STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNTUC-019
Version:	Version 1 06-Oct-2021
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
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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

ADI	Absolute dose intensity
AE	adverse event
AESI	adverse event of special interest
BC	breast cancer
BID	twice daily
CDISC	clinical data interchange standards consortium
CI	confidence interval
cORR	confirmed objective response rate
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	end of treatment
HER2	human epidermal growth factor receptor 2
ICR	independent central review
IDI	Intended dose intensity
IM	intramuscular
INV	investigator assessment
IRR	infusion-related reaction
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
PR	partial response
PT	preferred term
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SMQ	standard MedDRA query
SMC	Safety Monitoring Committee

TEAE	treatment emergent adverse event
SD	stable disease
SOC	system organ class
ULN	upper limit of normal

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGNTUC-019, 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". 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

2.1 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

2.2 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

2.3 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
- To evaluate patient-reported outcomes (PROs)

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint in this study is the confirmed objective response rate (ORR) according to RECIST v1.1, per investigator assessment. The ORR is defined as the proportion of subjects with confirmed complete response (CR) or partial response (PR), per RECIST v1.1. Only response assessments before first documented PD or new anti-cancer therapies will be considered.

3.2 Secondary Endpoints

- Disease control rate (DCR; confirmed CR or PR, or stable disease) per investigator assessment
- Duration of response (DOR; for confirmed CR or PR) per investigator assessment
- Progression-free survival (PFS) per investigator assessment
- Overall survival (OS)
- 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

3.3 Other Endpoints

- Concordance of HER2 alterations as detected by different testing methodologies
- Identify tumor-specific alterations that are associated with resistance to tucatinib
- 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)

4 STUDY DESIGN

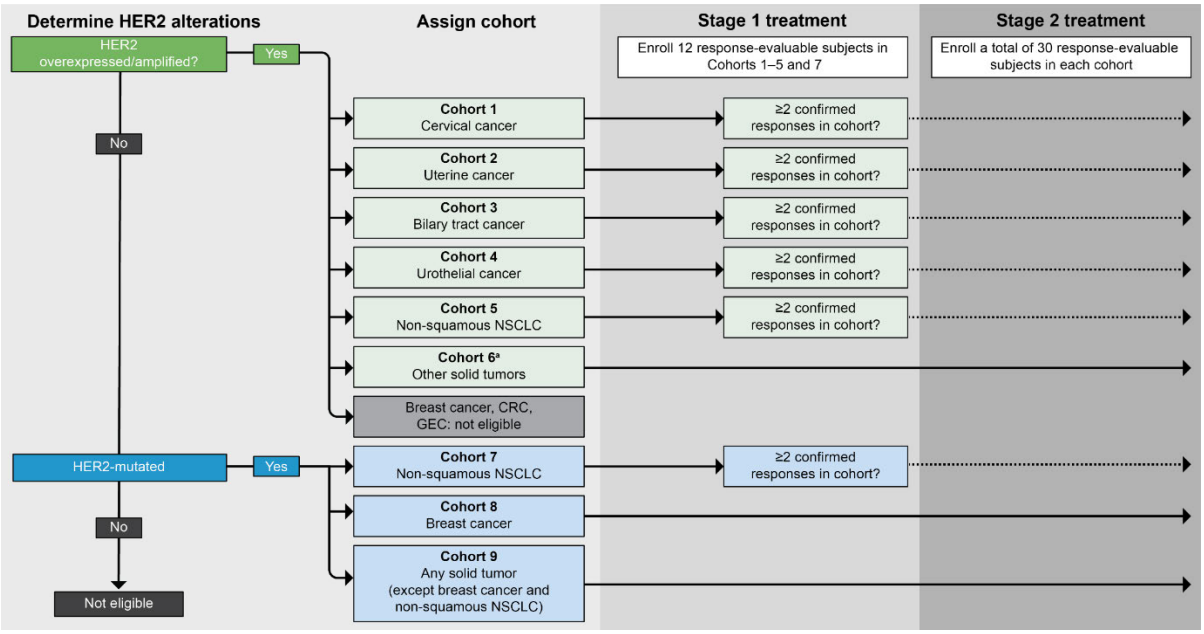
This multi-cohort, open label, multicenter, international Phase 2 clinical study is designed to assess the activity, safety, and tolerability of tucatinib in combination with trastuzumab for the treatment of selected solid tumors with HER2 alterations.

Subjects will be enrolled into separate cohorts based on tumor histology and HER2 alteration status (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 and [Cohort 7] breast cancer [Cohort 8]), and 2 cohorts which will enroll all other HER2 overexpressed/amplified 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).

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 6.10.1). 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 will be replaced.

Figure 2 Study Design



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. An SMC Charter will outline the committee's composition, members' roles and responsibilities, and describe SMC procedures.

The determination of antitumor activity will be based on the confirmed objective response rate as defined by RECIST v1.1 (Eisenhauer 2009). Clinical management decisions will be based on local investigator assessment (INV). Images will be collected by an independent central review (ICR) facility for possible future analysis. Clinical response of CR, PR, SD, non-CR/non-PD, 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. Response/Efficacy assessments will be performed at protocol-specified time points outlined in Protocol Section 7.2 and Schedule of Events.

5 ANALYSIS SETS

5.1 Full Analysis Set

The Full Analysis Set (FAS) will include all subjects who are enrolled in the study and received any amount of study treatment. PFS and OS will be analyzed using this analysis set.

5.2 Safety Analysis Set

The safety analysis set will include all subjects who receive any amount of study drug. Safety will be analyzed using this analysis set.

5.3 Response Evaluable Set

The Response-Evaluable analysis set includes all subjects who meet the following 3 criteria: (1) had a baseline disease assessment, (2) received study treatment, and (3) had post-baseline disease assessment or discontinued treatment due to documented disease progression or clinical progression. Response Evaluable Set will be used for analysis of selected efficacy endpoints.

5.4 PK Analysis Set

The PK analysis set will include all subjects in the safety set from whom at least one evaluable PK assessment was reported. The PK analysis set will be used for PK analysis.

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 90% level.

The two-sided 90% 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 analysis, 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). For tie-breaking method for survival analysis, we will use **Efron** in Cox regression.

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. Other statistical software, if used, will be described in the CSR.

6.2 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 6.10.1) 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%)

6.3 Randomization and Blinding

This is an open-label study. No randomization will be utilized. Blinding will not be performed.

6.4 Data Transformations and Derivations

6.4.1 Data Conventions, Definitions, and Formulas

The following data conventions will be used for the tables, listings, and figures.

- **Age**: Reported age in years will be used
- **Study treatment**: tucatinib, trastuzumab or fulvestrant. In this study, subjects are considered to be on study treatment if they are receiving any of the study drugs (tucatinib, trastuzumab, or fulvestrant).
- **Baseline:** Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study treatment

(tucatinib, trastuzumab, or fulvestrant). If there are multiple values that are qualified for baseline definition, for continuous values, the average of these values will be used as baseline value; for categorical values, the value of the assessment indicating better status will be used as baseline to be conservative for the analyses related to change from baseline.

- **Study Day**: Study day will be calculated for safety endpoints relative to the first dose of study treatment (tucatinib, trastuzumab or fulvestrant). 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. For subjects enrolled but not treated, Study day will be calculated relative to the date of enrollment. The date of enrollment will be 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

- **Duration of treatment** (except when calculating exposure) is defined as the time from first dose date to the earliest of the following dates:
  - The last dose date:
    - For tucatinib, the date of last dose
    - For trastuzumab, date of last dose +20
    - For fulvestrant, date of last dose +13 if last dose date is Cycle 1 Day 1 or Cycle 1 Day 15; date of last dose + 27 if last dose date is after first cycle.
  - Date of death
  - End of study date
  - Analysis data cutoff (DCO) date if the subject is still on study at the time of DCO.

- **Total cumulative dose administered of tucatinib (mg), trastuzumab (mg/kg) and fulvestrant (mg):**

  Total cumulative dose administered (*units*) = $\sum_{i=1}^{n}(dose_i)$

where i = dose number, $dose_i = i^{th}$ dose received (*units*), n = total number of doses received

- **Intended dose intensity (IDI):** the intended dose of drug per unit of time (day).

  For example,

  - tucatinib: IDI = 300mg BID = 600 (mg/day);

- **Absolute dose intensity (ADI):** the actual dose per unit of time that the subject received over the duration of exposure for that study drug.

  ADI = Total cumulative dose administered/ Duration of treatment (days), where the duration of treatment is similar to the definition above without taking into account the date of death, EOS or DCO.

- **Relative dose intensity (RDI):** the percent of the intended dose intensity over the entire treatment period:

  RDI = ADI/IDI * 100%

- **Adequate tumor 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.

- **Response assessment date:** 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

  In the cases where a PD occurs due to the fact that an equivocal new lesion was later confirmed to be an unequivocal new lesion, the PD date should be back dated to the visit when the equivocal new lesion was first identified if the equivocal new lesion continued to be present. If an equivocal new lesion was later absent or confirmed to be a benign lesion, then this new lesion is not considered to define a PD. Note: in cases where PD occurs at a date after an equivocal new lesion is identified, but the progression is not due to a change of the equivocal new lesion to an unequivocal lesion, but rather from progression of other lesions, the PD date will not be back dated, but will be the date when definitive PD is recorded.

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).

- **Best Overall Response:** The subject's best overall response 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 cORR.

  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 start of treatment and the subject does not qualify for confirmed CR or PR.

6.4.2 Dose Modifications

For tucatinib, dose held includes dose hold; dose reduced includes dose reduction; drug withdrawn is discontinuation of tucatinib permanently.

For trastuzumab, dose held includes dose delay and dose elimination; drug interrupted includes infusion interrupted (received full dose w/in 24hrs), and infusion stopped early (full dose not received); drug withdrawn is discontinuation of trastuzumab permanently.

For fulvestrant, dose held includes dose delay and dose elimination; dose reduced includes dose reduction; drug withdrawn is discontinuation of drug permanently.

6.5 Handling of Missing Data

Missing data will not be imputed unless otherwise specified.

For time-to-event endpoints, subjects who have no specific 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 for the purpose of calculating the time from prior therapy to first dose of study drug (see Appendix C for details).

Partial subsequent anticancer therapy start date will be imputed for the purpose of deriving the time-to-event endpoints as applicable (see Appendix D for details).

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 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 half of LLOQ (i.e. LLOQ/2) when a numeric value is required (e.g., calculating the mean) 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

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

6.7 Multiple Comparison/Multiplicity

No multiple comparison is planned and no alpha adjustment is needed.

6.8 Examination of Subgroups

No formal subgroup analysis is planned.

6.9 Covariates

No adjustment for covariates is planned in the analyses.

6.10 Timing of Analyses

Interim 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. If the minimal required responses are observed in fewer than 12 subjects, then the interim analysis may be performed earlier.

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.

The final analysis for this study will occur after all subjects have completed their treatment and the follow-up period or following study termination by the sponsor.

6.10.1 Interim Analysis

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. 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, i.e., if the minimal required responses are observed in fewer than 12 subjects.

7 PLANNED ANALYSES

The analyses will be summarized by:

(1) cohort;

(2) disease type, for instance, cohort 5+7, cohort 1+10, et.al;

(3) HER2 alteration, one table for HER2 overexpression/amplification cohorts and the other for HER2 mutations cohorts;

(3) all subjects combined.

7.1 Disposition

Subject enrollment and disposition will be summarized by cohort. The table will present the number and percentage of subjects who were enrolled, received study drug and participated in follow-up visits. The number and percentage of subjects who discontinued treatment will be summarized by the reason for treatment discontinuation. The number and percentage of subjects who discontinued the study will be summarized by the primary reason for study discontinuation.

Number of subjects who signed informed consent and number of subjects in each analysis set will be summarized.

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 subjects enrolled at each site will be summarized.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age at consent, sex, ethnicity, race, baseline height, weight, body mass index, ECOG performance status will be listed and summarized with descriptive statistics for safety analysis set per cohort.

Disease specific characteristics will be listed and summarized for the safety analysis set per cohort.

Summary of prior cancer-related therapies, including number of prior therapies, therapy type, setting of prior therapies, best response to prior therapies, and time from most recent prior therapy to first dose of study drug, will be presented for the safety analysis set.

In addition, the pre-existing conditions that are ongoing at baseline will be summarized.

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. 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.

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

- Total number of treatment cycles per subject
- Duration of treatment
- Total cumulative dose
- Percentage of subjects with dose reduced, held, and withdrawn infusions/doses overall and by reason
- Absolute dose intensity (ADI) and relative dose intensity (RDI).

IDI/ADI/RDI will only be summarized for tucatinib.

For tucatinib, the type, reason and time to first dose modification will be summarized. For all study treatment, the total number of dose modifications and reasons will also be summarized.

7.5 Efficacy Analyses

The efficacy analyses except for PFS and OS will be performed using the response evaluable set. Analyses of PFS and OS, as well as sensitivity analysis of cORR will be presented using the full analysis set.

The primary endpoint of this study is the cORR per investigator. 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. ORR per ICR may also be evaluated.

The cORR per investigator and its exact two-sided 90% CI will be calculated for the response evaluable set per cohort.

Duration of response (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.
- Subject have PD or death occurred after two or more consecutive missing scheduled response assessments will be censored at the date of last adequate response assessment of CR, PR, SD, or non-CR/non-PD

DOR per investigator will only be calculated for subjects achieving a confirmed CR or PR per investigator. DOR will be analyzed using Kaplan Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its two-sided 90% CI will be calculated. In addition, the DOR at 6 and 12 months will be summarized. DOR per ICR may also be evaluated. Sensitivity analysis for DOR taking clinical progression into account may be considered.

The maximum percent reduction from baseline in the sum of diameters per investigator will be calculated for each subject and presented graphically with a waterfall plot per cohort. Waterfall plot may also be presented for all response-evaluable subjects.

Time to response will be calculated as the time from the first dose of study treatment to the first documentation of objective response (CR or PR that is subsequently confirmed). Time to response per cohort will be summarized for the responders only.

Disease control rate (DCR) is defined as the proportion of subjects with confirmed CR, confirmed PR, or stable disease (SD or non-CR/non-PD) according to RECIST version 1.1. The DCR per investigator and its exact two-sided 90% CI will be calculated for the response evaluable set per cohort. DCR per ICR may also be evaluated.

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. The same derivation of PD date and censoring rules as for DOR will apply for PFS. PFS per cohort will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its two-sided 90% CI will be calculated for safety analysis set per cohort. Sensitivity analysis for PFS taking clinical progression into account may be considered.

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 (i.e., 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 (i.e., OS duration of 1 day).

7.6 Safety Analyses

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

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 5.0).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (version: June 2016 or more recent).

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, trastuzumab or fulvestrant). See for details regarding treatment-emergent classification in Appendix B.

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
- 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

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 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

The incidence of treatment emergent adverse events of special interest (AESI) will be summarized by PT or lab values and listings also produced. The AESI outputs will be generated based on lab data. In addition, serious AESI, treatment-emergent AESI that are related to study drug, leading to dose modification and study treatment discontinuation will be summarized.

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

Time to 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. In the analysis of time to onset of AE of a specific grade (e.g., grade 3 or higher), episode of events that are improved from a previous higher grade will not be included.

Resolution is defined as event outcome of 'recovered/resolved' or 'recovered/resolved with sequelae', or returning to baseline grade as of the latest assessment for conditions that are ongoing at baseline. 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. For events that return to baseline grade, time to resolution will be calculated as time from the start of treatment-emergent event to the date the event was last assessed.

For events that are not resolved, improvement is defined as decrease by at least one grade from the worst grade as of the latest assessment. For events that meet the definition of 'improvement', time to improvement will be calculated as time from the worst grade of the event to the date the event was last assessed.

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

7.6.4 Clinical Laboratory Parameters

All laboratory results (hematology and serum or plasma chemistry and liver function) up to the end of treatment visit 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 5.0) grade will be summarized for each lab test. Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results and NCI CTCAE (version 5.0) grades for hematology and serum chemistry will be presented in data listings. 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 (within 21 days of AST and/or ALT elevation) + 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 Deaths

Death information will be summarized and listed by subjects.

7.6.6 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.

7.6.7 Other Safety Analyses

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 performance status will be listed.

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

7.7 Health-Related Quality of Life

Health-related quality of life/health status using the EQ-5D-5L instrument will be analyzed for safety analysis set. Figures may be produced for utility score. The compliance rate of the PRO assessments will be summarized for each visit. Compliance rate is defined as the proportion of subjects who completed the instrument among those who are expected to complete at a given visit (i.e., subjects started the given cycle).

7.8 Pharmacokinetics Analyses

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

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

8 CHANGES FROM PLANNED ANALYSES

8.1 Changes from the Original SAP

Not Applicable.

9 REFERENCES

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10 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.
- 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
  2. AE Start Date on or after first dose date of study treatment
  3. AE Start Date ≤ last dose date of any study treatment + 30 days

- If the first episode (logline) is marked as TEAE, then all subsequent loglines should also be considered as TEAE, even if the later loglines may start after last dose date of any study treatment + 30 days.

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 treatment, whichever is earlier.

Appendix D: Imputation of Partial Missing Subsequent Anticancer Therapy Start Date

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

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