STATISTICAL ANALYSIS PLAN

Protocol Number:	SGNTUC-025
Protocol Version:	Amendment 2; 03-Dec-2021
Protocol Title:	A Single Arm, Open Label Phase 2 Study of Tucatinib in Combination with Trastuzumab Deruxtecan in Subjects with Previously Treated Unresectable Locally-Advanced or Metastatic HER2+ Breast Cancer
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APPROVAL SIGNATURES

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SAP Author:	PPD, Study Statistician

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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
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
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	end-of-treatment
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
HER2	human epidermal growth factor receptor 2
ICR	Independent Central Review
IDI	intended dose intensity
IHC	immunohistochemistry
ILD	interstitial lung disease
INV	investigator
IV	intravenous
LA/M	locally advanced/metastatic
LFT	liver function test
LLOQ	lower limit of quantification
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Affairs
NCI	National Cancer Institute
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PP	per protocol
PR	partial response
PRO	patient reported outcome

PT	preferred term
QoL	quality of life
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
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-025, entitled "A Single Arm, Open Label Phase 2 Study of Tucatinib in Combination with Trastuzumab Deruxtecan in Subjects with Previously Treated Unresectable Locally-Advanced or Metastatic HER2+ Breast 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

This study will evaluate the safety and efficacy of tucatinib in combination with trastuzumab deruxtecan in subjects with unresectable locally advanced/metastatic (LA/M) human epidermal growth factor receptor positive (HER2+) breast cancer, with and without brain metastases, who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab)..

2.1 Primary Objective

To determine the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan as measured by confirmed objective response rate (cORR) according to investigator (INV) assessment

2.2 Secondary Objectives

Efficacy

- To evaluate the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan as measured by progression-free survival (PFS) according to INV assessment
- To evaluate the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan as measured by duration of response (DOR) according to INV assessment
- To evaluate the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan as measured by disease control rate (DCR) according to INV assessment
- To assess overall survival (OS) in subjects treated with tucatinib given in combination with trastuzumab deruxtecan

Safety

- To assess the safety and tolerability of tucatinib given in combination with trastuzumab deruxtecan

2.3 Exploratory Objectives

Efficacy

- To evaluate the antitumor activity of tucatinib given in combination with trastuzumab deruxtecan according to independent central review (ICR) assessment

Pharmacokinetic

- To evaluate the pharmacokinetics (PK) of tucatinib

Biomarker

- To explore correlations between blood-based or tissue biomarkers and clinical outcomes

Patient Reported Outcomes

- To assess patient-reported outcomes (PROs) associated with tucatinib given in combination with trastuzumab deruxtecan

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- cORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 according to INV assessment

3.2 Secondary Endpoints

Efficacy

- PFS per RECIST v1.1 according to INV assessment
- DOR per RECIST v1.1 according to INV assessment
- DCR per RECIST v1.1 according to INV assessment
- OS

Safety

- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and lab abnormalities
- Frequency of dose modifications and treatment discontinuations
- Other relevant safety variables

3.3 Exploratory Endpoints

Efficacy

- cORR per RECIST v1.1 according to ICR assessment
- PFS per RECIST v1.1 according to ICR assessment
- DOR per RECIST v1.1 according to ICR assessment
- DCR per RECIST v1.1 according to ICR assessment

Pharmacokinetic

- Plasma concentrations of tucatinib

Biomarker

- Potential biomarkers of response, resistance, or toxicity from blood-based or tumor samples

Patient Reported Outcomes

- Change from baseline in PRO assessments of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L)

4 STUDY DESIGN

This is a single-arm, open-label, multi-center phase 2 trial designed to assess the safety and efficacy of tucatinib in combination with trastuzumab deruxtecan for the treatment of subjects with previously treated unresectable LA/M HER2+ breast cancer with or without brain metastases who have received prior treatment with a taxane and trastuzumab (with or without pertuzumab) in the LA/M setting or progressed within 6 months after neoadjuvant or adjuvant treatment involving a regimen including a taxane and trastuzumab (with or without pertuzumab).

There will be 2 cohorts in the study, 1 for subjects without brain metastases (Cohort A) and 1 for subjects with a history of brain metastases (Cohort B).

A Safety Monitoring Committee (SMC) will continuously monitor subjects for deaths, study treatment and study drug discontinuations, AEs, serious adverse events (SAEs), dose modifications, and laboratory abnormalities throughout the course of the study.

Safety Lead-in

Ten subjects will be enrolled, irrespective of cohort, in the safety lead-in portion of the study and receive tucatinib 300 mg PO twice daily (BID) and trastuzumab deruxtecan 5.4 mg/kg via intravenous (IV) infusion on Day 1 of each of 21-day cycle. The subjects enrolled in the safety lead-in will undergo the same efficacy, PK, and biomarker analyses as all other subjects with the exception of an additional PK assessment performed at Cycle 1, Day 12. Once 10 subjects are enrolled in the safety lead-in, enrollment will be paused until all

subjects have been followed for at least 1 cycle and a comprehensive review of the safety profile by the SMC has occurred. The SMC will make recommendations regarding continuing with enrollment if the safety and tolerability of the regimen is acceptable. If clinically significant safety events are observed at any point during the safety lead-in, enrollment will be paused until relatedness has been determined, and review by the SMC has occurred. Based on the totality of the safety data, the SMC may recommend proceeding with enrollment, evaluation of alternative dosing, or not proceeding with further enrollment. The SMC may also recommend expanding the safety lead-in to enroll up to approximately 10 additional subjects with continued monitoring for safety by the SMC.

Post-safety Lead-in

Following the safety lead-in, enrollment will continue until approximately 60 response evaluable subjects have been enrolled at the SMC recommended dose, with approximately 30 subjects enrolled into each cohort. All subjects, including those in the safety lead-in, treated at the SMC recommended dose, will be included in the efficacy analysis. Additional optional cohorts evaluating the combination of tucatinib and trastuzumab deruxtecan in earlier treatment lines for breast cancer, such as the first-line metastatic setting or neoadjuvant/adjuvant setting, may be added. Optional cohorts may also be opened in other malignancies, such as non-small cell lung cancer, urothelial cancer, gastric/gastroesophageal junction cancer, and colorectal cancer.

The incidence of diarrhea, though predominantly low grade, has resulted in dose modifications of tucatinib, and prophylactic antidiarrheals have been recommended by the SMC. Antidiarrheal prophylaxis will be required for all subjects following protocol amendment 2. Antidiarrheal prophylaxis will be administered for the first 42 days of study treatment. Following this initial 42-day period, subjects may continue on antidiarrheal prophylaxis or be switched to symptomatic treatment of diarrhea, at the investigator's discretion.

For all subjects in the study, measures of antitumor activity will be assessed by radiographic scans and additional imaging assessments (if applicable) at protocol-specified time points (outlined in Section 6 and Appendix A in the protocol), or if disease progression is suspected. Efficacy assessments will be made at each time point according to RECIST v1.1 (Eisenhauer 2009) by the investigator, with confirmation required ≥4 weeks from the first documentation of response. In addition, images will be collected by an ICR facility for possible future analysis.

5 ANALYSIS SETS

5.1 All Treated Subjects Analysis Set

The all treated subjects analysis set includes all subjects who receive any amount of study drug (tucatinib and/or trastuzumab deruxtecan). The analyses of PFS, OS, and safety will be based on this analysis set.

5.2 Response-evaluable Analysis Set

The response-evaluable analysis set is defined as all subjects with measurable disease who (1) had a baseline disease assessment, (2) received at least one dose of study drug (tucatinib and/or trastuzumab deruxtecan), and (3) had at least 1 post-baseline assessment or discontinued treatment due to PD, clinical progression, toxicity, or death. The analyses of cORR, DCR, and DOR will use the response-evaluable analysis set.

5.3 Pharmacokinetics (PK) Analysis Set

The pharmacokinetic analysis set will include all enrolled subjects who received at least one dose of study treatment and had at least one evaluable PK assessment.

5.4 PRO Analysis Set

The Patient Reported Outcomes (PRO) analysis set will include all subjects who received at least one dose of study treatment and have an evaluable (ie, completed at least one question of the PRO instrument) baseline PRO score and at least one evaluable post-baseline PRO assessment.

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 (Clopper & Pearson 1934) will be calculated for the response rates where applicable (eg, cORR).

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).

Unless otherwise specified, analysis tables will be presented by cohorts (cohort A- subjects without brain metastases; cohort B- subjects with brain metastases) where applicable. Protocol amendment 2 required antidiarrheal prophylaxis to be administered for the first 42 days of study treatment unless contraindicated, while previous versions of the protocol did not have this requirement. To review the effectiveness of this measure, safety outputs will be presented by prophylaxis group defined as subjects treated under protocol amendment 2 (with prophylaxis) and subjects treated under the previous protocol versions (no prophylaxis), unless otherwise specified.

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 9.4 or more recent. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

Approximately 60 to 70 subjects will be enrolled to ensure about 60 subjects will be treated at the SMC recommended dose, with approximately 30 per cohort (HER2+ MBC with or without brain metastases).

For illustration purposes, Table 6- summarizes the expected 95% CIs of cORR for the overall study (N=60) and by cohort (N=30), which shows reasonable precision for the estimation.

Table 6-1: Expected 95% CI of cORR for different number of responses

Number of subjects	Number of Responses	cORR	95% exact CI
60	40	66.7%	(53.3%, 78.3%)
	42	70.0%	(56.8%, 81.2%)
	44	73.3%	(60.3%, 83.9%)
	46	76.7%	(64.0%, 86.6%)
	48	80.0%	(67.7%, 89.2%)
	50	83.3%	(71.5%, 91.7%)
	52	86.7%	(75.4%, 94.1%)
30	20	66.7%	(47.2%, 82.7%)
	22	73.3%	(54.1%, 87.7%)
	24	80.0%	(61.4%, 92.3%)
	26	86.7%	(69.3%, 96.2%)

6.3 Randomization and Blinding

This is a single-arm and open-label study. Randomization and blinding will not be performed.

6.4 Data Transformations and Derivations

6.4.1 General

Age: Reported age in years will be used.

Study Day: Study day will be calculated as (assessment date – first dose date + 1) for dates on or after the first dose date. For dates prior to the first dose date, study day will be calculated as (assessment date – first dose date). For all calculation of study day, the first dose date will be the earliest date of treatment administration for tucatinib or trastuzumab deruxtecan.

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

The following unit conversion will be implemented unless otherwise specified:

Months=Days/30.4375

Years=Days/365.25

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 drug.

End-of-treatment (EOT) date: The end-of-treatment (EOT) date will be the date the EOT visit is performed or the decision-making date to end treatment if EOT visit date is not available; if an EOT visit is not performed and EOT decision date is not available, then the EOT date will be either the EOS date or 30 days after the last dose of any study drug, whichever is earlier.

6.4.2 Best Overall Response

The subject's best overall response will be the best response per RECIST v1.1. 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 from the first documentation of response) still shows response (CR or PR). A subject will have a best response of SD if there is at least one SD assessment (or better) ≥ 5 weeks after the start of treatment and the subject does not qualify for confirmed CR or PR.

6.4.3 Response Assessment Dates

At each response assessment time point, scans to evaluate tumor lesions can be performed on multiple dates. If the time point response is CR, PR or not evaluable (NE), 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, ie, 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 an equivocal new lesion was later confirmed to be a truly (unequivocal) new disease lesion, the PD date should be back dated to the visit when the equivocal new

lesion was first identified. The tumor response on the date when the equivocal new lesion was first identified will be changed to PD. 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. In cases where PD occurs on 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 CR or PR that is subsequently confirmed.

6.4.4 Adequate Response Assessment

An adequate tumor assessment must include a radiologic scan with the overall disease response of CR, PR, SD, non-CR/non-PD, or PD. Scans with the overall response not evaluable (NE) will not be considered an adequate response assessment for the purpose of PFS and DOR censoring.

6.5 Handling of Dropouts and Missing Data

With the exception of the scenarios covered in this section, missing data will not be imputed.

Subjects who do not have at least two (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders for analysis of cORR.

For time-to-event endpoints (eg, DOR, 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 duration of events and determining the 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).

Partial disease diagnosis dates will be imputed for calculating time to enrollment (see Appendix E for details).

For deriving time-to-event endpoint, partial death date will be imputed as specified in Appendix F.

Unless otherwise specified, lab values which are recorded or provided as being less than the lower limit of quantification (LLOQ) will be included in figures and analysis as LLOQ when a numeric value is required (eg, calculating the mean) and listed as "<LLOQ" in the listings.

6.6 Multicenter Studies

There are multiple centers in this study; however, it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

No multiple comparison is planned and no alpha adjustment is needed in this phase 2 study.

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)
- Hormone receptor status (positive, negative)
- HER2 testing result [immunohistochemistry (IHC) 3+, other]

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

6.9 Covariates

No adjustment for covariates is planned in the analyses.

6.10 Timing of Analyses

A safety analysis will be undertaken by the SMC when the first 10 treated subjects have been followed for at least 1 cycle (safety lead-in stage). The SMC will undertake similar analyses if alternative tucatinib and/or trastuzumab deruxtecan dose levels or schedules are evaluated in additional safety lead-in stage(s). Once the safety lead-in stage is completed, the SMC will evaluate the safety of the study regimen throughout the remainder of the study.

The primary efficacy analysis will be undertaken when approximately 60 response-evaluable subjects have been treated at the SMC recommended dose and followed for at least 6 months.

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

Analysis set: All Treated Subjects Set

Subject disposition will be summarized by cohort and total. The table will present the number of subjects who received study drug and participated in long-term follow-up. 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.

The number of subjects in each analysis set will be summarized by cohort and total.

The number of subjects who signed the informed consent will be summarized. The number of screen failures and the percentage relative to the total number of subjects screened will be summarized with reasons for screen failure. A listing of subjects screened will be produced, with reasons for screen failure.

Disposition data will be listed by subject using the All Treated Subjects analysis set.

7.2 Demographic and Baseline Characteristics

Analysis set: All Treated Subjects Set

Demographics and baseline characteristics, including age, sex, ethnicity, race, baseline height, weight, and ECOG performance status will be listed and summarized with descriptive statistics by cohort and total.

The following disease history, prior disease-related therapies and baseline disease-specific characteristics will be summarized.

- Time (months) from initial diagnosis of breast cancer to enrollment
- Time (months) from metastatic diagnosis to enrollment
- Unresectable locally advanced breast cancer (yes, no)
- Stage at initial diagnosis
- HER2 status
- History of brain metastases at study entry
- Estrogen/progesterone receptor status
- Non-CNS locally advanced unresectable or distant metastatic disease sites
- Brain metastases treatment status at baseline
    - Treated stable: subjects previously treated by resection, whole brain radiation or targeted radiation/stereotactic radiation surgery, had no progression at baseline
    - Treated progressive: subjects previously treated by resection, whole brain radiation or targeted radiation/stereotactic radiation surgery, had progressive tumor state at baseline
    - Untreated: subjects with brain metastases history, but was untreated and/or had new tumor state at baseline

- Time (months) from date of first diagnosis of brain metastases to enrollment in subject previously diagnosed with brain metastases
- Prior surgery and/or radiotherapy for brain metastases (yes, no)
- Type of prior radiotherapy for brain metastases (whole brain vs. targeted radiation/ stereotactic radiation surgery)
- Prior systemic therapies

7.3 Protocol Deviations

Analysis set: All Treated Subjects Set

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 will be summarized by category. A list of subjects with important protocol deviations will be presented.

7.4 Treatment Administration

Analysis set: All Treated Subjects Set

Treatment administration will be summarized for each treatment agent by prophylaxis group and total. Summary statistics for duration of treatment and the number of cycles per subject will be presented. Absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of subjects whose dose was ever modified for each study drug will be summarized in tables by modification type (eg, dose reduction, dose delay, dose hold, and dose interruption as applicable); listings may be presented as well.

The type, reason, and time to first dose modification will also be summarized.

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

1. For tucatinib, the date of last dose; For trastuzumab deruxtecan, date of last dose + 20.
2. Date of death
3. End of study date
4. Analysis data cutoff (DCO) date if the subject is still on treatment 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.

- **Tucatinib:** the planned dose is 300 mg BID. Thus, the IDI is 600 mg/day.

- **Trastuzumab deruxtecan:** the planned dose is 5.4 mg/kg on Day 1 of each 21-day cycle. Thus, the IDI=5.4 mg/kg/3-weeks.

Cumulative Dose is the sum of the actual doses that a subject received across all cycles.

Absolute Dose Intensity (ADI) is defined as the actual dose of study drug per unit of time that a subject received over the exposure duration, ie, ADI = cumulative dose/exposure duration.

The exposure duration is defined as time from the first dose date to the last dose date for tucatinib, and time from the first dose date to the last dose date + 20 for trastuzumab deruxtecan.

Relative Dose Intensity (RDI) = ADI/IDI * 100%.

7.5 Efficacy Analyses

Efficacy analyses will be provided for all subjects and by cohorts. In situations when the total number of events is less than 5 in any cohort, PFS will only be summarized for all subjects. Similarly, in situations when the total number of events is less than 5 in any cohort, OS will only be summarized for all subjects.

7.5.1 Primary Endpoint

Analysis set: Response-evaluable Analysis Set

The primary endpoint of this study is the cORR according to INV assessment. The cORR is defined as the proportion of subjects with a confirmed CR or PR per investigator according to RECIST v1.1 (Eisenhauer 2009). Only tumor assessments up to the first documented PD and before the start of any new anti-cancer therapies will be considered. For a response to be considered 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 according to INV assessment and its exact two-sided 95% CI will be calculated by cohort and total.

In addition, the cORR according to INV assessment may be summarized by selected subgroups defined in Section 6.8.

The maximum percent reduction from baseline in the target lesion sum of diameters according to INV assessment will be calculated for each subject and presented graphically with a waterfall plot.

Time to response according to INV assessment may be calculated as the time from the start of study treatment to the first documentation of objective response (CR or PR that is subsequently confirmed).

7.5.2 Secondary Endpoints

7.5.2.1 Progression-free Survival (PFS) According to Investigator (INV) Assessment

Analysis set: All Treated Subjects Set

PFS is defined as the time from the start of the study treatment to the first documentation of PD per RECIST v1.1 or death due to any cause, whichever comes first.

Specifically,

PFS (days)=date of the first documented PD or death or censoring– start date of the study treatment (tucatinib or trastuzumab deruxtecan) +1.

PFS will be censored as described below:

1. Subjects who have no post-baseline response assessment will be censored on the start date of the study treatment.
2. Subjects who do not have PD or death at the time of an analysis will be censored on the date of the last adequate response assessment documenting absence of PD.
3. Subjects who have started a new anti-cancer treatment (systemic, radiation or surgery) prior to documentation of PD or death will be censored on the date of the last adequate response assessment prior to the start of the new treatment.
4. Subjects who progressed or died after ≥2 consecutive missed response assessments will be censored on the date of the last adequate response assessment prior to the missed visits.

PFS according to INV assessment will be analyzed using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS will be provided by cohort and total, with its two-sided 95% CI calculated using the complementary log-log transformation method (Collett,1994). In addition, the probability of PFS at different timepoints (for instance, 6, 12 months etc.) will also be calculated using the Kaplan-Meier estimate.

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

7.5.2.2 Duration of Response (DOR) According to Investigator (INV) Assessment

Analysis set: Response-evaluable Analysis Set

DOR is defined as the time from the date of the first documented objective response (CR or PR that is subsequently confirmed) to the date of the first documented PD per RECIST v1.1 or death due to any cause, whichever comes first. DOR will be censored according to the censoring rules for PFS outlined in Section 7.5.2.1 above.

DOR will only be calculated for subjects achieving a confirmed CR or PR. DOR according to INV assessment will be analyzed using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of response and its two-sided 95% CI using the complementary log-log transformation method (Collett,1994) will be calculated by cohort and total. In addition, the progression-free probability at different timepoints (for instance, 6, 12 months etc.) will be estimated using the Kaplan-Meier methodology.

7.5.2.3 Disease Control Rate (DCR) According to Investigator (INV) Assessment

Analysis set: Response-evaluable Analysis Set

DCR is defined as the proportion of subjects with confirmed CR, PR or stable disease (SD or non-CR/non-PD) per RECIST v1.1. Subjects in the analysis set whose disease response cannot be assessed will be classified as non-responders for calculating the DCR.

DCR according to INV assessment will be summarized by cohort and total. An exact two-sided 95% CI will be calculated using the Clopper-Pearson method.

7.5.2.4 Overall Survival (OS)

Analysis set: All Treated Subjects Set

OS is defined as the time from the start of study treatment to the date of death due to any cause:

OS=Date of death– start date of the study treatment (tucatinib or trastuzumab deruxtecan) +1.

In the absence of confirmation of death, OS will be censored on the date the subject is last known to be alive. Subjects who died after the analysis cutoff date or who are found to be alive after the analysis cutoff date from the long-term/survival follow-up visits will be censored on the analysis cutoff date. Subjects lacking data beyond the start of the study treatment will have their survival time censored on the start date of the study treatment.

OS will be analyzed using the Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its two-sided 95% CI using the complementary log-log transformation method (Collett,1994) will be provided by cohort and total. In addition, the probability of OS at different timepoints (for instance, 6, 12 months etc.) will also be calculated using the Kaplan-Meier estimate.

Duration of follow-up for OS will be summarized using the reverse KM method (Schemper and Smith, 1996).

7.5.3 Exploratory Endpoints

ICR assessments were not done for this study. The exploratory efficacy endpoints will not be analyzed.

7.6 Safety Analyses

Analyses of safety will be based on the All Treated Subjects set and summarized by prophylaxis group (as described in Section 6.1) and total, unless otherwise specified.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 27.0 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 the World Health Organization (WHO) Drug Dictionary (version Global B3 2024Mar or higher).

7.6.1 Adverse Events

Analysis set: All Treated Subjects Set

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 deruxtecan) and up through 30 days after the last dose of study treatment. See Appendix B 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 by PT (will be summarized by prophylaxis group and by cohort)
- Grade 3 or higher TEAEs by PT (will be summarized by prophylaxis group and by cohort)
- TEAEs leading to dose reduction/dose delay/dose hold/drug interruption/treatment discontinuation by PT
- Treatment-related TEAEs leading to dose reduction/dose delay/dose hold/drug interruption/treatment discontinuation by PT
- TEAEs leading to death by PT
- Treatment-related TEAEs by PT
- Treatment-related grade 3 or higher TEAEs
- TEAEs by SOC, PT and maximum severity. At each SOC or PT, multiple occurrences of events 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

Analysis set: All Treated Subjects Set

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

- Incidence of treatment emergent SAEs (TESAEs) by PT (will be summarized by prophylaxis group and by cohort)
- Incidence of treatment-related TESAEs by PT

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

7.6.3 Adverse Events of Special Interest

Analysis set: All Treated Subjects Set

The incidence of treatment-emergent adverse events of special interest (AESI) will be summarized by PT and maximum severity or lab values where applicable, and listings may also be produced. Treatment-emergent AESI leading to dose modification or study treatment discontinuation may be summarized.

The following AESIs to be summarized are also described in the protocol Section 7.7.1.1:

1. **Hepatotoxicity**

Any of the following types of liver function test (LFT) elevations by lab parameters:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations that are > 3 × upper limit of normal (ULN) with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 × ULN
- AST or ALT elevations > 20 × ULN
- Bilirubin elevation > 10 × ULN

Since hepatotoxicity is an important identified risk for tucatinib, the TEAEs based on the standard MedDRA query (SMQ) of Drug related hepatic disorders - comprehensive search (narrow) will also be summarized.

2. **Interstitial lung disease (ILD)/pneumonitis**

Potential events of ILD/pneumonitis will be identified based on the Interstitial lung disease SMQ search with narrow scope and including all severity grades.

3. **Left Ventricular Ejection Fraction (LVEF) decrease**

The following 2 types of LVEF decrease are considered AESIs:

- An asymptomatic decline in LVEF leading to a change in study treatment or discontinuation of study treatment. Use the term "ejection fraction decreased" and severity Grades 2 to 4 to report asymptomatic LVEF decrease.
- Symptomatic congestive heart failure (CHF). Use the term "heart failure" and severity Grades 2 to 5 to report symptomatic CHF.

4. **Diarrhea**

    - ≥ Grade 3 diarrhea
    - Grade 2 diarrhea with concomitant Grade 2 nausea and/or vomiting

Events above will be identified by single PT of "Diarrhoea", "Nausea" and/or "Vomiting".

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

Time to onset is defined as time from the date of first dose to the start date of the first treatment-emergent AESI event. Time to onset will be summarized at the subject level.

Resolution of selected adverse events will be defined as events with the outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'. Time to resolution will be calculated as time from the event start date to the event end date. Time to resolution will be summarized at the event level.

7.6.4 Clinical Laboratory Parameters

Analysis set: All Treated Subjects Set

All laboratory results (hematology, coagulation and serum chemistry) up through 30 days after the last dose of study treatment will be included. The collection schedules are specified in the Appendix A in the study protocol.

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 selected laboratory tests. Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results for hematology, serum chemistry, and coagulation will be presented in data listings with NCI CTCAE grade and flagged when values are outside the normal reference range. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented for selected hematology and serum chemistry tests.

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 the AST and/or ALT elevation) + Alkaline Phosphatase < 1.5 × ULN (within 21 days of the AST and/or ALT elevation) and (AST and/or ALT) > 3 × ULN, 5 × ULN, 10 × ULN, and 20 × ULN will also be summarized.

7.6.5 Ejection Fraction

Analysis set: All Treated Subjects Set

The minimum (worst) post-baseline ejection fraction and the maximum decrease from baseline will be summarized. Time to the worst post-baseline ejection fraction may also be tabulated for subjects with ≥ 10% decrease from baseline. Subject level ejection fraction data will be listed.

7.6.6 Vital Signs

Analysis set: All Treated Subjects Set

Vital signs (weight, body temperature, respiratory rate, heart rate, and systolic and diastolic blood pressure values) will be listed by subject and visit.

The frequency and percentage of subjects 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), respiratory rate > 20 breaths per min and oxygen saturation < 88%. Blood pressure will be summarized for subjects with systolic blood pressure ≥ 120 mmHg or diastolic blood pressure ≥ 80 mmHg, 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 Performance Status

Analysis set: All Treated Subjects Set

Shift from baseline to the worst post-baseline ECOG status will be tabulated. ECOG values up through 30 days after the last dose of study treatment will be included.

ECOG performance status for each scheduled visit will be listed.

7.6.8 Deaths

Analysis set: All Treated Subjects Set

The number of total deaths, deaths that occur within 30 days of the last study treatment, and deaths that occur more than 30 days after the last study treatment as well as the relationship to disease will be summarized. In addition, cause of death due to AE will be identified by MedDRA preferred term and summarized. Death information will be listed by subject.

7.6.9 Concomitant Medications

Analysis set: All Treated Subjects Set

Concomitant medications will be summarized by the WHO Drug Anatomical Therapeutic Chemical (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.

Antidiarrheal medication administration will be summarized for subjects in the 'With prophylaxis' group.

7.7 HER2 Status

Analysis set: All Treated Subjects Set

The analysis described in this section may be produced for an exploratory biomarker analysis.

HER2 levels may be summarized with descriptive statistics to explore potential thresholds for HER2 expression correlating with response to tucatinib. Additional analyses may be performed and described in a separate biomarker analysis plan.

7.8 Pharmacokinetics

Analysis set: PK Analysis Set

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

Individual (subject) plasma tucatinib and deruxtecan concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will also be calculated. Additional exploratory PK analyses may be conducted. Exploratory analyses investigating the relationship between tucatinib and/or deruxtecan exposure and efficacy and safety endpoints may be conducted.

For the calculation of summary statistics, <LLOQ results are imputed to ½ LLOQ value. The summary statistics for a timepoint will not be calculated if more than 50% of the results are <LLOQ.

7.9 Biomarker Analyses

Exploratory analyses for biomarker parameters will be defined in a separate Biomarker Plan and may be included in a separate report.

7.10 Patient Reported Outcomes

Analysis set: PRO Analysis Set

Electronic PRO (ePRO) assessments will include the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L). ePROs will be administered at Cycle 1 – Cycle 4 before study treatment and every 2 cycles starting at Cycle 6 through the end of treatment [EOT].

The EQ-5D-5L is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). In addition, this questionnaire also records the respondent's self-rated health status on a vertical visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

The following will be calculated for EQ-5D-5L by scheduled assessments by prophylaxis group and total:

- Compliance rate for EQ-5D-5L assessment
- Completion rate for EQ-5D-5L assessment
- Summary statistics of the actual value and change from baseline for VAS

Compliance rate is defined as the proportion of subjects who completed at least one question of the instrument among those who are expected to complete at a given visit.

7.11 Subsequent Anti-cancer Therapy

Analysis set: All Treated Subjects Set

The number and percentage of subjects who received subsequent systemic anti-cancer therapies will be summarized by cohort and total. Listing of subsequent anti-cancer therapy (including systemic, radiation or other therapies) will be provided by subject.

8 INTERIM ANALYSIS

There is no formal interim analysis planned. The SMC will review available safety and PK data once the first 10 subjects treated in the safety lead-in stage have been followed for at least 1 cycle. If alternative tucatinib and/or trastuzumab deruxtecan dose levels or schedules are evaluated, the SMC will undertake similar assessments in up to the first 10 subjects.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

- PRO analysis (exploratory endpoint): analysis of subscales and individual item scores included in protocol section 9.3.8 will not be provided. PRO analyses that will be performed are described in this analysis plan.
- Clinical laboratory analysis: changes from baseline in laboratory values by scheduled visit will not be summarized as specified in protocol section 9.3.9.3. Laboratory results by visit will be provided in data listings.

- ECOG analysis: summary of ECOG for each scheduled visit described in protocol section 9.3.9.4 will not be provided. Instead, ECOG by visit data will be provided in a listing. Shift from baseline to the worse post-baseline value will be tabulated.
- Data listings may be combined where appropriate, which may be different from the listings specified in protocol section 9.3.

9.2 Changes from the Original SAP

Not Applicable.

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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 cutoff 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 cutoff 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 cutoff 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. 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 any study treatment.
- 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 study treatment + 30 days

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 14 days before the first dose of study drug, whichever is earlier.
- For date of progression on prior therapy, impute the last day of the month or the day before study enrollment, 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.

- If the year of the subsequent anticancer therapy start date is the same as the year of the EOT date,
    - If the month of subsequent anticancer therapy start date is the same as the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the EOT date.
    - If the month of the subsequent anticancer therapy start date is later than the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the first day of the month.
    - If the month of the subsequent anticancer therapy start date is earlier than the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the last day of the month.
- If the year of the subsequent anticancer therapy start date is later than the year of the EOT date, then the subsequent anticancer therapy start date will be imputed as the first day of the month.
- If the EOT date is missing, then the EOT date will be the end-of-study (EOS) date or 30 days after the last dose of any study drug, whichever is earlier.

Appendix E: Imputation of Partial Missing Disease Diagnosis Dates

For calculating time to enrollment, partial disease diagnosis dates (eg, initial disease diagnosis date, earliest date disease was considered unresectable locally advanced, or earliest date disease was considered distant metastatic) will be imputed as below.

- If both month and year are present and only day is missing, impute to the first day of the month.
- If year is present and month and day are missing, impute to January 1 of the year.

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-known-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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