringe of fulvestrant will be labeled in compliance with applicable regulatory requirements.

5.2.3.6 Preparation

Fulvestrant should be prepared and administered per instructions in the fulvestrant package insert. Fulvestrant will be administered IM under the direction of the investigator.

5.3 Dose Modifications

Dose modification recommendations (including dose holds, dose reduction, or discontinuation of drugs) in response to AEs are described in Section 5.3.1 for tucatinib, Section 5.3.2 for trastuzumab, and Section 5.3.3 for fulvestrant. Dose reductions or treatment interruption/discontinuation for reasons other than those described in the following sections may be made at the discretion of 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 and trastuzumab. 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 trastuzumab. If trastuzumab is discontinued, protocol-defined visits will proceed using a 21-day cycle starting from the last trastuzumab Day 1, regardless of tucatinib 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 >6 weeks due to a treatment-related AE should be discontinued, unless a longer delay is approved by the study medical monitor. If one of the study drugs is discontinued, study treatment can continue with the remaining study drug.

5.3.1 Tucatinib Dose Modifications

Up to 3 dose reductions of tucatinib are allowed (Table 6). Subjects who would require a dose reduction to below 150 mg BID should discontinue treatment with tucatinib. Dose reductions of larger intervals than those described in Table 6 may be made at the discretion of the investigator, with approval by the medical monitor.

Table 6: Tucatinib: Recommended dose reduction schedule for AEs

Dose Reduction Schedule	Tucatinib 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 (ie, 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 may not be dose reduced below 150 mg BID.

General dose modification guidelines for tucatinib are provided in Table 7 and Table 8. For subjects with documented Gilbert's disease, contact the medical monitor for guidance regarding dose modifications for LFT abnormalities.

Table 7: Dose modifications for clinical AEs related to tucatinib

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.
Other adverse reactions	
Grade 3	Hold tucatinib until recovery to ≤ Grade 1 or baseline Reduce tucatinib dose
Grade 4	Permanently discontinue tucatinib.

Table 8: Dose modifications of tucatinib for LFT abnormalities, regardless of relationship to tucatinib*

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 elevation >3 × ULN AND bilirubin elevation >2 × ULN	Permanently discontinue tucatinib.

*If the LFT abnormalities are determined to be exclusively related to biliary obstruction, subjects may be allowed to continue on tucatinib following resolution of the obstruction and approval by the medical monitor.

5.3.2 Trastuzumab Dose Modifications

In the event of Grade ≥3 trastuzumab-related AEs, hold trastuzumab until the AE has resolved to Grade ≤1 or pretreatment levels. Resume trastuzumab at the same dose; the trastuzumab dose may not be reduced. If the Day 1 dosing of trastuzumab is delayed by >1 week, the IV loading dose of 8 mg/kg should be given per approved dosing instructions. If dosing of trastuzumab is held for >6 weeks due to a treatment-related AE, medical monitor approval is required before restarting trastuzumab.

Trastuzumab dose modification guidelines for left ventricular dysfunction and cardiomyopathy are presented in Section 5.3.2.1, for IRR in Section 5.3.2.2, and for hypersensitivity reactions in Section 5.3.2.3.

5.3.2.1 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 dose modification guidelines for left ventricular dysfunction, regardless of relationship to study drug, are provided in Table 9.

Table 9: Trastuzumab 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 49%	
<10% decrease from baseline	Resume treatment with trastuzumab
≥10% decrease from baseline	Discontinue trastuzumab
- LVEF <45%	Discontinue trastuzumab

5.3.2.2 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.

Decrease the rate of infusion for mild or moderate infusion reactions. Interrupt trastuzumab infusion in all subjects experiencing dyspnea or clinically significant hypotension, and administer supportive therapy (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, paracetamol, and oxygen). Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms. Subjects who experience infusion-related or injection-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions/injections.

Discontinue trastuzumab in subjects with severe or life-threatening IRRs.

5.3.2.3 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, ie, 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.

Any allergic/hypersensitivity reaction related to trastuzumab should be managed according to the product label and/or institutional standard of care.

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death (NCI CTCAE, version 5.0 and (Rosello 2017).

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

5.3.3 Fulvestrant Dose Modification

For subjects who develop moderate hepatic impairment (Child-Pugh class B) on study, a discussion with the medical monitor is required. If the subject is approved by the medical monitor to continue on study, a dose reduction to fulvestrant 250 mg is required.

5.4 Required Premedication and Postmedication

Subjects who experience infusion-related or injection-related symptoms may be premedicated with paracetamol and antihistamines for subsequent infusions/injections.

5.5 Concomitant Therapy

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

5.5.1 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 tucatinib and trastuzumab, whichever is later, or 8 weeks after the last dose of fulvestrant, if applicable, are to be recorded in the CRF.

- 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
- Supportive care medications such as antidiarrheals and antiemetics are permitted. Prophylactic use of anti-diarrheals are permitted at the discretion of the investigator. Prophylactic and symptomatic treatment of nausea and vomiting may be used per standard-of-care
- Thoracentesis or paracentesis may be performed, if needed for comfort
- If surgical intervention or localized radiation become indicated (either for palliation or down-staging of previously nonresectable tumor). These 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 indicated.
- Concomitant prednisone (or equivalent) may be used at a dose of ≤20 mg/day.
- Routine prophylaxis with vaccines is permitted

5.5.2 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 (fulvestrant is allowed for subjects with HR+ HER2-mutant breast cancer)
- 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 must be held 7 days prior to and 7 days after radiation therapy.

- Strong inducers of CYP3A4 are prohibited as concomitant medications during study treatment and within 1 week of discontinuation of tucatinib (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 (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.

5.6 Management of Treatment-Emergent Adverse Events

For management of IRRs, allergic/hypersensitivity reactions, and anaphylaxis, see Section 5.3.2.2 and Section 5.3.2.3.

5.6.1 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 (eg, exact amount of tucatinib administered, subject weight) and AEs, if any.

Any AE associated with an overdose of study drug should be recorded on the AE electronic Case Report Form (eCRF) with the diagnosis of the AE. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Refer to the package insert for overdose information for trastuzumab and fulvestrant.

5.7 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 and confirmed by pill counts. The pharmacist or designee will record the number of tucatinib tablets dispensed to each individual subject, and the number of tablets returned to the clinic at the end of each cycle.

Data regarding the administration and dose of trastuzumab will also be collected by the site after each cycle. Data regarding the administration and dose of fulvestrant will also be collected by the site. Dose modifications and interruptions of any study drug will be documented in the source documents and the CRF. Following implementation of Amendment 5 and entry of remaining on-treatment subjects into the LTEP, treatment administration data will no longer be collected in CRFs. Refer to Section 8.2 for further details on LTEP data collection requirements.

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 7.6.1.2). Any study protocol-related AE (defined in Section 7.6.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum or plasma chemistry panel and complete blood count [CBC] with differential), physical exam, weight, and performance status may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Tumor biopsies performed during the study should be made available to the Sponsor if feasible (see Section 7.4).

Subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study treatment during the LTEP. During this phase of the study, only pregnancies, SAEs, and AESIs will be collected by the Sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

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

6.2 Screening Period

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

If HER2 alterations have not been detected in pre-study assessments, subjects may consent to submit a blood sample for central assessment of HER2 alterations by NGS assay of ctDNA up to 3 months before the Screening visit (Pre-screening period). Subjects must be informed that HER2 testing consent is not informed consent for the study and participation in HER2 testing does not guarantee study eligibility.

- HER2 alterations testing consent
- Submission of sample for HER2 testing: Blood sample for NGS assay of HER2 amplification and mutations in ctDNA

6.2.2 Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Height
- Collection of archived tissue. If tumor blocks are not available, 20 freshly-cut slides may be submitted following approval by the medical monitor. The archival sample should be the most recent available

- Tumor lesion biopsy, if no archival tissue sample is available, a tumor lesion is available for biopsy, and the subject consents, once the subject has been approved for enrollment by the medical monitor
- Blood sample for hepatitis B and C serology
- 12-lead 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) (with oral and/or IV contrast), 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, but the same imaging modality as used at screening/baseline should be used throughout the study, unless otherwise clinically indicated. Subjects with breast or lung cancer will undergo contrast brain MRI.

6.2.3 Baseline Visit (Days –7 to Day 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 respiratory rate) and weight
- Physical exam
- ECOG performance status
- Blood samples for laboratory testing (as listed in Section 7.6.3):
  - CBC with differential
  - Serum or plasma chemistry panel

6.3 Tucatinib and Trastuzumab Treatment Period (21-day cycles)

6.3.1 Cycle 1 Day 1

- EQ-5D-5L questionnaire (Section 7.5.1; to be completed prior to evaluation by study personnel [physical examination, review of AEs] and administration of study treatment)
- Documentation of AEs
- Documentation of concomitant medications
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate) and weight *
- Physical exam *
- ECOG performance status *
- Blood samples for laboratory testing (as listed in Section 7.6.3; Results must be reviewed and eligibility confirmed prior to first dose):
  - CBC with differential *
  - Serum or plasma chemistry panel *

- Serum or urine β-hCG pregnancy test for subjects of childbearing potential (see Section 4.3); to be done within 24 hours predose for urine pregnancy tests or 72 hours for serum tests
- Blood sample (predose) for NGS assay of ctDNA, if the subject did not undergo pre-screening. However, the blood sample does not need to be drawn if a pre-study NGS assay of cDNA has previously been obtained by the sponsor since the end of prior therapy
- Dispense tucatinib and provide dosing diary to subject. Administer the first dose of tucatinib. (Subject will self-administer the remainder of doses during the treatment cycle and document in the diary)
- Administer trastuzumab 8 mg/kg IV loading dose, unless trastuzumab IV was administered within the previous 4 weeks, in which case administer trastuzumab 6 mg/kg IV

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

6.3.2 Cycles 1 and 2 Day 12 (-1 to +3 days)

- Blood samples for laboratory testing (as listed in Section 7.6.3):
  - CBC with differential *
  - Serum or plasma chemistry panel *
  - Documentation of AEs
  - Documentation of concomitant medications

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

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

- Day 1 of every second cycle from Cycle 2: EQ-5D-5L questionnaires (Section 7.5.1); to be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment
- Documentation of AEs
- Documentation of concomitant medications
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate) and weight *
- Physical exam *
- ECOG performance status *
- Blood for laboratory testing (as listed in Section 7.6.3):
  - CBC with differential *
  - Serum or plasma chemistry 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. Pregnancy testing will continue every 3 weeks for subjects of child-bearing potential during the LTEP.

- Cycles 2 to Cycle 6: Tucatinib predose PK samples (see Section 7.3)
- Cycle 3: Tucatinib PK sample 1 to 4 hours after the tucatinib dose
- Review subject diary and pill count for tucatinib drug compliance from previous cycle, dispense tucatinib, 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 trastuzumab 6 mg/kg IV

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

6.3.4 Every 6 Weeks as Determined by Cycle 1 Day 1, through Week 24, then Every 12 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 modality as used at screening/baseline should be used throughout the study. In subjects with lung cancer, scans of the pelvis do not need to be undertaken after the screening assessment unless lesions were detected at screening, or as clinically indicated. Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (eg, CR at Week 6, confirmatory scans at Weeks 10–12, next assessment due at Week 12). Tumor imaging should also be performed whenever disease progression is suspected.
- Subjects with known or suspected brain lesions should undergo contrast brain MRIs during treatment and follow-up according to the same assessment schedule as for other disease assessments.
- 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

6.3.5 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.

6.4 Fulvestrant Treatment Period (if applicable)

- For subjects with HR+ HER2-mutant breast cancer, administer fulvestrant 500 mg IM once every 4 weeks starting from Cycle 1 Day 1, as well as on Cycle 1 Day 15.

6.4.1 Cycle 1 Day 1

- Administer fulvestrant 500 mg IM.

6.4.2 Cycle1 Day 15 (±1 day)

- Administer fulvestrant 500 mg IM.

6.4.3 Every 4 weeks after Cycle 1 Day 1 (±3 days)

- Administer fulvestrant 500 mg IM.

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

- End of Treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs. For subjects who have received fulvestrant, the EOT visit should be undertaken no sooner than 8 weeks after the last dose of fulvestrant.
- EQ-5D-5L questionnaire (Section 7.5.1); to be completed prior to evaluation by study personnel (physical examination, review of AEs) and administration of study treatment
- Documentation of AEs
- Documentation of concomitant medications
- Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate) and weight
- Physical exam
- ECOG performance status
- Blood samples for laboratory testing (as listed in Section 7.6.3):
  - CBC with differential
  - Serum or plasma chemistry panel
- 12-lead 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 modality as used at screening/baseline should be used throughout the study, unless otherwise clinically indicated. Not required if imaging was performed within 30 days of discontinuing study treatment.

- Review subject diary and pill count for tucatinib 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 trastuzumab and, if applicable, for 2 years after the last dose of fulvestrant. 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). If a subject discontinues study treatment, every attempt should be made to follow the subject until death or administrative study closure.

6.6.1 Disease Progression Follow-up (Every 6 Weeks as Determined by Cycle 1 Day 1, through Week 24, then Every 12 Weeks [±7 days])

For subjects who discontinue study treatment prior to disease progression (per RECIST version 1.1), the following assessments must be undertaken at least every 6 weeks (±7 days) until 24 weeks from treatment initiation then every 12 weeks, until investigator-assessed disease progression (per RECIST version 1.1), death, withdrawal of consent, lost to follow-up, or study closure:

- 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 modality as used at screening/baseline should be used throughout the study, unless otherwise clinically indicated.

6.6.2 Survival Follow-up (Every 12 Weeks from EOT [±14 days])

Once subjects have discontinued study treatment, they will undergo long-term survival follow-up every 12 weeks (±14 days) from the EOT visit, 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.
- Echocardiogram/MUGA assessments should be undertaken every 6 months for at least 2 years following trastuzumab discontinuation.
- For persons of childbearing potential (for 7 months after the last dose of trastuzumab):
    - 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 trastuzumab

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

6.6.3 Long-term Extension Phase (LTEP)

As of Amendment 5, subjects still receiving clinical benefit and remaining on treatment may continue receiving study drug during the LTEP. During this phase of the study, only pregnancies, SAEs, and AESIs will be collected by the sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.

6.7 Subject End of Study/End of Follow-up

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

7 STUDY ASSESSMENTS

7.1 Screening/Baseline Assessments

Screening/Baseline assessments will be conducted to establish study baseline status and determine study eligibility. Only subjects who meet all inclusion and exclusion criteria specified in Section 4 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 6.2.2, and the Schedule of Events: physical exam, height, vital signs, weight, ECOG performance status, CT with contrast/PET-CT/MRI scan for baseline disease assessment, CBC with differential, serum or plasma chemistry panel, 12-lead ECG, echocardiogram or MUGA, hepatitis B and C screening, and serum or urine β-hCG pregnancy test (for females of childbearing potential).

Blood and tissue samples will be collected for biomarker assessments (see Table 10).

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) (Appendix C), as assessed by the investigator. Radiographic scans and additional imaging assessments (if applicable) will be performed at protocol-specified time points outlined in Section 6 and Schedule of Events. Clinical management decisions will be based on local investigator assessment. Images will be collected by an independent central review (ICR) facility for possible future analysis. Copies of tumor images must be made available for review by the sponsor (or its designee) upon request. All imaging will be submitted or uploaded to the ICR facility as soon as reasonably possible (eg, 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 ICR facility.

Disease assessments will be performed at screening/baseline, and every 6 weeks for the first 24 weeks then every 12 weeks, irrespective of dose holds or interruptions. Subjects that discontinue study treatment for reasons other than documented progressive disease or death, will continue to have disease assessments at least every 6 weeks until 24 weeks after treatment initiation then every 12 weeks, until the occurrence of documented disease progression per RECIST version 1.1, death, withdrawal of consent, lost to follow-up, or study closure.

Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. The schedule for response assessments should not be adjusted after the confirmatory scan (eg, CR at Week 6, confirmatory scans at Weeks 10–12, next assessment due at Week 12). Tumor imaging should also be performed whenever disease progression is suspected.

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 contrast is contraindicated (ie, 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 (if an MRI is not feasible, a non-contrast CT scan is acceptable). At the investigator's discretion, other appropriate imaging should be used to assess additional known sites of disease. The same imaging modality as used at screening/baseline should be used throughout the study, unless otherwise clinically indicated. In subjects with lung cancer, scans of the pelvis do not need to be undertaken after the screening assessment unless lesions were detected at screening, or as 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. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression of the lesion.

In subjects with breast or lung cancer, a contrast MRI scan of the brain should be performed at screening. Subjects with known or suspected brain lesions should undergo contrast brain MRIs during treatment and follow-up according to the same assessment schedule as for other disease assessments.

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 is documented or the investigator determines clinical progression has occurred. Demonstration of an unequivocal new lesion constitutes disease progression.

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. Refer to the Study Manual for instructions on collecting and submitting tumor imaging studies to the ICR.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

7.3 Pharmacokinetic Assessments

In all subjects, blood samples will be collected for assessment of trough tucatinib concentrations on Day 1 of Cycles 2 to 6 prior to administration of tucatinib. On Day 1 of Cycle 3, a blood sample will be collected 1 to 4 hours after administration of tucatinib for assessment of peak levels of tucatinib concentrations (Table 10).

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

or interruptions. Plasma concentrations of tucatinib will be determined using validated liquid chromatography (LC)-mass spectrometry (MS)/MS methods.

Table 10: Pharmacokinetic and biomarker sample collection timepoints

Visit	Study day	Time	Window	Relative Time	Blood Samples		FFPE Tumor Specimen
					PK	NGS assay of ctDNA	
Pre-screening	-3 months to -29 days	N/A	N/A	N/A		X	
Screening/ baseline	-28 to 1	N/A	N/A	N/A			X[a]
Cycle 1	Day 1	Predose	N/A	Time of administration of tucatinib		X[b]	
Cycle 2	Day 1	Predose	Within 2 hours	Time of administration of tucatinib	X		
Cycle 3	Day 1	Predose	Within 2 hours	Time of administration of tucatinib	X		
		Post-dose	Within 1-4 hours	Post-dose of tucatinib	X		
Cycles 4, 5, and 6	Day 1	Predose	Within 2 hours	Time of administration of tucatinib	X		
End of Treatment						X	

FFPE=formalin-fixed paraffin-embedded.

a Tumor tissue sample is to be collected once the subject has been approved for enrollment by the medical monitor. If archived tissue is not available, a new biopsy of a tumor lesion should be obtained, if there is a lesion available for biopsy and the subject consents. Subjects with no archival tissue, and whose tumors are considered not accessible or appropriate for biopsy are eligible for enrollment, following approval by the medical monitor.

b If not obtained during pre-screening, and if a pre-study NGS assay of ctDNA has not previously been performed by the sponsor since the end of prior therapy.

7.4 Biomarker Studies

See Table 10 for the schedule of biomarker assessments.

7.4.1 Evaluation of HER2 Status

Study eligibility requirements for HER2 overexpressing/amplified disease and HER2-mutated disease are to be met by assays performed pre-study (assessments undertaken prior to any study-related activities) or in pre-screening (Table 11), as follows:

- Previously established HER2 alterations: HER2 eligibility can be demonstrated via HER2 overexpression or amplification in an IHC/ISH assay of tumor tissue or HER2 amplification or activating mutations in an NGS assay of ctDNA or tumor tissue, processed locally in a CLIA- or ISO-accredited laboratory before enrollment in the study.
- Pre-screening for HER2 alterations: if HER2 alterations have not been detected in pre-study assessments, HER2 eligibility may alternatively be established during pre-screening, up to 3 months prior to the Screening visit, via an NGS assay of ctDNA evaluating the presence of HER2 amplification or mutations.

Additional biomarker analyses: For the evaluation of the exploratory biomarker objectives, all subjects will provide a blood sample for NGS assay of ctDNA and archival tumor tissue or a fresh tumor biopsy, if available. The blood sample will be collected during pre-screening or on Cycle 1 Day 1, if not collected during pre-screening. However, the blood sample does not need to be drawn if a pre-study NGS assay of ctDNA has previously been performed by the sponsor since the end of prior therapy. The tumor tissue sample will be collected during screening, once the subject has been approved for enrollment by the medical monitor.

If eligibility is determined by local testing, information concerning the local test, such as the test name, methodology/technology used, device description, specimen type used, will be collected in the eCRF. Other available characteristics should be retained and made available to the sponsor on request.

Table 11: Timing of prospective assays used to determine HER2 status for eligibility

HER2 assay	Visit		
	Pre-study	Pre-screening	Screening
NGS assay showing HER2 alterations in ctDNA	If done pre-study and test is positive	If not done pre-study	Not done
IHC/ISH assay showing HER2 overexpression in tissue	If done pre-study and test is positive	Not done	Not done
NGS assay showing HER2 alterations in tissue	If done pre-study and test is positive	Not done	Not done

Pre-study refers to all HER2 assessments undertaken prior to any study-related activities.

Testing of HER2 amplification and mutation in ctDNA will be done using a CLIA-certified liquid blood-based NGS assay. HER2 expression in tissue will be evaluated using IHC and FISH, according to either the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) 2018 guideline "HER2 Testing in Breast Cancer" or the ASCO/CAP 2016 guideline "HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma", using an FDA-approved test for breast cancer or GEC (Bartley 2017; Wolff 2018). Testing of HER2 amplification and mutation in tissue will be done using an FDA-approved tissue-based NGS assay for HER2 in breast cancer. The list of acceptable known activating mutations are detailed in the inclusion criteria (Section 4.1). As specified, subjects with exon 20 insertions in HER2 are eligible. Subjects with HER2 activating mutations not listed in the inclusion criteria may be eligible, if supported by scientific literature and approved by the medical monitor.

In all subjects, the most recent archival tumor block is to be collected during the screening visit, once the subject has been approved for enrollment by the medical monitor. If tumor blocks are not available, 20 freshly-cut slides may be submitted, following approval by the medical monitor (if 20 slides are not available, consultation with the medical monitor is required). If archival samples are not available, a fresh biopsy from a lesion that has not been previously irradiated should be undertaken, if the subject consents. Subjects are still eligible if archival or fresh tumor tissue samples cannot be obtained, following approval by the medical monitor. Additionally, tumor biopsies performed while the subject is on study should

be made available to the Sponsor if feasible. For example, if a biopsy on residual tumor is performed at the end of treatment or at progression, a sample will be collected (if available).

Tissue samples obtained via resection, excision, punch (skin lesions only), or core needle from a tumor site are suitable for testing. Fine needle aspiration, brushing, cell pellets from pleural effusion, forceps, and lavage samples are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content; eg, 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.

See the Central Laboratory Manual for more details.

7.4.2 Other Biomarker Assessments

Biomarker assessments will be performed in peripheral blood and tumor tissue as specified in this section and Table 10. The assessments will be used to determine the concordance of HER2 alterations as detected by tissue and blood-based HER2 testing methodologies. In addition, they are to be used to identify tumor-specific alterations that are associated with resistance to tucatinib. Assays may include NGS, IHC, and ISH. These assessments may provide insights into treatment-related changes associated with tucatinib.

7.4.3 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. 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.

7.5 Patient-Reported Outcomes

The EQ-5D-5L questionnaires will be administered according to the schedule specified in Schedule of Events and Section 6.3, until the EOT visit. The questionnaire will be administered to subjects in their local language, if available. The objective is to evaluate improvements, deteriorations, and stabilization in HRQoL by cohort. 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.

7.5.1 EQ-5D-5L – Utility Measurement

The 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 visual analog scale (VAS; APPENDIX G).

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.

7.6 Safety Assessments

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

Only pregnancies, SAEs, and AESIs will be collected by the Sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

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

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

- From the time of informed consent through the day prior to study 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 study Cycle 1 Day 1 that increase in NCI 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 NCI 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 7.6.1.2). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.

- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, 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 below for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, version 5. 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 drug (tucatinib and trastuzumab) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, 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 (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, 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

Overdose, Medication Error, Misuse, and Abuse

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

Medication error refers to an unintentional error in dispensing or administration of the study treatment not in accordance with the protocol.

Misuse is defined as any situation where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

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

Overdoses, medication errors, abuse, or misuse will be collected as part of study treatment dosing information and/or as a protocol violation, as required. Any AE associated with an overdose, medication error, misuse, or abuse of study drug should be recorded on the AE CRF with the diagnosis of the AE. Overdose per se will not be reported as an AE/SAE, unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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.

During the LTEP, pregnancies, SAEs, and AESIs will be reported to the sponsor using SAE/pregnancy report forms and will not be recorded within the CRF.

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.
- During the LTEP, SAEs will be reported to the Sponsor solely on the SAE form and will not be recorded within the CRF, following the same reporting guidelines as outlined in this section.

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 tucatinib and trastuzumab, whichever is later, or 2 years after the last dose of fulvestrant, if applicable, 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), or, if applicable, within 8 weeks of last dose of fulvestrant, will also be recorded on the Adverse Events CRF. Pregnancies that occur during the LTEP will be reported using the Pregnancy Report Form and will not be recorded within the 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 7.6.1.1) 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 (ie, elevated serum or plasma 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 an SAE and reported promptly to the Sponsor.

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

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum or plasma ALT or AST to >3 × ULN should be followed by repeat testing within 48 to 72 hours of serum or plasma 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.

7.6.1.2 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Cycle 1 Day 1 (predose) through 30 days after the last dose of tucatinib or trastuzumab, whichever is later, or 8 weeks after the last injection of fulvestrant, if applicable. 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.

7.6.1.3 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.

7.6.1.4 Adverse Events of Special Interest

An 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.

AESIs need to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 7.6.1.3).

During the LTEP, AESIs will be reported to the sponsor using an SAE form only and will not be recorded within the CRF.

AESIs for this study are:

- **Hepatotoxicity**: either of the following types of LFT 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 × ULN
  - Bilirubin elevations >10 × 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.

7.6.2 Vital Signs

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

7.6.3 Clinical Laboratory Tests

Samples will be drawn for local labs. Local laboratory testing will include the following institutional standard tests for evaluating safety and making clinical decisions:

- The chemistry panel is to include the following tests: ALT, AST, alkaline phosphatase, total bilirubin (and direct bilirubin when total bilirubin is > ULN), albumin, bicarbonate (if available), blood urea nitrogen, magnesium, phosphorus, calcium, chloride, glucose, potassium, sodium, total protein, creatinine
- The CBC with differential is to include the following tests: hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (lymphocytes, and neutrophils)
- The estimated GFR should be calculated using the MDRD equation as applicable, with serum or plasma creatinine reported in mg/dL.
  GFR (mL/min/1.73 m^2) = 175 x (Serum or plasma creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- In subjects with baseline GFR <50 mL/min/1.73 m^2, cystatin C will be evaluated at baseline and whenever serum or plasma creatinine is evaluated
- 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 polymerase chain reaction is required to confirm. If the hepatitis B core antibody is positive, and there is no evidence of long-term immunity, a hepatitis B virus DNA test by polymerase chain reaction is required to confirm.
- Serum or urine β-hCG pregnancy tests for subjects of childbearing potential

Following implementation of Amendment 5, local laboratory testing with the exception of pregnancy testing will be performed per institutional guidelines and investigator-determined usual and customary care. Pregnancy testing will continue every 3 weeks for subjects of child-bearing potential.

7.6.4 Physical Examination

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

7.6.5 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, at Cycle 1 Day 1 (within 24 hours predose for urine pregnancy tests or 72 hours for serum tests), within 7 days prior to Day 1 of each treatment cycle starting from Cycle 2, and at the EOT visit. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests will be performed once a month for 7 months after the last dose of any study drug, and for 2 years after the last dose of fulvestrant, if applicable. 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 IRB/IEC or if required by local regulations.

During the LTEP, pregnancy reporting should continue and will be collected by the Sponsor using the Pregnancy Report Form. See Section 7.6.1.1 for further details on pregnancy reporting requirements.

7.6.6 Cardiac Function

7.6.6.1 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 echocardiogram or MUGA should be performed every 12 weeks as determined by the date of the most recent interim assessment. Echocardiogram/MUGA assessments should also be undertaken every 6 months for at least 2 years following trastuzumab discontinuation. The modality chosen in screening should be used for all subsequent cardiac assessments throughout the study for comparison. During the LTEP, cardiac function assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

7.6.6.2 Electrocardiogram

ECGs (12-lead) will be performed at baseline and at the EOT visit. To correct for heart rate, corrected QT intervals (QTc) should be calculated using the Fridericia formula.

During the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

7.7 Appropriateness of Measurements

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

Response will be assessed according to RECIST version 1.1 (Eisenhauer 2009), which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

The EQ-5D-5L is a validated instrument for use as a measure of HRQoL (Janssen 2013). This PRO has 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 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.

Following implementation of Amendment 5 and entry of remaining on-treatment subjects into the LTEP, data will no longer be collected in CRFs. Only pregnancies, SAEs, and AESIs will be collected by the Sponsor during the LTEP, utilizing the Pregnancy Report Form and SAE form (for both SAEs and AESIs). See Section 7.6.1.1 for further details on pregnancy, SAE, and AESI reporting requirements.

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.
- During the LTEP, CRFs will not be collected.

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 and/or electronic patient diaries (eDiary) 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

For cohorts that will have interim futility analysis (Cohorts 1 to 5 and 7), up to 12 response-evaluable subjects will be enrolled in Stage 1. Cohorts that successfully pass the interim analysis for futility (see Section 9.3.11) may, at the sponsor's decision, continue to enroll up to an additional 18 response-evaluable subjects, totaling up to 30 response-evaluable subjects for each tumor cohort.

Cohorts 6, 8, and 9 will each enroll 30 response-evaluable subjects without an interim analysis.

Approximately 162 to 270 subjects may be enrolled in the study. This is comprised of up to approximately 12 to 30 subjects in each of Cohorts 1 to 5 and Cohort 7, and up to approximately 30 subjects in each of Cohorts 6, 8, and 9. Additional subjects may be enrolled if optional cohorts are opened.

If a sufficient number of subjects with a particular tumor type are enrolled in Cohorts 6 or 9, the sponsor may evaluate that tumor type in a separate cohort, drawn from optional Cohorts 10 to 15. If any optional cohort is opened, all subjects enrolled in Cohorts 6 or 9 with the applicable tumor type will be reassigned to the new tumor-specific cohort and will not count towards the sample size of Cohorts 6 and 9.

For a sample size of 30 subjects, assuming confirmed ORR is between 10% and 30%, the 2-sided 90% exact CIs are summarized below:

Confirmed ORR	90% Exact CI (N=30)
10%	(3%, 24%)
20%	(9%, 36%)
30%	(17%, 47%)

9.2 Study Endpoint Definitions

9.2.1 Objective Response Rate

ORR is defined as the proportion of subjects with best overall response of confirmed CR or confirmed PR per investigator assessment according to RECIST version 1.1. Only response assessments before first documented disease progression or new anticancer therapies will be considered. ORR per ICR may be evaluated in selected cohorts.

9.2.2 Duration of Response

DOR is defined as the time from first documentation of objective response of confirmed CR or confirmed PR to the first documentation of disease progression per RECIST version 1.1 or death from any cause, whichever occurs first. Only subjects with an objective response will be included in the analysis of DOR. DOR per ICR may be evaluated in selected cohorts.

9.2.3 Disease Control Rate

DCR is defined as the proportion of subjects with confirmed CR, confirmed PR, or stable disease (SD or non-CR/non-progressive disease) according to RECIST version 1.1. DCR per ICR may be evaluated in selected cohorts.

9.2.4 Progression-free Survival

PFS is defined as the time from the date of treatment initiation 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. PFS per ICR may be evaluated in selected cohorts.

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

9.2.5 Overall Survival

OS is defined as the time from treatment initiation 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 (ie, the date of last contact). Subjects lacking data beyond the day of treatment initiation will have their survival time censored on the date of treatment initiation (ie, OS duration of 1 day).

9.2.6 Pharmacokinetic Analysis

PK parameters will be calculated using non-compartmental analysis for tucatinib.

9.2.7 Exploratory Endpoints

9.2.7.1 Biomarker Analysis

Relationships of biomarkers to antitumor activity may be evaluated.

9.2.7.2 Patient-Reported Outcomes

Changes in HRQoL will be measured based on PROs according to the EQ-5D-5L.

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 (eg, adding baseline assessments to define a subgroup). The SAP will be finalized prior to the first interim analysis. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.3.1 General Considerations

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, by cohort.

Unless otherwise specified, CIs will be calculated at 2-sided 90% level.

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

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

9.3.1.1 Randomization and Blinding

Blinding will not be performed.

9.3.1.2 Adjustments for Covariates

There will be no adjustment for covariates.

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.

9.3.1.6 Data Transformations and Derivations

Time variables based on 2 dates (eg, 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 analysis plan.

9.3.1.7 Analysis Sets

The Safety Analysis set includes all subjects who receive any amount of study drug.

The Response-Evaluable analysis set includes all subjects with measurable disease who meet the following 3 criteria: (1) had a baseline disease assessment with measurable disease (ie, at least one target lesion at baseline), (2) received study treatment, and (3) had post-baseline disease assessment or discontinued treatment due to documented disease progression or clinical progression.

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

9.3.1.8 Examination of Subgroups

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

9.3.1.9 Timing of Analyses

Interim efficacy and safety analyses will be undertaken in Cohorts 1 to 5 and 7 when the first 12 response-evaluable subjects in each cohort have been followed for at least 12 weeks or have documented disease progression.

Final efficacy analyses will be undertaken separately for each cohort when 30 response-evaluable subjects in each cohort have been followed for at least 12 weeks or have documented disease progression.

Supplementary analyses may be undertaken after the final analysis to evaluate PFS and OS.

9.3.2 Subject Disposition

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

9.3.3 Subject Characteristics

The following baseline characteristics will be summarized by treatment group:

- Subject demographics
- Disease history
- Prior disease-related therapies
- 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 study drug. 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

Confirmed ORR, DOR, and DCR per RECIST version 1.1 per investigator assessment will be evaluated by cohort in response-evaluable subjects. In addition, the same disease type from different cohorts might be combined for efficacy analysis. The point estimate of confirmed ORR, and DCR and their corresponding 90% 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 90% CIs will be calculated by treatment group, as appropriate. Detailed methodology will be provided in the SAP.

Sensitivity efficacy analyses may be conducted per ICR if deemed necessary.

9.3.7 Pharmacokinetic Analyses

Individual (subject) plasma concentrations at each sampling time will be listed for tucatinib; corresponding summary statistics at each sampling time will also be calculated.

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

Details will be described separately in the SAP.

9.3.8 Biomarker Analyses

Relationships of biomarkers to antitumor activity and associated data that are determined to be of interest may be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.9 Patient Reported Outcomes Analyses

Descriptive summaries of observed data will be provided at each scheduled assessment timepoint. Time to deterioration in HRQoL will be assessed utilizing the EQ-5D-5L VAS

item and defined as a change of ≥7 points. Further investigation of missing patterns and details of imputation may be provided in the SAP.

9.3.10 Safety Analyses

Safety analysis will be conducted in the safety analysis set, separately for each cohort.

9.3.10.1 Extent of Exposure

Duration of treatment will be summarized and listed.

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by cohort. Dose modifications will also be summarized. Details will be provided in the SAP.

9.3.10.2 Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. Adverse events 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 cohort, stage, study site, subject number, and cycle. All serious AEs and AESIs (see Section 7.6.1.4) will be analogously listed, separately.

9.3.10.3 Deaths and Serious Adverse Events

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

9.3.10.4 Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by scheduled visit. Laboratory values will be listed with grade per NCI CTCAE version 5.0 and flagged when values are outside the normal reference range.

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

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

9.3.10.5 Other Safety Analyses

Vital Signs

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

ECOG Status

ECOG shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled 12-lead ECG, and shifts from baseline may be tabulated.

LVEF

The minimal post baseline ejection fraction and the maximum decrease from baseline will be summarized for each cohort.

9.3.11 Interim Analyses

Interim futility analyses will be performed separately for Cohorts 1 to 5 and 7 after approximately 12 subjects of a given cohort (Stage 1) have been treated and had at least two response assessments post-baseline or had disease progression.

The Bayesian predictive probability approach will be used to determine the futility criteria. At the time of each interim analysis, the predictive probability of success (PPoS) will be calculated (Lee 2008). PPoS is the probability of achieving "success" should the cohort be continued to the maximum sample size of 30, given the data observed at the interim analysis. A cohort is considered a "success" if the posterior probability is >80% that the ORR exceeds the response rate of current standard of care, which is 10% for biliary tract and urothelial cancer, and 15% for cervical, uterine and non-small cell lung cancer (Bregar 2014; Garon 2014; Lamarca 2014; Raggi 2016; Borcoman 2017). If at least 2 responders are observed in 12 subjects at the interim analysis in any cohort, then the PPoS for that cohort will be greater than 20%. A PPoS <20% indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the study given the interim result. Based on activity and safety data, together with the PPoS, a cohort may be stopped early by the sponsor.

Cohorts that successfully pass the interim analysis for futility may, at the sponsor's decision, continue to enroll up to an additional 18 response-evaluable subjects, totaling up to 30 response-evaluable subjects for each tumor cohort. A cohort may be expanded to Stage 2 earlier if the futility rule is cleared before 12 subjects, ie, if the minimal required responses are observed in fewer than 12 subjects.

Interim data from the study may be presented at scientific meetings such as the annual meetings of ASCO and the European Society of Medical Oncology.

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. For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations.

10.1 Informed Consent

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

10.2 Ethical Review

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

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

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

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

- The IRB/IEC periodic (eg, 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.

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 Data Protection

For clinical sites covered by the General Data Protection Regulation (GDPR), personal data in this study will be protected in accordance with the General Data Protection Regulation (EU) 2016/679 (GDPR) including those which govern the transfer of data and the management of any potential personal data breaches. The sponsor will ensure equivalent guarantees regarding personal data protection standards before transferring the encoded data to non-EU countries by the use of standard contractual clauses which are included in data protection agreements.

For all other clinical sites, in the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notification as required by law.

10.6 Clinical Trial Agreement

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

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APPENDIX A: PERFORMANCE STATUS SCALES CONVERSION

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

APPENDIX B: 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, and, if applicable, at least 2 years after the final dose of fulvestrant; see Section 4.1).

Acceptable methods for highly effective birth control (preventing conception)

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

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant or breastfeeding person must use a male condom (even if the subject has had a vasectomy). In addition, it is recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in the section titled "Acceptable combinations of contraceptive methods".

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 C: RESPONSE EVALUATION CRITERIA FOR SOLID TUMORS V1.1

Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009)	
Term	Definition
Complete response (CR)	• Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm • Cannot have previously met criteria for progressive disease • Confirmation required only for non-randomised studies
Partial response (PR)	• A ≥30% decrease in the sum of diameters of target lesions (longest for non-nodal target lesions and the short axes for nodal target lesions), taking as reference the baseline sum diameters • Cannot have previously met criteria for progressive disease • Confirmation required only for non-randomised studies
Stable disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study • Cannot have previously met criteria for progressive disease • Confirmation is not required
Progressive disease (PD)	• A ≥20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase ≥5 mm • The appearance of 1 or more new lesions is also considered progression • Confirmation is not required unless equivocal.
New measurable or non-measurable lesions	• Always represent progressive disease
Non-target lesions	• Changes contribute to defining CR, PR, SD, and PD

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

AUC=area under the concentration-time curve.

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 : EQ-5D-5L

Health Questionnaire

English version for the UK

CCI

[redacted]

CCI

[redacted]

APPENDIX H: INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled

A Phase 2 Basket Study of Tucatinib in Combination with Trastuzumab in Subjects with Previously Treated, Locally-Advanced Unresectable or Metastatic Solid Tumors Driven by HER2 Alterations

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 I: DOCUMENT HISTORY

Version	Date
Original	08-Sep-2020
Amendment A01	27-Oct-2020
Amendment A02	03-Nov-2020
Amendment A03	16-Aug-2021
Amendment A04	02-Dec-2022
Amendment A05	24-Apr-2024

SUMMARY OF CHANGES IN AMENDMENT 1

Amendment A01

Section(s)	Change	Rationale
Title page	Added EudraCT number.	The study will be conducted in the EU.
Synopsis	In the pharmacokinetics (PK) section, changed "Day 1 of Cycles 3 to 6" to "Day 1 of Cycles 2 to 6".	Consistency with the PK schedule.
Sections 6.6.1, 6.6.2, 7.6.6.1, Schedule of Events	Specified that echocardiogram/ multigated acquisition scan (MUGA) assessments of left ventricular ejection fraction (LVEF) should be performed every 6 months for at least 2 years after the discontinuation of trastuzumab.	Conformity with Herceptin (trastuzumab) EU product information.
Section 4.1, Synopsis	It was specified that subjects with cervical cancer are not subject to the provisions in inclusion criterion #2 regarding required prior therapy.	A specific inclusion criterion (#6) has been created for pretreatment of subjects with cervical cancer and per health authority request.
Section 4.1, Synopsis	Inclusion criterion #3 was modified to specify that subjects with metastatic hormone receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2)-mutated disease must have received a prior CDK4/6 inhibitor in the metastatic setting	In order to ensure that subjects with HR+ breast cancer have received standard prior therapy and per health authority request.
Section 4.1, Synopsis	Inclusion criteria #3b and #4 were modified to say that subjects must have progressed on or after ≥1 prior line of treatment, rather than have completed.	To ensure that subjects have failed prior therapy.
Section 4.1, Synopsis	Inclusion criterion #6 was added to specify required prior therapy for subjects with metastatic or with locally-advanced unresectable cervical cancer.	In order to ensure that subjects with cervical cancer have received standard prior therapy and per health authority request.
Section 4.1, Synopsis	The last bullet of inclusion criterion #7b (formerly #6b in the A00 version) was modified to specify that HER2 mutations which are not listed in criterion #7b will require support by the scientific literature to serve as evidence of the presence of HER2 activating mutations.	In order to implement a more rigorous selection process for mutations that are not listed in criterion #7b and per health authority request.
Section 4.2, Synopsis	Exclusion criterion #4 was modified to specify that an unacceptable prior cumulative anthracycline dose is >360 mg/m² doxorubicin-equivalent, and to also specify a limit in terms of cumulative epirubicin-equivalent dose.	Clarification of text concerning the change to ">360". The limit for epirubicin-equivalent dose was added in order to provide more guidance concerning patients who have received other anthracyclines.
Section 4.2, Synopsis	Removed "based on criteria described under central nervous system (CNS) inclusion criteria b" from exclusion criterion #17c.	Correction, as there is no inclusion criterion b referring to CNS disease.
Section 5.2.2.1	Updated the indications for which trastuzumab is approved.	To include indications cited in SmPC.

Amendment A01

Section(s)	Change	Rationale
Section 5.2.2.3	Specified infusion durations for trastuzumab and added instructions for surveillance of IRRs during trastuzumab infusions.	Conformity with EU product information.
Section 5.3.2.1	Revised trastuzumab dose modification criteria in the event of LVEF dysfunction.	New dose modification guideline for LVEF dysfunction to accommodate decreases of LVEF between 45-50%
Sections 5.3.2.2, 5.4	Revised treatment of infusion-related reactions (IRRs) to include paracetamol, and changed premedication in the event of IRRs to be paracetamol and antihistamines.	Conformity with EU product information.
Section 7.4.1	Specified that information concerning local tests used for eligibility, such as the test name, methodology/technology used, device description, specimen type used, are to be collected in electronic Case Report Form (eCRF), and that other information on the test is to be made available to the sponsor on request.	In order to ensure that pertinent information regarding subject eligibility is collected.
Section 7.6.1.2	Changed “Adverse Events and Pre-Existing Conditions CRF” to “Adverse Events CRF”.	Consistency with other mentions of this Case Report Form (CRF) page.
Throughout the document	Changed the sponsor name, Seattle Genetics, Inc., to Seagen Inc.	Company name change.

SUMMARY OF CHANGES IN AMENDMENT 2

Section(s)	Change	Rationale
Sections 6.2.2, 6.3.1, 7.3, 7.4.1, Synopsis, Schedule of Events	Moved the NGS assay of ctDNA from the Screening visit to predose on Cycle 1 Day 1.	To ensure that this NGS assay is only done in eligible subjects.
Sections 6.2.2, 6.3.1, 7.4.1, Synopsis, Schedule of Events	Clarified the conditions under which a blood sample for the NGS assay does not have to be obtained on Cycle 1 Day 1.	Clarification.
Section 7.3 Table 10	Added line for pre-screening biomarker samples.	Correction.

SUMMARY OF CHANGES IN AMENDMENT 3

Amendment A03

Section(s)	Change	Rationale
Section 2, Synopsis	Moved the objective to evaluate the PK of tucatinib from exploratory to secondary.	Reevaluation of the importance of the assessment of PK in this study.
Section 2, Synopsis	Modified the exploratory biomarker objective to be: "To determine the concordance of HER2 alterations as detected by tissue and blood-based HER2 testing methodologies". Modified the corresponding endpoint to be: "Concordance of HER2 alterations as detected by different testing methodologies".	Clarification of planned biomarker assessments.
Section 2, Synopsis	Added an exploratory biomarker objective to identify tumor-specific alterations that are associated with resistance to tucatinib and corresponding objective.	Clarification of planned biomarker assessments.
Section 3.1, Synopsis	Removed "(gallbladder cancer and cholangiocarcinoma)" from the line concerning biliary tract cancer.	Consistency.
Sections 3.1, 6.1, 6.2.3, 6.5, 7.1, 7.6.3, Schedule of Events	Removed the assessments of coagulation function.	The study regimen has been determined not to affect coagulation.
Sections 3.1, 4.4.1, 6.6.2, Schedule of Events	Specified that the Survival Follow-up visits are to be undertaken following EOT, rather than following disease progression.	To ensure that information on survival and further anticancer therapies is collected from the time of treatment discontinuation.
Sections 3.1, 4.1, Synopsis	Replaced inclusion criteria #2 to #6 with a single inclusion criterion #2 pertaining to prior therapy. The following changes were made, with respect to inclusion criteria #2 to #6: • For disease types other than breast cancer, biliary tract cancer, non-squamous NSCLC, and cervical cancer changed from "Disease progression on or after the most recent systemic therapy " to "progressed during or after ≥1 prior line of systemic therapy" • Created a single criteria #2.b covering all disease types except non-squamous NSCLC • Removed specifications of types of systemic therapy applicable from criteria #3.b and #4	To simplify and harmonize the specification of prior therapy requirements.
Section 4.1, Synopsis	Modified inclusion criterion #2.a (formerly #5) concerning subjects with non-squamous NSCLC: to require that subjects must have progressed on or after standard treatment rather than relapsed from or be refractory to standard treatment.	Clarification.

Amendment A03

Section(s)	Change	Rationale
Sections 3.1, 4.1, Synopsis	Added new inclusion criterion #3: Progression during or after, or intolerance of, the most recent line of systemic therapy.	To ensure that all subjects had failed the last line of prior therapy.
Sections 4.1, 7.4.1, Synopsis	Inclusion criterion #4.b (formerly #7.b): Specified that subjects with HER2 exon 20 insertion mutations are eligible.	To extend the range of HER2 activating mutations that can support enrollment.
Section 4.1, Synopsis	Modified inclusion criterion #9.b (formerly #12.b) to allow subjects with known history of Gilbert's syndrome to have direct bilirubin ≤1.5 × ULN rather than normal, if AST, and ALT are eligible.	In subjects with Gilbert's syndrome, direct bilirubin direct bilirubin ≤1.5 × ULN provides sufficient assurance of adequate hepatic function.
Section 4.1, Synopsis	Removed former inclusion criterion #15, concerning limits on coagulation parameters.	The study regimen has been determined not to affect coagulation.
Section 4.2, Synopsis	Exclusion criterion #1: replaced "GEC" with "gastric or gastroesophageal junction adenocarcinoma"	Clarification
Sections 3.1, 4.2, Synopsis	Exclusion criterion #2 regarding the exclusion of subjects who have received prior HER2-directed therapy: added that subjects with HER2-mutated gastric or gastroesophageal junction adenocarcinoma without HER2-overexpression/amplification are allowed to have received prior trastuzumab.	It is anticipated that subjects with HER2-negative, HER2-mutated GEC may benefit from the study regimen despite prior administration of trastuzumab.
Section 4.2, Synopsis	Added "major surgery" to exclusion criterion #5 regarding limitations on prior treatment modalities within 3 weeks of treatment initiation.	To ensure that recent major surgery does not impact the safety of study subjects.
Sections 5.2.2.3, 5.3, 5.3.2	Specified that subjects are to discontinue trastuzumab in the event of treatment delay >6 weeks due to a treatment-related AE, rather than for any delay >3 weeks.	To allow subjects who may potentially benefit from study treatment to resume treatment despite a prolonged delay, if the nature of and severity of the adverse event (AE) allow for re-initiation.
Section 5.3.2.1	Added trastuzumab dose modification guidelines for symptomatic CHF.	Conformity with product label.
Section 5.3.2.2	Modified the criteria for discontinuation of trastuzumab in the event of IRRs from "Grade 3 to 4" to "severe or life-threatening".	Conformity with product label.
Section 5.5.1	Added specification that supportive care medications such as antidiarrheals and antiemetics are permitted and removed requirement to consult the medical monitor prior to performing thoracentesis or paracentesis.	To allow symptomatic treatment with antidiarrheals and antiemetics.
Sections 5.5.1, 5.5.2	Removed the prohibition on live vaccines.	Live vaccines are not considered to pose a threat when administered during study treatment.

Amendment A03

Section(s)	Change	Rationale
Section 5.6.1	Revised the specific that overdose should be reported as an AE on the eCRF, to state that AEs associated with overdose should be reported. Revied the specification that overdose should be reported according to the procedures used for SAEs, to say it should not be reported as an AE/SAE, unless it is an intentional overdose taken with possible suicidal/self-harming intent	Revision to Seagen reporting procedures.
Sections 6.1, 6.2.3, 7.1, 7.6.3, Schedule of Events	Removed urinalysis.	Renal toxicity has not been observed with the study regimen.
Sections 6.2.1, 6.2.2, 7.1, 7.3, 7.4.1, Synopsis, Schedule of Events	Removed collection of tumor tissue samples during pre-screening.	Given the timeframe within which tissue samples must be assayed for HER2 alterations once they have been collected, the assays would often have to be done prior to patient enrollment, leading to a significant number of assays done in patients who are not eventually enrolled.
Sections 6.2.2, 7.3, 7.4.1, Synopsis, Schedule of Events	Specified that tumor tissue samples are to be collected once the subject has been approved for enrollment by the medical monitor.	To avoid assay of tissue in subjects who are screen failures.
Sections 6.3.1, 6.3.3, 7.6.1.1, 7.6.5, Schedule of Events	Changed the window for pregnancy tests on Cycle 1 Day 1 from within 7 days predose to 24 hours predose for urine pregnancy tests or 72 hours for serum tests.	To ensure a shorter window for pregnancy assessment prior to first administration.
Section 6.3.2, Schedule of Events	Changed the Cycle 1 Day 8 and 15 visits to Cycles 1 and 2 Day 12, changed the window of the visit from ±1 day to -1 to +3 days, and added documentation of AEs and concomitant medications.	To ensure that mid-cycle laboratory function is evaluated in first 2 cycles.
Sections 6.3.4, 7.2, Synopsis, Schedule of Events	Specified that in subjects with lung cancer, scans of the pelvis do not need to be undertaken after the screening assessment unless lesions were detected at screening, or as clinically indicated.	Lesions involving the pelvis are uncommon in subjects with lung cancer.
Section 6.6.1, Schedule of Events	Removed echocardiogram/MUGA-scan and pregnancy test assessments from the Progression Follow-up visits.	Survival Follow-up visits now begin at EOT rather than after disease progression and these assessments are already undertaken in the survival follow-up.
Section 7.2, Synopsis, Schedule of Events	Added specification that in subjects for who contrast is contraindicated, can have a CT-scan of abdomen and pelvis if an MRI is not feasible.	To allow for non-feasibility of MRI scans in this situation.
Section 7.4.1, Synopsis	Specified the nature of assessments undertaken for exploratory biomarker objectives.	Clarification of planned biomarker assessments.

Amendment A03

Section(s)	Change	Rationale
Sections 6.2.2, 7.4.1	Concerning the supply of an archival tumor tissue sample, specified that medical monitor approval, not consultation, is required to supply slides rather than blocks and added that at least 20 freshly-cut slides would be required.	To control the use of slides in the place of blocks
Section 7.4.2	Changed blood draw for biomarker from screening to Cycle 1 Day 1.	Consistency.
Section 7.4.2, Synopsis	Revised the description of additional biomarker assessments to be undertaken.	Clarification of planned biomarker assessments.
Section 7.6.1.1	Added a section with definitions of overdose, medication error, misuse, and abuse to section on AE definitions, moving an existing section on dosing errors to the new section.	Revision to Seagen reporting procedures.
Section 7.6.1.4	Changed one part of the criteria for a hepatotoxicity AESI from Grade 4 AST, ALT, or bilirubin elevation to AST or ALT elevation >20 × ULN or bilirubin elevation >10 x ULN.	Consistency with formulation of other hepatotoxicity AESI criterion.
Section 7.6.3, Schedule of Events	Indicated that in laboratory tests bicarbonate should be evaluated only if the test is available in the laboratory.	To allow for site laboratories that do not evaluate bicarbonate.
Section 7.6.3, Schedule of Events	Removed lactase dehydrogenase from the chemistry panel laboratory assessments.	This test is not expected to be useful for the evaluation of subject safety.
Section 9.2.7.1	Removed the specification “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” and specified that relationships of biomarkers to antitumor activity may be evaluated.	Revised analysis plan.
Section 9.3.8	Revised biomarker analysis methods to remove specification that relationships of biomarker parameters with safety and PK parameters will be evaluated.	Revised analysis plan.
Appendix B	Modified the methods for preventing secondary exposure to seminal fluid to specify that they apply even if the subject has had a vasectomy and recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in the appendix.	To ensure that appropriate barrier methods are used to avoid secondary exposure.
Throughout the protocol	Administrative changes.	

SUMMARY OF CHANGES IN AMENDMENT 4

Amendment A04

Section(s)	Change	Rationale
Synopsis and Title Page	Changed version A03 to A04 and changed date from 16-Aug-2021 to 02-Dec-2022	Administrative change to update version.
Schedule of Events footnote text & Section 7.6.3	Added language related to hepatitis B screening	Clarification on follow-up testing required to assess hepatitis B status
Schedule of Events table	Updated schedule of events table to align with section 6.3.3, visit window for Cycles >1, Predose day 1 is now -1, +3	Updated to align with Section 6.3.3.
Section 3.2.4	Updated regions where tucatinib is currently approved	Updated to align with most recent approvals
Section 5.2.1.2	Deleted "On the day of dosing, the individual unit dose of the tucatinib tablet may be exposed to ambient temperature for up to 6 hours prior to dose."	Removed for consistency with tucatinib pharmacy instructions
Section 5.3.1	Added footnote to Table 8 liver function test abnormality table to clarify dose modification requirements.	In subjects where biliary obstruction was clearly the cause of the LFT abnormality, those subjects may potentially continue on treatment once the obstruction and LFT abnormalities resolve and with medical monitor approval as this etiology is not related to tucatinib treatment.
Section 6.3.1	Updated language to include that blood samples for laboratory testing must be reviewed and eligibility must be confirmed prior to first dose.	To clarify that subject eligibility should be confirmed prior to first dose.
Section 9.3.1.7	Added language to describe response-evaluable analysis set	To clarify the definition of response-evaluable dataset, as only subjects with measurable disease can have a response per RECIST v1.1.

SUMMARY OF CHANGES IN AMENDMENT 5

Section(s)	Change	Rationale	Substantial (Yes/No)
Cover page	Indicated that Seagen Inc. has been acquired by Pfizer Inc.	Seagen is part of Pfizer as of 14 Dec 2023	No
Throughout	Added an LTEP for subjects who are still receiving treatment.	All study objectives have been met. LTEP being added to allow subjects still receiving clinical benefit to remain on study treatment.	No
Synopsis, HER2 Testing for Eligibility and Biomarker Assessments	• Added: "Pre-screening for HER2 alterations: if HER2 alterations have not been detected in pre-study assessments, HER2 eligibility may alternatively be established during pre-screening, up to 3 months prior to the Screening visit, via an NGS assay of ctDNA evaluating the presence of HER2 amplification or mutations."	Bullet point restored to align with Section 7.4.1	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Synopsis, Study Design, Section 3.1 Summary of Study Design	Added that subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue to receive study drug during the LTEP.	To allow subjects who are still receiving clinical benefit to remain on treatment.	No
Synopsis, Efficacy Assessments Section 9.3.1.7 Analysis Sets	Defined measurable disease as at least one target lesion at baseline	Clarification to align with SAP.	No
Synopsis, Duration of Treatment, Section 6.1 Schedule of Events	Added: "Subjects still receiving clinical benefit and remaining on study treatment as of Amendment 5 may continue receiving study drug during the LTEP. During this phase of the study, only pregnancies, SAEs, and AESIs will be collected by the Sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care."	LTEP added to allow subjects still receiving clinical benefit to remain on study treatment and clarification of data collection during the LTEP.	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Synopsis, Efficacy Assessments and Section 7.2 Response/Efficacy Assessments	Added: "During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care."	To clarify collection of efficacy assessments during the LTEP.	No
Synopsis, Safety Assessments, Section 7.6 Safety Assessments	Clarified that only pregnancies, SAEs, and AESIs will be collected by the Sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.	Clarification of data collection during LTEP.	No
Schedule of Events	Added LTEP	Column added to indicate assessments to be done during the LTEP.	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Section 3.1.3 End of Study	Added: "As of Amendment 5, all subjects still on study who are not entering the LTEP will have a last visit/contact. The study will end when the last LTEP subject has had their last visit/contact. The sponsor will provide continued access to study treatment for any subject who is still on treatment receiving clinical benefit based on the investigator's assessment."	Defined end of study for subjects entering LTEP.	No
Section 4.4 Removal of Subjects From Therapy or Assessment	Added that for subjects continuing to LTEP, data will only be documented in the subject's medical record.	Clarification of data collection during LTEP.	No
Section 5.7 Treatment Compliance	Added that treatment administration data will no longer be collected during the LTEP.	Clarification of data collection during LTEP.	No
Section 6.3.3 Cycles >1 Day 1 (-1 to +3 days)	Added that pregnancy testing will continue every 3 weeks for subjects of child-bearing potential during the LTEP	To clarify that pregnancy testing per protocol specified frequency will continue during the LTEP.	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Section 6.6.3 Long-term Extension Phase (LTEP)	Added long-term extension phase for subjects still receiving clinical benefit and remaining on treatment. During this phase of the study, only pregnancies, SAEs, and AESIs will be collected by the sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.	Clarification of safety data collection during LTEP.	No
Section 7.6.1 Adverse Events	Identified that SAEs should be reported to the Sponsor solely on the SAE form.	Clarification of data collection during LTEP.	No
Section 7.6.1.1 Definitions/Procedures for Eliciting and Recording Adverse Events/Recording Serious Adverse Events/Pregnancy	Clarified that during the LTEP, pregnancies, SAEs, and AESIs will be reported to the Sponsor on the SAE/pregnancy forms and will not be recorded within the CRF.	Guidance on steps to follow when recording safety data during the LTEP.	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Section 7.6.1.4 Adverse Events of Special Interest	Clarified that during the LTEP, AESIs will be reported to the sponsor using an SAE form only and will not be recorded within the CRF.	Clarification of data collection during LTEP.	No
Section 7.6.3 Clinical Laboratory Tests	Clarified that local laboratory testing will be performed per institutional guidelines and investigator-determined usual and customary care.	Consistency with updates made in the document.	No
Section 7.6.5 Pregnancy Testing	Clarified that during the LTEP, pregnancy reporting should continue and will be collected by the Sponsor using the Pregnancy Report Form.	Guidance for data collection of pregnancies that occur during the LTEP.	No
Section 7.6.6.1 MUGA or Echocardiogram	Added the following text: “During the LTEP, cardiac function assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.”	Guidance regarding cardiac function assessments during the LTEP.	No
Section 7.6.6.2 Electrocardiogram	Added the following text: “During the LTEP, ECG assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care.”	Guidance regarding ECG assessments during the LTEP.	No

Section(s)	Change	Rationale	Substantial (Yes/No)
Section 8.2 Data Management Procedures	Added text to indicate data collection needed during LTEP.	Guidance for data collection during the LTEP.	No
Section 8.4 Accuracy and Reliability of Data	Added text to indicate CRFs will not be collected during LTEP	eCRFs will not be collected during the LTEP.	No
Section 10 Informed Consent, Ethical Review, and Regulatory Considerations	Added: "For studies conducted in the European Union (EU)/European Economic Area (EEA) countries, the investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) or applicable European local regulations."	To ensure compliance with EU regulations.	No
Section 10.3.2 Protocol Amendments and Study Termination	Deleted: "The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination."	The study is being terminated	No
Section 10.5 Data Protection	Added new section to describe data protection features and steps to take in the event of a data breach.	To clarify data protection policy.	No