STATISTICAL ANALYSIS PLAN

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Protocol Title:	MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

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

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BICR	blinded independent central review
BID	twice daily
CDISC	clinical data interchange standards consortium
CI	confidence interval
cORR	confirmed objective response rate
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	data cutoff
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ED	emergency department
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life 30-item Core Questionnaire
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQol five dimensions
HER2	human epidermal growth factor receptor 2
IRR	infusion-related reaction
FAS	Full analysis Set
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Affairs
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PP	per protocol
PR	partial response
PRO	patient reported outcome
PT	preferred term
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan

SAE	serious adverse event
SMQ	standard MedDRA query
SMC	Safety Monitoring Committee
SSQ	sponsor specific query
TEAE	treatment emergent adverse event
SD	stable disease
SOC	system organ class
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNTUC-017, entitled "MOUNTAINEER: A Phase 2, Open Label Study of Tucatinib Combined with Trastuzumab in Patients with HER2+ Metastatic Colorectal Cancer". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

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

2 STUDY OBJECTIVES

The study consists of 3 cohorts. Cohort A includes approximately 40 subjects treated with the doublet regimen (tucatinib + trastuzumab). All subjects enrolled in the randomization cohorts of the trial will be randomized in a 4:3 ratio to receive tucatinib given in combination with trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). Enrollment will continue until approximately 30 subjects have been randomized to and treated in Cohort C, and approximately 40 subjects have been randomized to and treated in Cohort B.

2.1 Primary Objective

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

2.2 Secondary Objectives

Efficacy

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

- To assess the progression-free survival (PFS) in subjects treated with tucatinib given in combination with trastuzumab (RECIST 1.1), in Cohorts A+B, according to BICR assessment.
- To assess the overall survival (OS) in subjects treated with tucatinib given in combination with trastuzumab, in Cohorts A+B

Safety

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

2.3 Exploratory Objectives

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

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint of this study is confirmed objective response rate (cORR, confirmed complete response [CR] or partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) according to blinded independent central review (BICR) assessment, in pooled Cohorts A+B.

3.2 Secondary Endpoints

Efficacy

- ORR by 12 weeks of treatment, per BICR, in Cohorts A+B, and Cohort C
- DOR (confirmed CR or PR) per BICR, in Cohorts A+B, and Cohort C.
- PFS per BICR, in Cohorts A+B
- OS, in Cohorts A+B

Safety

- Frequency and severity, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria or higher, of all treatment-emergent adverse events (TEAEs) and treatment-related TEAEs, in Cohorts A+B, and Cohort C
- Frequency of serious adverse events (SAEs) and deaths due to adverse events (AEs), in Cohorts A+B, and Cohort C
- Frequency of treatment modifications and permanent treatment discontinuations due to AEs, in Cohorts A+B, and Cohort C
- Frequency and severity of laboratory abnormalities, in Cohorts A+B, and Cohort C
- Vital signs and other relevant safety variables, in Cohorts A+B, and Cohort C

3.3 Exploratory Endpoints

- Plasma concentrations of tucatinib
- To explore potential biomarkers of response, resistance or toxicity from archived paraffin-embedded tumor samples and circulating tumor DNA (ctDNA) isolated from plasma samples.
- PFS per BICR, in Cohort C
- OS, in Cohort C
- PRO per EQ-5D-5L, in Cohorts B and C
- PRO per EORTC QLQ-C30, in Cohorts B and C
- Cumulative incidence of health resource utilization, including length of stay, hospitalizations, and emergency department (ED) visits in Cohorts A+B, and Cohort C

4 STUDY DESIGN

This is a randomized, open-label, multicenter Phase 2 study of tucatinib, administered as monotherapy and in combination with trastuzumab, in patients with human epidermal growth factor receptor 2 (HER2)-positive, RAS wild-type, unresectable or metastatic CRC. Eligible patients are required to have previously received and failed, unless contraindicated, systemic therapy with fluoropyrimidines, oxaliplatin, irinotecan, and an anti-VEGF mAb; patients with dMMR or MSI-H disease must also have received an anti-PD-(L)1 mAb, if indicated.

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

Subjects enrolled in Cohort A and those randomized to Cohort B will continue to receive study treatment until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure. Subjects randomized to Cohort C will be allowed to crossover and receive doublet (tucatinib + trastuzumab therapy), if they experience radiographic progression at any time point (as determined by investigator assessment using RECIST 1.1), or if they have not achieved a PR or CR by the week 12 assessment.

Measures of anticancer activity will be assessed by either CT with contrast or MRI scans at protocol-specified time points. Subjects must be evaluated using the same imaging method throughout the study for efficacy assessments. Tumor response will be assessed by BICR as well as by investigator per RECIST v1.1 (Eisenhauer 2009). Clinical response of CR, PR, SD, or PD will be determined at each assessment. Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. Tumor assessments will continue until the subject has radiologically confirmed disease progression per RECIST 1.1 by the investigator, initiates a new anticancer therapy, dies, withdraws consent, or the study closes, whichever comes first.

Subjects that discontinue treatment for reasons other than disease progression per RECIST v1.1 will continue to have disease assessments approximately every 9 weeks until disease progression, death, withdrawal of consent, study closure, or alternative therapy.

Following progression or initiation of new anticancer therapy, subjects will be contacted every 12 weeks (±2 weeks) to obtain information on subsequent anticancer therapy, and survival status until death, study closure, withdrawal of consent, or subject is lost to follow-up, whichever occurs first.

Safety assessments will consist of the surveillance and recording of AEs including SAEs, vital signs, pregnancy testing, recording of concomitant medication, medical history, measurements of protocol-specified physical examination findings and laboratory tests.

On a periodic basis, approximately every 6 months starting from the first patient enrollment, a safety monitoring committee (SMC) will monitor the safety of subjects participating in this trial. The SMC will be guided by an independent charter and will focus on the aggregate safety evaluation of all enrolled and treated patients. The SMC will make recommendations to either continue the study as planned, to continue the study with modifications, to suspend the enrollment, or to terminate the study. The final decision to act on the SMC recommendations will be made by Seagen. An ongoing real-time review of subject safety and SAEs will also be conducted by the sponsor's Drug Safety Department.

5 ANALYSIS SETS

5.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled subjects in Cohort A and all randomized subjects in Cohort B and C. Subjects will be analyzed according to the cohort assigned at enrollment (Cohort A) or randomization (Cohort B and C) regardless of any actual treatment received.

5.2 Full Analysis Set

The full analysis set (FAS) will include all subjects who are enrolled and have received any amount of study treatment and have HER2+ tumors as defined by one or more protocol required local tests.

5.3 Safety Analysis Set

The safety analysis set will include all subjects who are enrolled and have received any amount of study treatment.

5.4 Patient Reported Outcome Set

The patient reported outcome (PRO) analysis set will include subjects in the FAS who have an evaluable (i.e., complete a PRO instrument and at least one domain or single item can be computed) baseline PRO score and at least one post-baseline evaluable PRO assessment in Cohorts B or C.

5.5 Pharmacokinetics (PK) Analysis Set

The pharmacokinetic analysis set will include all randomized subjects who received at least one dose of tucatinib and have at least one evaluable PK assessment in Cohorts B or C.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

Descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages per category for categorical variables.

Unless otherwise specified, confidence intervals (CIs) will be calculated at two-sided 95% level.

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

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

Any analysis not described in this plan will be considered exploratory and will be documented in the CSR as a post hoc analysis.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.3 or higher. Sample size calculations were performed using EAST®, version 6.0. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

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

The primary efficacy analysis will be performed by providing the point estimate and the 2-sided 95% exact Clopper Pearson CI for the confirmed ORR (pooled Cohorts A and B).

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

For illustration purposes, Table 6-1 summarizes the expected 95% CIs for subjects treated with tucatinib given in combination with trastuzumab (Cohorts A+B) and subjects treated with tucatinib monotherapy (Cohort C) at the proposed sample sizes of 80 and 30 respectively. No formal statistical comparisons between cohorts are planned.

Table 6-1: Estimated ORR

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

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

6.3 Randomization and Blinding

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

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

This is an open label study.

6.4 Data Transformations and Derivations

6.4.1 General

Reported age in years will be used; if not available, age at informed consent in years will be calculated with the SAS® INTCK function (with method specified as "continuous") using informed consent date and birth date.

Study Day will be calculated as (Date – First Dose Date + 1) for dates on or after the first dose date. The date of first dose will be Study Day 1. For dates prior to the first dose date, Study Day will be calculated as (Date – First Dose Date). For example, the date before the first dose date will be Study Day -1.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months=Days/30.4375

Years=Days/365.25

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

6.4.2 Best Overall Response

The subject's best overall response per BICR will be the best response to date that has been confirmed, (i.e., for PR and CR). Response after the start of subsequent anticancer therapy will not be included in the derivation of best overall response. The subject's best overall response will be used in determining the ORR per BICR.

A response (CR or PR) will be considered confirmed if the subsequent response assessment (at least 4 weeks after the initial response) still shows response (CR or PR). A subject will have a best response of non-CR/non-PD or SD if there is at least one non-CR/non-PD or SD assessment (or better) ≥ 5 weeks after the efficacy start date (treatment start date for Cohort A; randomization date for Cohort B and Cohort C) and the subject does not qualify for confirmed CR or PR.

6.4.4 Response Assessment Dates

At each response assessment time point, scans could be performed on multiple dates. If the time point response is CR or PR, then the latest date of all radiologic scans at the given response assessment time point will be the date of response. If the time point response is SD or non-CR/non-PD, then the earliest date of all radiologic scans at the given response assessment time point will be the date of response. If the time point response is PD, then the earliest date that PD has been documented will be the date of PD, i.e., the earliest of:

- Date of target lesion assessments when the target lesion response is PD.
- Date of non-target lesion assessments when the lesion status is unequivocal progression.
- Date of documenting new lesions

For subjects whose best overall response is a confirmed CR or PR, the date of objective response will be the date of initial documentation of response (i.e., CR or PR that is subsequently confirmed).

6.4.5 Adequate Response Assessment

An adequate tumor assessment must include a radiologic scan with the overall disease response of CR, PR, non-CR/non-PD, SD, or PD.

6.4.6 Action Taken with Study Treatment

Action taken with study treatment includes dose modification and drug withdrawn. For tucatinib, dose modification includes dose held (i.e., dose delay), dose reduced, or dose error. For trastuzumab, dose modification includes dose held (i.e., dose elimination or dose delay) and unplanned dose adjustment. For trastuzumab, unplanned dose adjustment includes dose error not leading to interruption or stoppage of dose, infusion interrupted due to AE (received full dose w/in 24hrs), infusion interrupted for other reason (received full dose w/in 24hrs), infusion stopped early due to AE (full dose not received), or infusion stopped early due to other reason (full dose not received). Drug withdrawn includes tucatinib discontinuation and trastuzumab discontinuation.

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified.

For time-to-event endpoints (e.g., duration of response, PFS, and OS), subjects who have no specified event will be censored as specified for each respective endpoint in Section 7.5.

Missing or partial AE dates will be imputed for the purpose of calculating treatment-emergent status (see Appendix A for imputation details and Appendix B for treatment-emergent definition).

Partial prior therapy dates will be imputed (see Appendix C for details) for the purpose of deriving time since last prior therapy to study start.

Partial subsequent anticancer therapy start and end dates will be imputed for the purpose of deriving the time-to-event endpoints as applicable. Partial missing hospitalization dates will be imputed for the purpose of deriving total length of hospitalization stays. (see Appendix D for details).

Partial diagnosis date will be imputed for the purpose of calculating the time from initial diagnosis, the time from first diagnosis of metastatic or unresectable diseases (see Appendix E for details).

Partial missing death dates will be imputed for the purpose of deriving the time-to-event endpoints as applicable (see Appendix F).

Unless otherwise specified, if the numeric value of a laboratory test is not available because it is below the lower limit of quantification (LLOQ), the result will be analyzed as equal to LLOQ when a numeric value is required (e.g., calculating the mean) and be listed as "< LLOQ" in the listings.

For PK analysis, if the numeric value is not available because it is below the lower limit of qualification (LLOQ), the result will be analyzed as equal to half of the LLOQ (i.e., LLOQ/2) when a numeric value is required (e.g., calculating the mean, geometric mean, geometric coefficient of variation) and be listed as "<LLOQ" in the listings. The summary statistics for a timepoint will not be calculated if more than 50% of the results are <LLOQ.

6.6 Multicenter Studies

Approximately 110 subjects will be enrolled to the study from approximately 55 sites worldwide.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints (primary and secondary efficacy endpoints). Subgroups may include but are not limited to the following:

- Age (<65, ≥65 years old)
- ECOG performance score at baseline (0, 1-2)
- Primary site of disease:
    - Left sided primary (rectum, rectosigmoid junction, sigmoid colon, splenic flexure, descending colon)
    - All other primary types (transverse colon, right sided, multiple/overlapping sites)
- Geographic Region: North America, Europe

A subgroup analysis may not be performed if the number of subjects in the subgroup is not sufficiently large (e.g., <10%).

6.9 Covariates

No adjustment for covariates is planned in the analyses.

6.10 Timing of Analyses

The final analysis of the primary endpoint and secondary endpoints will be conducted when all treated subjects have been followed for at least 6 months or have been discontinued from study treatment.

Additional cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

7 PLANNED ANALYSES

7.1 Disposition

Patient enrollment and disposition will be summarized by cohort and total. The table will present the number and percentage of patients who were enrolled or randomized in each cohort, received study drug, and participated in long-term follow-up. The number and percentage of patients who discontinued treatment will be summarized by the reason for treatment discontinuation. The number and percentage of patients who discontinued the study will be summarized by the primary reason for study discontinuation. The summary of disposition will be conducted for ITT analysis set.

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

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

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

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age at consent, sex, ethnicity, race, ECOG performance status will be listed and summarized with descriptive statistics for the FAS by cohort. In addition, these may also be summarized for Cohort A and Cohorts B+C to show comparability between the non-randomized cohort and randomized cohorts.

Disease specific characteristics, including primary tumor site, RAS mutation status, HER2 result by IHC, HER2 status by FISH/CISH and HER2 result by NGS, time from initial diagnosis, time from first diagnosis of metastatic or unresectable disease will be listed and summarized for the FAS.

Summary of prior cancer-related therapies, including number of prior therapies, therapy type, setting of prior therapies will be presented for the FAS.

In addition, the pre-existing condition of diarrhea that are ongoing at baseline, gastrointestinal-related history of prior surgical treatment and prior radiation therapy will be summarized using the Safety Analysis Set.

7.3 Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of subjects with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized for the safety analysis set separately for Cohorts A+B and Cohort C.

The following information will be summarized separately for trastuzumab and tucatinib:

- Total number of treatment cycles per subject
- Duration of treatment
- Percentage of subjects with reduced, interrupted, and withdrawn infusions/doses overall and by reason.

Dose reduction, absolute dose intensity (ADI) and relative dose intensity (RDI) will only be summarized for tucatinib.

For tucatinib, the type, reason and time to first dose modification will be summarized. The number of subjects with dose modifications due to AE will also be summarized.

Duration of treatment (except when calculating exposure) is defined as the time from first dose date to the earliest of the following dates:

- The exposure end date:
  - For tucatinib, the date of last dose
  - For trastuzumab, date of last dose + 20
- Date of death
- End of study date
- Analysis data cutoff (DCO) date if the subject is still on study at the time of DCO.

Intended dose intensity (IDI) is defined as the intended dose of study drug per unit of time according to the protocol.

ADI is defined as the actual dose of study drug per unit of time that a subject received over the entire exposure period, i.e., ADI = cumulative dose/(exposure end date – first dose date+1).

RDI is defined as the ADI over the IDI (i.e., RDI = ADI/IDI * 100%).

7.5 Efficacy Analyses

The analyses for efficacy endpoints, including the primary endpoint of cORR, the secondary endpoints of ORR by 12 weeks of treatment, DOR, PFS and OS will be performed for the FAS by for cohort A+B and cohort C separately, unless otherwise specified.

Sensitivity analyses of cORR and DOR for cohort A+B may be performed for subjects in:

(1) FAS with HER2+ tumors centrally confirmed by IHC breast algorithm;

(2) FAS with HER2+ tumors centrally confirmed by IHC breast algorithm including samples analyzed outside the stability window that meet scientific justification criteria;

(3) Safety Analysis Set.

7.5.1 Primary Endpoint: Confirmed Objective Response Rate (cORR) per BICR

The primary endpoint of this study is the cORR per BICR in pooled Cohorts A+B. cORR is defined as the proportion of subjects whose best overall response is a confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009). Only tumor assessments before first documented PD or new anti-cancer therapies will be considered. For a response to be considered as confirmed, the subsequent response needs to be at least 4 weeks after the initial response. Subjects who do not have at least two (initial response and confirmation scan) post-baseline response assessments will be considered non-responders.

The cORR per BICR and its exact two-sided 95% CI will be calculated for the FAS in Cohorts A+B.

In addition, the cORR per BICR will be summarized by the subgroups defined in Section 6.8.

The maximum percent reduction from baseline in the sum of diameters per BICR will be calculated for subject with baseline and post-baseline target lesion measurement and presented graphically with a waterfall plot.

Time to response per BICR will be calculated as the time from the start of study treatment (Cohort A) or date of randomization (Cohorts B and C) to the first documentation of objective response (CR or PR that is subsequently confirmed). Time to response per BICR will be summarized for the responders only. For Cohort C pre-crossover, time to response will be summarized for the responders defined in Section 7.5.2.1.

All above analyses for cORR per BICR will also be performed for cORR per investigator, as sensitivity analysis.

A summary of the concordance between investigator and BICR assessment will be provided. The percent agreement will be calculated as the proportion of subjects whose best overall response (responder vs. non-responder) per BICR match the best overall response (responder vs. non-responder) per investigator.

Percent agreement = (Number of matched responders + Number of matched non-responders) / Total number of subjects assessed.

7.5.2 Secondary Endpoints

7.5.2.1 Objective Response Rate (ORR) by 12 Weeks of Treatment

ORR by 12 weeks of treatment is defined as the proportion of subjects with CR or PR by 12 weeks of treatment or time of crossover, whichever comes earlier, as determined per RECIST v1.1. Responses do not need to be confirmed to be scored as responders for the purpose of determining ORR by 12 weeks of treatment. Subjects who do not have at least one post-baseline response assessment by 12 weeks of treatment will be considered non-responders. The ORR by 12 weeks per BICR and its exact two-sided 95% CI will be calculated for the FAS in Cohorts A+B. The analyses will be performed per INV as sensitivity analyses.

A summary of the concordance between investigator and BICR assessment will be provided only for Cohort C.

7.5.2.2 Duration of Response (DOR)

DOR is defined as the time from the date of first documented response (CR or PR that is subsequently confirmed) to the date of first documented PD per RECIST v1.1 or death due to any cause, whichever comes first.

DOR will be censored as described below:

- Subjects who do not have PD and are still on study at the time of an analysis will be censored at the date of the last adequate response assessment documenting absence of PD
- Subjects who have started a new anticancer treatment prior to documentation of PD will be censored at the date of the last adequate response assessment prior to start of new treatment
- Subjects who discontinue from the study prior to documentation of PD will be censored at the date of the last adequate response assessment documenting absence of PD.
- Subjects who progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed response assessments) will be censored at the date of the last adequate response assessment prior to the missed visits.

DOR per BICR will only be calculated for subjects achieving a confirmed CR or PR per BICR. DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided if there are at least 5 events. The median DOR and its two-sided 95% CI will be calculated. In addition, the DOR at different timepoints (for instance, 6 and 12 months) will be summarized.

DOR per investigator will be analyzed in the same way as the DOR per BICR, as sensitivity analysis.

For Cohort C pre-crossover, DoR will be summarized for the responders defined in Section 7.5.2.1.

7.5.2.3 Progression-free Survival (PFS)

PFS is defined as the time from start of study treatment (Cohort A) or date of randomization (Cohorts B and C) to first documentation of PD per RECIST v1.1 or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 7.5.2.2 for DOR will be applied to PFS. In addition, subjects who have no post-baseline response assessment will be censored at the date of start of study treatment (Cohort A) or the date of randomization (Cohort B and C).

PFS per BICR for Cohorts A+B will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its two-sided 95% CI will be calculated. In addition, the probability of PFS at different timepoints (for instance, 6 and 12 month) will be summarized.

A sensitivity analysis may be conducted by not considering new anti-cancer treatment as a censoring reason. Additional sensitivity analysis may be conducted by considering new anti-cancer treatment as an event.

All the analyses for PFS per BICR will also be performed for PFS per investigator, as sensitivity analysis.

7.5.2.4 Overall Survival (OS)

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

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its two-sided 95% CI will be calculated. In addition, the probability of OS at different timepoints (for instance, 6 and 12 months) will be summarized.

7.5.3 Special considerations for Efficacy Analyses for Cohort C

Subjects randomized to Cohort C will be allowed to crossover and receive doublet tucatinib + trastuzumab therapy if they experience radiographic progression at any time point, or if they have not achieved a PR or CR by 12 weeks of treatment. Crossover start date is the date of first dose of tucatinib or trastuzumab (whichever came first) in the first cycle of trastuzumab. Subjects who crossover will have new baseline assessment per RECIST 1.1. The re-baseline visit time point is defined as following:

- If subject crossover due to PD per RECIST 1.1, the re-baseline timepoint is the assessment of PD.
- If subject had no PD and have not achieved a PR or CR per RECIST 1.1 by 12 weeks and crossover, then the re-baseline time point is the last response assessment before crossover.

In addition to the analyses described for the overall study in previous sections, the efficacy analyses for Cohort C that need special consideration due to the potential crossover are described in this section.

7.5.3.1 ORR by 12 Weeks of Treatment

Subjects who experience radiographic progression and crossover before 12 weeks of treatment will be analyzed using best overall response before crossover. Any response assessment before 12 weeks of treatment but after crossover will not be counted.

7.5.3.2 PFS

Besides the censoring rules specified in Section 7.5.2.3, subjects who do not have PFS event by 12 weeks of treatment and crossover to receive doublet regimen will be censored at the time of re-baseline.

7.5.3.3 DOR

For the summary of DOR in cohort C pre crossover, all responders by 12 weeks of treatment will be included in the analysis, regardless if the responses are confirmed or not.

7.6 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 24.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03 or higher).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (version: WHODrug Global 2021Mar B3 or higher).

Safety analyses will be performed for Cohorts A+B and Cohort C. For subjects in Cohort C who crossover, safety analyses will be performed separately before and after crossover. Crossover start date is the date of first dose of tucatinib or trastuzumab (whichever came first) in the first cycle of trastuzumab.

Summary of adverse events (AEs), clinical laboratory parameters, left ventricular ejection fraction, ECOG, and vital signs includes post-baseline data collected up through 30 days after the last dose of study treatment (tucatinib or trastuzumab).

7.6.1 Adverse Events

Adverse events (AEs) will be summarized by MedDRA preferred term (PT) in descending frequency of occurrence unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same system organ class (SOC) or PT, the subject will be counted only once for that specific SOC or PT.

A treatment-emergent adverse event (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment (tucatinib or trastuzumab). See for details regarding treatment-emergent classification.

An overall summary of TEAEs will be provided. Summaries of TEAEs by MedDRA classification will also be provided for the following:

- TEAEs
- Grade 3 or higher TEAEs
- Serious TEAEs
- TEAEs leading to dose reduction/dose hold/drug withdrawal
- TEAEs leading to death
- Treatment-related TEAEs
- Treatment-related grade 3 or higher TEAEs
- Treatment-related serious TEAEs
- Treatment-related TEAEs leading to dose reduction/dose hold/drug withdrawal
- Treatment-related TEAEs leading to death
- TEAEs by SOC, PT and maximum severity. At each SOC or PT, multiple occurrences of the same event within a subject are counted only once at the highest severity
- TEAEs by SOC and PT

All TEAEs, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be listed.

7.6.2 Serious Adverse Events

Serious adverse events (SAEs) will be summarized by preferred term and SOC using counts and percentages. The following summaries of SAEs will be produced.

- Incidence of treatment emergent SAEs (TESAEs) by decreasing frequency of preferred term
- Incidence of TESAEs by decreasing frequency of SOC and preferred term
- Incidence of treatment related TESAEs by decreasing frequency of preferred term

In addition to summary tables, listings of SAEs will be produced.

7.6.3 Adverse Events of Special Interest and Additional Risks

The incidence of treatment emergent adverse events of special interest (AESI) will be summarized by PT or lab values and listings will also be produced. The following AESIs to be summarized are described in the protocol Section 7.7.1 and are as the following:

1. Potential drug-induced liver injury

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

Laboratory Test	Laboratory Value
AST	>3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 × ULN
ALT	>3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 × ULN

2. Asymptomatic left ventricular systolic dysfunction

   Treatment-emergent asymptomatic left ventricular systolic dysfunction will be considered as another event of special interest. The search strategy for asymptomatic decline in LVEF is defined as follows:

   1- TEAEs captured on the "AESI-Asymptomatic LVEF Decline" CRF form and leading to a change in study treatment or discontinuation of study treatment belong to this category.

   2- TEAEs with preferred terms defined by cardiomyopathy SMQ (narrow) and cardiac failure SMQ (narrow) leading to a change in study treatment or discontinuation of study treatment belong to this category.

In addition to the protocol defined AESIs, the incidence of treatment emergent adverse events for additional risks will be summarized by PT or lab values and listings will also be produced. The TEAEs for the following additional risks to be summarized are:

1. Hepatotoxicity

Treatment emergent hepatotoxicity events will be summarized using SMQ and SSQ search strategies defined below:

Hepatotoxicity	Two set of outputs for the following: 1. Drug related hepatic disorders - comprehensive search SMQ (Narrow) 2. Cluster of the following PTs (SSQ): • Acute hepatic failure • Acute on chronic liver failure • Alanine aminotransferase abnormal • Alanine aminotransferase increased • Aspartate aminotransferase abnormal • Aspartate aminotransferase increased • Bilirubin conjugated increased • Blood bilirubin abnormal • Blood bilirubin increased • Coma hepatic • Drug-induced liver injury • Gamma-glutamyltransferase abnormal • Gamma-glutamyltransferase increased • Hepatic cytolysis • Hepatic encephalopathy • Hepatic enzyme abnormal • Hepatic enzyme increased • Hepatic failure • Hepatic necrosis • Hepatitis • Hepatitis acute • Hepatitis fulminant • Hepatitis toxic • Hepatocellular injury • Hepatorenal failure • Hepatotoxicity • Hyperbilirubinaemia • Hypertransaminasaemia • Jaundice hepatocellular • Liver function test increased • Liver injury • Mitochondrial aspartate aminotransferase increased

	• Mixed liver injury • Subacute hepatic failure • Transaminases abnormal • Transaminases increased

2. Diarrhea

   Treatment emergent diarrhea events will be summarized using search strategy defined by single PT term “Diarrhoea”.

3. Serum Creatinine and Blood Urea Nitrogen (BUN)

   Boxplots of serum creatinine and blood urea nitrogen by visits will be produced.

4. Infusion/injection Related Hypersensitivity Reactions (IHR) and Infusion Related Reactions (IRR).

   Treatment emergent IHR/IRR events will be summarized by PT and by maximum severity.

In addition, treatment-emergent AESI leading to dose modification and study treatment discontinuation that are related to study drug will be summarized.

For selected AESI, time to first onset or resolution will be analyzed as appropriate.

Time to first onset of a specific AESI will be calculated as time from the first dose of study drug to the start of first treatment-emergent event that meets the respective search criteria.

Resolution is defined as event outcome of ‘recovered/resolved’ or ‘recovered/resolved with sequelae’. For events with an outcome of ‘recovered/resolved’ or ‘recovered/resolved with sequelae’, time to resolution will be calculated as time from the event start date to end date.

Time to first onset will be summarized at the subject level. Time to resolution will be summarized at the event level.

7.6.4 Clinical Laboratory Parameters

All laboratory results (hematology and serum chemistry) up to the date of last dose of any study treatment + 30 days will be presented in standardized units. The incidence of laboratory toxicities by grade will be summarized. Shift from baseline to maximum post-baseline NCI CTCAE (version 4.03 or higher) grade will be summarized for each lab test. Serum creatinine will be graded using NCI CTCAE version 5.0. Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results and NCI CTCAE (version 4.03 or higher) grades for hematology and serum chemistry will be presented in data listings. Serum creatinine will be graded using NCI CTCAE version 5.0. Normal ranges will be documented and out-of-range values will be

flagged. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

7.6.4.1 Liver Safety Assessment

The incidence of potential drug-induced liver injury will be summarized. In addition to the laboratory abnormalities defined for AESI in Section 7.6.3, (AST and/or ALT) > 3 × ULN + Total Bilirubin > 2 × ULN + Alkaline Phosphatase < 1.5 × ULN and (AST and/or ALT) > 3 × ULN, 5 × ULN, 10 × ULN, and 20 × ULN will also be summarized.

7.6.5 Left Ventricular Ejection Fraction

The minimal post baseline ejection fraction and the maximum decrease from baseline will be summarized for each treatment group. Time to minimal post baseline ejection fraction may also be tabulated.

7.6.6 Vital Signs

Vital signs (weight, body temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation) will be listed. The frequency and percentage of patients with post baseline clinically significant vital signs will be summarized. The clinically significant vital signs are defined as: heart rate >100 bpm; Temperature >=38.0 degrees C (100.4 F), and oxygen saturation <88%. Blood pressure will be summarized both for subjects with systolic blood pressure >=120 mmHg or diastolic blood pressure >=80 mmHg, as well as for subjects with systolic blood pressure >=140 mmHg or diastolic blood pressure >=90 mmHg, and subjects with systolic blood pressure >=160 mmHg or diastolic blood pressure >=100 mmHg.

7.6.7 ECOG

Shift from baseline ECOG status to worst post-baseline ECOG status up to the date of last dose of any study treatment + 30 days will be provided.

7.6.8 Deaths

Death information will be summarized and listed by subjects.

7.6.9 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug ATC class and preferred name. The number and percentage of subjects who take concomitant medications will be tabulated. Multiple occurrences of the same medication within a subject will be summarized only once. Concomitant medications will be listed by subject.

7.7 Additional Analyses

7.7.1 HER2 Status

Central confirmation of HER2 status by IHC analysis will be performed with IHC scoring of samples using the breast and gastric criteria. Subjects with an IHC 3+ result or an IHC 2+ with a Fluorescence In Situ Hybridization (FISH) positive result were classified as HER2 positive per the package insert for HER2 testing.

Concordance between the two IHC scoring algorithms (breast and gastric) will be assessed by overall HER2 status and HER2 IHC score. Additional analyses may be performed and described in a separate biomarker analysis plan.

7.7.2 Pharmacokinetics

The analyses described in this section will be produced for the pharmacokinetics analysis set.

Tucatinib levels will be summarized with descriptive statistics at each PK sampling time point. Additional PK and PK/PD analyses may be performed and described in a separate pharmacometric analysis plan.

7.7.3 Patient Reported Outcomes

7.7.3.1 EORTC QLQ-C30

The EORTC QLQ-C30, Version 3.0 (Aaronson 1993) comprises nine multiple-item scales and six single-item scales. The multiple-item scales include five functional scales (Physical, Role, Emotional, Cognitive, and Social), three symptom scales (Fatigue, Nausea and Vomiting, Pain), and a global health status/QOL score. The single-item scales of the EORTC QLQ-C30 include Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties. Patients assessed how true each statement in the questionnaire is for them on a four-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much), whereas Global Health Status or QOL was assessed using a seven-point Likert scale (ranging from "poor" to "excellent") for two items.

Scale scores are calculated by averaging items within scales and transforming average scores linearly. All the scales range in score from 0 to 100. High scores for global health status/QOL and functional scales represent high/healthy level of QOL or functioning; whereas high scores for symptom scales or items represent higher level of symptomatology.

For each QLQ-C30 scale, score will be calculated and missing data will be accounted for according to the EORTC QLQ-C30 scoring manual. Descriptive summary of actual value and change from baseline will be presented by visit for subjects who have a baseline and at least one post baseline assessment. Line graphs for mean change from baseline in EORTC QLQ-C30 scores with 95% confidence intervals will be prepared. Visits with less than 5 subjects with assessment will not be displayed in line graphs.

The absolute change from baseline of 10 points in QLQ-C30 scale score is considered conventionally as a minimum important difference (Osoba et al., 1998). For the global health status/QoL and functioning scales, the scale score change from baseline will be categorized as follows:

- Improved: change from baseline ≥ 10
- Stable: -10 < change from baseline < 10
- Worsened: change from baseline ≤ -10 or "Patient was too ill" is answered as the reason for not completing the QLQ-C30 form at visit

For QLQ-C30 symptom scales/item (i.e. Fatigue, Nausea and Vomiting, Pain, Appetite Loss) the scale score change from baseline will be categorized as follows:

- Improved: change from baseline ≤ -10
- Stable: -10 < change from baseline < 10
- Worsened: change from baseline ≥ 10 or "Patient was too ill" is answered as the reason for not completing the QLQ-C30 form at visit

The number and percentage of subjects who have a response of Improved, Stable, or Worsened will be summarized by visit and by cohort. In the reporting of the proportion of patients who have a response of Improved, Stable, or Worsened, the denominator will be all patients with non-missing corresponding QLQ-C30 scale scores at baseline and at each corresponding visit.

The compliance and completion rate of EORTC QLQ-C30 will be summarized for each visit and by cohort. Compliance rate is defined as the proportion of subjects who completed the instrument among those who are expected to complete at a given visit. Completion rate is defined as the proportion of subjects who completed the instrument among the PRO analysis set.

7.7.3.2 EuroQol-5D-5L

The EQ-5D-5L is a widely used, self-administered questionnaire designed to assess health status in adults (Herdman et al., 2011). The measure is divided into two distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Respondents rate their perceived health state today as presenting "no problems," "slight problems," "moderate problems," "severe problems," or "unable to/extreme problems." The second section of the questionnaire, the visual analog scale (EQ-VAS), measures self-rated Global Health Status using a vertically oriented visual analog scale (VAS), where 100 represents the "best imaginable health state" and 0 represents the "worst imaginable health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period of the questionnaire is "today."
A distribution (numbers and percentages of subjects) for the EQ-5D-5L responses for each of the five dimensions will be summarized for each visit and by cohort.

Visual analogue scale (VAS) actual value and change from baseline will be summarized with descriptive statistics by visit for subjects who have a baseline and at least one post baseline assessment.

The compliance and completion rate of EQ-5D will be summarized for each visit and by cohort.

7.7.4 Health Resource Utilization

Descriptive summary of health resource utilization, including type of hospitalization (i.e. inpatient or outpatient), length of stay, ED visits, and reason for hospitalization will be

summarized by cohort in safety analysis set from the date of first dose of study treatment to the date of last dose of study treatment + 37 days.

7.7.5 Subsequent Anticancer Therapy

The number and percentage of subjects who receive subsequent anticancer therapies will be summarized for the FAS.

7.7.6 Efficacy Analyses for Cohort C post-crossover

cORR and DOR per BICR and per INV will be summarized for subjects in cohort C post-crossover. The baseline for response post-crossover is the re-baseline timepoint as described in section 7.5.3.

7.7.7 Duration of Follow-up

Duration of study follow-up will be summarized using reverse KM method (Schemper and Smith, 1996) for FAS by cohort.

7.7.8 Biomarker related exploratory endpoint(s)

The analyses for biomarker related exploratory endpoint(s) maybe specified in a separate biomarker analysis plan and reported outside of the clinical study report.

8 INTERIM ANALYSIS

No interim analysis for the primary endpoint is planned.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Protocol

9.1.1 Additional analyses for Cohort C Post-Crossover

Summary of confirmed objective response rate (cORR) and duration of response (DoR) per BICR and per INV for Cohort C post-crossover will be provided.

9.1.2 Additional analyses for Adverse Event of Interest

Summary of additional risk categories hepatotoxicity (SMQ), hepatotoxicity (SMQ), Diarrhea (PT), serum creatinine by lab, blood urea nitrogen (BUN) by lab, infusion related reactions(IRR)/Infusion related hypersensitivity reactions (IHR) will be provided.

9.2 Changes from the Original SAP

Section	Changes to Original SAP
Global change	The Sponsor name "Seattle Genetics" was updated with "Seagen".
2	Language of enrollment objective was updated per Protocol SGNTUC-017 Amendment 11.

4	"Subjects that discontinue for reasons other than disease progression per RECIST v1.1..." was updated with "Subjects that discontinue *treatment*..." for clarification.
5	Added and modified the definition of analysis sets
6.4.2	Replaced "start of treatment" with "efficacy start date (treatment start date for Cohort A; randomization date for Cohort B and Cohort C)" when deriving valid SDs.
6.4.6	Language concerning the definition of treatment modification was updated to make it more explicit and clearer.
6.5	Imputations of partially missing dates were clarified. Handling of lab and PK values below LLOQ was clarified.
6.10	Timing of analyses was updated to "…at least 6 months or have been discontinued from study treatment" per Protocol SGNTUC-017 Amendment 11.
7.2	Summary of demographic and baseline characteristics was updated to use FAS (instead of using ITT). Baseline weight, height and body mass index were removed from summary. Summary of pre-existing conditions were clarified.
7.2	Best response to prior therapy and time from most recent pior therapy to first does of study drug were removed.
	Time from initial diagnosis and time from first diagnosis of metastatic or unresectable disease were added.
7.4	1. Summary of "total cumulative dose" was removed; 2. Language for ADI, RDI was clarified. 3. Duration of treatment and exposure end date derivation rule was updated
7.5	Efficacy analyses was updated to use FAS (instead of using ITT). Sensitivity analysis for cohort A+B were specified.
7.5.1	Summary of maximum percent reduction from baseline in the sum of diameters per BICR were clarified.
7.5.2.1	The “by Week 12 of Treatment” efficacy summaries were clarified.
7.5.2.2	Language was added to clarify DoR derivation for Cohort C pre-crossover.
7.5.2.2	“KaplanMier plot will be produced if there are at least 5 events” was added.
7.5.2.3	Sensitivity analysis by treating new anti-cancer therapy as PFS events was added.
7.5.2.4	Derivation of overall survival date was updated. Text “in Cohorts A+B” were removed. Overall survival for Cohort C will also be summarized.

7.5.3	Crossover start date was defined in efficacy analyses.
7.5.3.3	Language was added to clarify DOR derivation in Cohort C pre crossover.
7.6	MedDRA and WHODrug versions were updated.
7.6	1. Crossover start date was defined in safety analyses. 2. safety summary ascertainment period was clarified.
7.6.3	1. Search strategy of AESI and risks were updated. 2.Definition of AESI resolution was updated. 3. Time to improvement was removed from analyses. 4. “First” was added to clarify time to first onset.
7.6.4	1. The end date of lab summary ascertainment period "end of treatment" was replaced with "date of last dose of any study treatment + 30 days". 2. "Serum creatinine will be graded using NCI CTCAE version 5.0." was added.
7.6.6	Vital sign summary categories were updated.
7.6.7	Summary of shift from baseline ECOG status to worst post-baseline ECOG status was added.
7.7.1	1. Central confirmation of HER2 status was specified. 2. Concordance between 2 IHC scoring algorithms (breast and gastric) was added.
7.7.3.2	"The EQ-5D health state dimension scores will be converted into a health state index using the time trade-off valuation method and the US-based value set (Shaw 2005)." was removed.
7.7.4	Summary of health utilization was updated.
7.7.5	"Subsequent anticancer therapy" will be summarized using FAS (instead of ITT).
7.7.6	Efficacy analyses for Cohort C post-crossover were added.
7.7.7	Duration of follow-up was added.
7.7.8	Conduction of biomarker related exploratory endpoint(s) were specified.
Appendix B	Treatment emergent AE Cohort C pre-crossover and Cohort C post-crossover was defined.
Appendix E	Imputation of disease diagnosis was added.

Appendix F	Imputation of partial missing death dates was added.

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11 APPENDICES

Appendix A: Imputation of Partially Unknown Adverse Event Dates

For an adverse event (AE) with a partial start or end date, if it can be determined that the event occurred prior to the date of first dose of study treatment, the partial date will not be imputed; Otherwise, the partial date will be imputed using the rules described below. AE start dates should be imputed before imputation of AE condition end date in all cases.

Incomplete AE Start Date:

AE day only is missing

If the month/year is the same as the month/year of first dose of any study treatment:
AE start date will be imputed as the first dose date of any study treatment
If the month/year is after the month/year of first dose of any study treatment:
AE start date will be imputed as the first day of the month

AE day and month are missing, or month only is missing

If the year is the same as the year of first dose of any study treatment:
AE start date will be imputed as the first dose date of any study treatment
If the year is after the year of first dose of any study treatment:
AE start date will be imputed as January 1st

AE day, month and year are missing, or year only is missing

AE start date will be imputed as the first dose date of any study treatment

If AE condition end date* is not missing, and the imputed start date is after the end date, the start date will be set to the AE condition end date.
* only use condition end date if known and full end date is available.

Incomplete AE End Date:

If AE outcome is “not recovered/resolved”, “unknown”, or blank: AE condition end date will not be imputed.

If AE outcome is “recovering/resolving”, “recovered/resolved”, “recovered/resolved with sequelae”, or “fatal” apply the following:

AE day only is missing

AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year, EOS date)

AE day and month are missing, or month only is missing

If the year is equal to the year of the last dose date:
AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date, December 31st of the end date year, EOS date)

If the year is not equal to the year of the last dose date:

AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year, EOS date)

AE day, month and year are missing, or year only is missing

AE condition end date will not be imputed

Within a single record, if the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Example

AE Number 4: Condition/Event NAUSEA
First dose date 02APR2012

Prior to imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	UNAPR2012	2	recovering/resolving
2	UNAPR2012	04MAY2012	1	recovered/resolved

Post imputation

Log Line	Start date	Condition end date	Severity	Outcome
1	25APR2012	**30**APR2012	2	recovering/resolving
2	**02**APR2012	04MAY2012	1	recovered/resolved

Appendix B: Definition of the Term "Treatment-Emergent" with Respect to AE Classification

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which is newly occurring or worsening in severity, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

- For each subject, determine the first dose date, which is the earliest date the subject receives any amount of study drug (trastuzumab or tucatinib).
    - An AE record from AE page will be classified as a TEAE if it meets all the following three conditions:

1. Onset period = Started after first dose of any study treatment (i.e., tucatinib or trastuzumab)

2. AE Start Date on or after first dose date of study treatment (i.e., tucatinib or trastuzumab)
3. AE Start Date before last dose date of study treatment (i.e., trastuzumab or tucatinib) + 30 days

- TEAEs pre-crossover are defined as AEs that are newly onset or worsened (increase in AE grade, AE becoming serious, or related to study drug) on or after receiving the first dose of tucatinib and up to 30 days after last dose of tucatinib for patients who didn't crossover, or the day before cross-over for patients who crossed over.

- TEAEs post-crossover are defined as AEs that are newly onset or worsened (increase in AE grade, AE becoming serious, or related to study drug) on or after crossover (date of first dose of tucatinib or trastuzumab (whichever came first) in the first cycle of trastuzumab) and up to 30 days after the last dose of study treatment (tucatinib or trastuzumab).

NOTE:

- **For summaries which include only treatment emergent AEs include all AEs which are classified as TEAEs as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if onset period is not known - missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent.**

Appendix C: Imputation of Partial Missing Prior Therapy Dates

Prior therapy dates will be imputed if both month and year are present and only day is missing.

- For prior therapy start date, impute the first day of the month.
- For prior therapy end date, impute the last day of the month or the date of first dose of any study drug, whichever is earlier.

Appendix D: Imputation of Partial Missing Subsequent Anticancer Therapy Dates and Hospitalization Dates

Subsequent anticancer therapy and hospitalization start date and end date will be imputed if both month and year are present and only day is missing.

- For start date, impute to first day of the month or the date of first dose of any study drug, whichever is later.
- For end date, impute to last day of the month or the end of study, date of death, data cutoff date whichever is earlier.

Appendix E: Imputation of Partial Missing Disease Diagnosis Dates

Disease diagnosis dates (i.e. initial diagnosis date, date of first diagnosed with metastatic disease, date of first diagnosed with unresectable disease) will be imputed to the 1st day of the month if both month and year are present and only day is missing.

Appendix F: Imputation of Partial Missing Death Dates

Death dates are imputed if only the day is missing.

The imputation of partial missing death date depends on the last-know-alive date derived from eCRF.

If the last-known-alive date is in the same month and year of the partial missing death date, then the partial missing death date is imputed as the later of the following dates,

- The last-known-alive date.
- Day 15 of the month and year.

If the last-known-alive date is not in the same month and year of the partial missing death date, then the partial missing death date is imputed as day 15 of the month and year.

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