

Protocol C4251007 (SGNTUC-028)

A randomized, double-blind, phase 3 study of tucatinib or placebo in combination with trastuzumab and pertuzumab as maintenance therapy for metastatic HER2+ breast cancer (HER2CLIMB-05)

Statistical Analysis Plan (SAP)

Version: 2

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associat ed Protocol Amendm ent	Rationale	Specific Changes
1 13 Feb 2025	3 27 Aug 2024	N/A	N/A
2 15 Aug 2025	3 27 Aug 2024	- Regulatory input (FDA request) - Following Pfizer TLF reduction guidance - Clarification	- Clarified the Lan-DeMets O'Brien-Fleming approximation spending function will be employed to determine the boundaries for both pre-planned interim and final OS analyses (sections 5.1, 5.7, 6.5.1.1, 6.5.2.1, 8). - Removed or modified some TLFs (sections 5.8, 6.1.1, 6.2, 6.4, 6.6.1, 6.6.2, 6.6.4, 6.6.5, 6.7). - Included imputation rule of partial dates for corticosteroid (section 5.2, appendix 5), clarified which parties will be unblinded at the primary analysis for PFS (section 5.4.2), explained the arm used for the participants who switched regimen (section 6.4), added CNS-PFS censoring table (section 6.5.3.2), updated MedDRA and WHODrug version (section 6.6), deleted non-SAP related protocol language (section 6.6.1.1) while added lab based language (section 6.6.2), defined pregnancy SMQ search strategy (section 6.6.7), elucidated meaningful deterioration is adopted (section 6.8.1.1), stated exploratory biomarker analyses will be outlined in a separate analytical document (section 6.9), updated references (section 8), deleted unused abbreviations and added missed ones (appendix 6), and minor edits throughout the file to increase clarity.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4251007/SGNTUC-028.

2.1. Modifications to the Analysis Plan Described in the Protocol

N/A

2.2. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary	Compare progression-free survival (PFS) by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 between treatment arms	PFS, defined as the time from randomization to investigator-assessed documented disease progression per RECIST v1.1, or death from any cause, whichever occurs first
Key secondary	Compare overall survival (OS) between treatment arms	OS, defined as the time from randomization to death from any cause
Other secondary	Evaluate PFS by blinded independent central review (BICR) per RECIST v1.1	PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST v1.1), or death from any cause, whichever occurs first
	Assess the change in health-related quality of life (HRQoL)	Time to deterioration of HRQoL, defined as time to 10-point decrease in the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30)
	Evaluate PFS in the brain	Central nervous system (CNS)-PFS, defined as the time from randomization to investigator assessed- disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first
	Evaluate the safety and tolerability of tucatinib in combination with trastuzumab and pertuzumab	• Adverse events (AEs) • Clinical laboratory assessments • Incidence of dose holding, dose reductions, and discontinuations of tucatinib • Incidence of dose holding and discontinuations of trastuzumab • Incidence of dose holding and discontinuations of pertuzumab
	Evaluate the pharmacokinetics (PK) of tucatinib	Plasma concentrations of tucatinib
Exploratory	CCI [REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]

Type	Objective	Endpoint
		CCI

2.3. Study Design

This is a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and pertuzumab as maintenance therapy in participants with advanced HER2+ breast cancer who have had prior treatment with a taxane, trastuzumab, and pertuzumab. After signing informed consent and meeting all eligibility criteria, participants will be randomized in a 1:1 ratio to receive 21-day cycles of either tucatinib or placebo in combination with trastuzumab and pertuzumab in one of the following two treatment groups:

- Control arm: placebo given orally twice a day (PO BID) plus trastuzumab and pertuzumab every 21 days,
- Experimental arm: tucatinib 300 mg PO BID plus trastuzumab and pertuzumab every 21 days.

Trastuzumab and pertuzumab will be administered as follows:

- Trastuzumab will be given intravenously (IV) at a dose of 6 mg/kg or subcutaneously (SC) at a fixed dose of 600 mg, once every 21 days.

AND

- Pertuzumab will be given IV at 420 mg every 21 days.

OR

- Fixed dose combination of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase will be given SC, once every 21 days, in lieu of trastuzumab and pertuzumab individually.

Approximately 650 participants will be randomized in the study in a 1:1 ratio. Randomization will be stratified by diagnosis (de novo versus recurrent), hormone receptor status (positive versus negative), and presence or history of brain metastases (yes versus no).

Dose reductions of tucatinib or placebo will be allowed. Dose holding or discontinuation of tucatinib or placebo, trastuzumab, and/or pertuzumab will also be allowed as needed for participant safety. In the absence of progression, participants who discontinue trastuzumab and pertuzumab due to drug-related toxicity may continue receiving tucatinib/placebo alone, and participants who discontinue tucatinib/placebo may continue to receive trastuzumab and pertuzumab. If a participant discontinues either of the trastuzumab or pertuzumab, they are required to discontinue both. Any study drug that requires a delay ≥ 6 weeks between

sequential doses should be discontinued. These participants will still be required to complete all assessments as outlined in the Schedule of Events.

Study treatment will continue until unacceptable toxicity, disease progression (ideally verified radiologically per RECIST v1.1), withdrawal of consent, or study closure. No crossover from placebo to tucatinib will be allowed.

Disease response per RECIST v1.1 (Eisenhauer 2009) will be assessed by both investigator and BICR. This will include measurement of all known sites of tumor (including at a minimum the chest, abdomen, and pelvis), preferably by high quality spiral contrast computed tomography (CT), at baseline and every 9 weeks until progression per RECIST (irrespective of dose holds) or end of treatment (EOT), whichever is later. Any imaging that is conducted as per standard of care will be collected for retrospective BICR. Positron emission tomography (PET)/CT (if diagnostic-quality CT scan included), and/or MRI scan may also be done as appropriate, as well as additional imaging of any other sites of disease (e.g., skin lesion photography for skin lesions, imaging of the neck, or imaging by CT or MRI of bone metastases not captured by imaging of the chest, abdomen, or pelvis). Bone scans will be required at screening only for participants with known or suspected bone metastases and are to be repeated every 27 weeks (~6 months). Bone lesions identified at baseline and followed per RECIST v1.1 may be assessed via CT scan at response assessments where a bone scan is not performed. PET-CT scans (if high quality CT scan is included) may also be used as appropriate, but the same imaging modality as used at screening/baseline should be used throughout the study. Contrast-enhanced brain MRI is required for all participants at screening and at EOT and is to be repeated only for participants with a history of, or baseline, brain metastasis every 9 weeks. For participants without a history of, or baseline, brain metastasis, contrast-enhanced brain MRI is to be repeated every 27 weeks (~6 months). Additional contrast MRIs of the brain may be performed as clinically appropriate.

Treatment decisions will be made based upon local assessment of radiologic scans. Response assessments for each participant will continue until disease progression per RECIST v1.1 by investigator assessment has been documented or EOT, whichever is later. Survival and other follow-up assessments will continue until study closure or withdrawal of consent.

Participants will be assessed throughout the study for safety. Safety assessments including physical examinations, vital signs, collection of AEs and laboratory values (including pregnancy testing) and concomitant medications will be performed on Day 1 of each cycle throughout study treatment and approximately 30 days after the last dose of the last study drug. Day 1 of each cycle is determined by the dosing date of trastuzumab and pertuzumab. If participants have discontinued trastuzumab and pertuzumab, cycles will be defined as 21 days for tucatinib/placebo dosing. Laboratory assessments will be performed locally. Additional assessments may be added as clinically indicated. Assessment of cardiac ejection fraction will be performed by MUGA or ECHO at screening and at least once every 12 weeks thereafter until study discontinuation irrespective of dose delays or interruption, and at the EOT visit (unless done within 12 weeks prior to the EOT Visit, excluding screening/baseline assessment). AE and laboratory abnormality severity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.

A detailed study assessment schedule can be found in the protocol.

An external data monitoring committee (E-DMC) will monitor the safety of participants and provide an ongoing clinical assessment of the study treatment's evolving safety profile as the trial progresses. The E-DMC will review blinded and unblinded data that include study enrollment, treatment exposure, AEs, SAEs and selected clinical lab results. The E-DMC will meet on a regular basis and make recommendations to the sponsor regarding the conduct of the trial. Further details regarding the E-DMC activity are described in a separate E-DMC charter.

3. ENDPOINTS

3.1. Primary Endpoint

- PFS, defined as the time from randomization to investigator-assessed documented disease progression per RECIST v1.1, or death from any cause, whichever occurs first

3.2. Key Secondary Endpoint

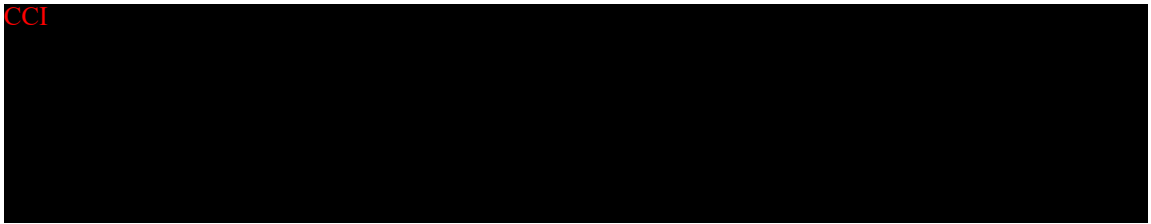
- OS, defined as the time from randomization to death from any cause

3.3. Other Secondary Endpoint(s)

- PFS, defined as the time from randomization to documented disease progression (as determined by BICR per RECIST v1.1), or death from any cause, whichever occurs first
- Time to deterioration of HRQoL, defined as time to 10-point decrease in the global health status/QoL scale of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30)
- Central nervous system (CNS)-PFS, defined as the time from randomization to investigator-assessed disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first
- Adverse events (AEs); Clinical laboratory assessments; Incidence of dose holding, dose reductions, and discontinuations of tucatinib; Incidence of dose holding and discontinuations of trastuzumab; Incidence of dose holding and discontinuations of pertuzumab.

3.4. Exploratory Endpoints

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4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database. Exceptions if any will be documented prior to unblinding per standard operating procedures.

Participant Analysis Set	Description
Intent-to-Treat (ITT) Analysis Set	The ITT analysis set will include all randomized participants. Participants will be analyzed according to the treatment arm assigned at randomization regardless of actual treatment received.
Safety Analysis Set	The safety analysis set will include all randomized participants who receive at least one dose of study treatment (tucatinib or placebo, or trastuzumab or pertuzumab). Treatment groups will be determined using the actual treatment received. A participant will be considered as in tucatinib treatment group in the Safety Analysis Set as long as this participant received any dose of tucatinib.
Patient Reported Outcomes (PRO) Analysis Set	The PRO Analysis Set will include all randomized participants who have received at least one dose of study treatment and have completed at least one instrument for baseline and at least one instrument for post-baseline. An instrument is considered completed for a visit if at least one valid score was available for that visit. Participants will be analyzed according to the treatment arm assigned at randomization regardless of actual treatment received.
Pharmacokinetics (PK) Analysis Set	The PK analysis set for tucatinib will include all randomized participants who received at least one dose of tucatinib and from whom at least one blood sample was collected and evaluable (i.e. at least one non-missing PK result) for PK test. Participants will be evaluated based on the actual treatment received. The PK analysis set will be used for the PK analyses.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. General Methods

Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables. The median survival time will be estimated using the Kaplan-Meier method; the associated confidence interval (CI) will be calculated based on the complementary log-log transformation ([Brookmeyer and Crowley 1982](#), [Kalbfleisch and Prentice 2002](#)).

Unless otherwise specified, all statistical tests will be performed using a two-sided alpha of 0.05. Confidence intervals will be calculated at a two-sided 95% level. Multiplicity adjustment for alpha level is discussed in Section [5.7](#).

Any analysis not described in this plan will be considered exploratory and will be documented in the clinical study report (CSR) as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR.

All statistical tables, listings, and figures will be produced using SAS, version 9.3 or more recent. Other statistical software, if used, will be described in the CSR.

5.2. Methods to Manage Missing Data

Except for the scenarios covered in this section, missing data will not be imputed.

Missing disease diagnosis date will be imputed for the purpose of calculating the time from diagnosis to date of randomization ([Appendix 1](#)).

Missing AE dates will be imputed for the purpose of calculating duration of events ([Appendix 2](#)).

Missing start and end date of subsequent cancer-related therapy, subsequent cancer-related therapy procedure, and prior treatment date will be imputed for the purpose of deriving the time-to-event endpoints and other applicable analysis as applicable ([Appendix 3](#)).

Missing date of death will be imputed for deriving time-to-event endpoints ([Appendix 4](#)).

Partial Missing First and Last Dates of Corticosteroid Administration will be imputed ([Appendix 5](#)). 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 summaries as LLOQ.

Missing values for PK measurements will be listed as missing and excluded from the calculation of summary statistics. PK values which are recorded as being less than the lower limit of quantification (LLOQ), will be included in figures and summaries as LLOQ/2.

5.3. Determination of Sample Size

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Sample size and power were calculated using EAST® version 6.4, by Cytel Inc.

5.4. Randomization and Blinding

5.4.1. Randomization

Participants will be assigned to the tucatinib or placebo arms (in combination with trastuzumab and pertuzumab) in a 1:1 ratio using a centralized randomization with the following three stratification factors:

- diagnosis: *de novo* vs. recurrent,
- hormone receptor status: negative vs. positive,
- presence or history of brain metastases: yes vs. no.

5.4.2. Blinding

This is a double-blinded trial. Study participants, site investigators and personnel, the sponsor, and all other individuals involved in the monitoring, data management, and/or conduct of the trial will be blinded. There are a few designated unblinded personnel who may access the unblinded data. Please refer to Data Flow and Maintenance of the Blind for more details.

Unblinding a participant's treatment assignment prior to study closure must be limited to emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the clinical management of the participant. In the event of such an emergency circumstance, a formal unblinding procedure, carried out by a third-party organization will be followed to allow the investigator to immediately access a participant's treatment assignment (see Study Manual). Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, the sponsor is to be notified within 24 hours of the occurrence. Details regarding unblinding procedures are described in the Study Manual.

Unblinded data including deaths, discontinuations, dose reductions, adverse events (serious and non-serious) and laboratory data will be monitored regularly by an E-DMC. The independent statistical reporting group (ISRG) preparing outputs for the E-DMC will be unblinded and have access to the overall randomization scheme.

At the time of the primary analysis for the primary endpoint (PFS per investigator), sponsor personnel will be unblinded to prepare related CSR, however the investigators and staffs at the clinical sites and the participants will remain blinded to individual subject treatment assignments (tucatinib/placebo) until the final analysis for the key secondary endpoint of OS.

5.5. Data Transformations and Derivations

Age: Reported age in years will be used.

Baseline: Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of any study treatment (for participants who received at least one dose of any study treatment) or randomization (for randomized participants who did not receive any dose of study treatment).

Study Day: For participants receiving treatment, study day starts on the date of the first dose (date - date of the first dose + 1) for dates on or after the first dose date. For dates prior to the first dose date, study day is calculated as date - date of the first dose. The first dose date is the earliest date of administration of any study treatment.

For participants who did not receive treatment, study day starts on the date of randomization (date – date of randomization + 1) for dates on or after randomization date. For dates prior to randomization date, study day is calculated as date – date of randomization.

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:

$$\text{Months} = \text{Days}/30.4375$$

$$\text{Years} = \text{Days}/365.25$$

Response assessment date: At each response assessment time point, scans to evaluate tumor lesions can be performed on multiple dates.

- The date of response for CR or PR will be recorded as the date of the last radiographic evaluation included in the series for that assessment.
- The date of response for non-CR/non-PD or SD will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.
- The date of progression (PD) will be recorded as the earliest date that PD has been documented, i.e., the earliest of the following:
 - Earliest date of target lesion assessment when the target lesion response is PD,
 - Date of non-target lesion assessment when the lesion status is unequivocal progression,
 - Date of documenting new lesion.

In the cases where a PD occurs due to the fact that an equivocal new lesion was present and later confirmed to be an unequivocal new lesion, the PD date should be back dated to the date 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 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.

5.6. Multicenter Studies

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

5.7. Multiple Comparison/Multiplicity

To maintain strong control of the family-wise type I error rate at 0.05 (two-sided), a fixed sequential testing procedure will be used to test the primary endpoint of PFS and the key secondary endpoints of OS.

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The Lan-DeMets O'Brien-Fleming approximation spending function will be used for the calculation of the alpha level at the interim and the final OS analyses based on the actual number of OS events observed.

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Table 2.

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5.8. Examination of Subgroups

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

- Diagnosis: (*de novo*, recurrent);
- Hormone receptor status (negative, positive): hormone receptor is defined as positive if either estrogen receptor or progesterone receptor is positive, negative otherwise;
- Brain metastases at baseline (yes, no): brain metastases at baseline are defined as having either presence or history of brain metastases prior to screening/baseline MRI or having newly diagnosed or progressive brain lesions found on the screening/baseline MRI, or having brain lesions of equivocal significance at screening/baseline MRI. The subgroup of participants with brain metastases at baseline will henceforth be referred to as "BrainMets" in this document. Participants not meeting the above criteria will be assigned to the 'no' subgroup for this variable;
- Prior Anti-HER2 therapy (yes, no);
- Best response to induction (CR or PR, SD or Non-CR/Non-PD);
- Disease Type (visceral, non-visceral);
- Baseline ECOG (0, 1): the latest ECOG on or before the date of the first dose of study treatment (or before randomization if the participant did not receive study treatment);

- Geographic Region (North America, Europe, Asia-Pacific, Rest of World);
- Age (< 65 years, ≥ 65 years);
- Race (White, Asian, African American, Others): African American may be combined with others if either subgroup is less than 10% of the total population.

Subgroup analysis of CNS-PFS per investigator assessment will be evaluated by brain metastases at baseline (yes, no).

Subgroups will be defined using data recorded in the eCRF. If the number of participants in a subgroup is less than 10% of the total population, analysis of that subgroup will either be combined with another subgroup or will not be performed. Subgroup analyses will be conducted using stratified log-rank tests and stratified Cox proportional hazards model using randomization stratification factors. If the subgroup is a stratification factor, then the stratified models will control for the other stratification factors.

5.9. Covariates

Stratified analyses specified in Section 6 will include adjustment for the stratification factors as recorded at randomization.

5.10. Timing of Analyses

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6. ANALYSES AND SUMMARIES

6.1. Disposition

6.1.1. Screening

The number and percentage of participants who signed informed consent will be summarized. The number of screen failures and the percentage relative to the total number of participants screened will be summarized.

6.1.2. Discontinuation and More

Analysis set: ITT Analysis Set

An accounting of study participants by disposition will be tabulated by treatment arm and total. Reasons for discontinuation of treatment and study will be summarized.

The number of participants randomized in each country and at each site will be summarized by treatment arm and total. Follow up time of PFS and OS and subsequent treatment information will be summarized. Duration of follow up of PFS and OS will be summarized per reverse Kaplan-Meier method.

6.2. Demographic and Baseline Characteristics

Analysis set: ITT Analysis Set

Demographics and baseline characteristics, including age, gender, ethnicity, race, and ECOG will be listed and summarized; summaries will be presented for each treatment arm and total using the ITT analysis set. Disease specific characteristics, including time from diagnosis will be listed and summarized for each treatment arm and the total. Prior systemic therapy in adjuvant or neoadjuvant settings will be summarized for each treatment arm and the total.

6.3. Protocol Deviations

Analysis set: ITT Analysis Set

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

6.4. Treatment Administration

Analysis set: Safety Analysis Set

Exposure will be summarized by treatment arm using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables. The following information will be summarized by treatment group separately for tucatinib, trastuzumab, pertuzumab, and trastuzumab+pertuzumab fixed dose combination:

- Total number of treatment cycles per participant,
- Duration of treatment (months),
- Dose modification by type (dose reduced, dose interrupted, dose held) and by reason, if applicable,
- Drug discontinuation due to AE,
- Dose holds due to AE,
- Duration of dose holds due to AE,
- Absolute dose intensity (ADI) and relative dose intensity (RDI) for tucatinib/placebo

Duration of treatment is defined, per treatment, as the time from first dose date to the earliest of following dates:

- Exposure end date:
 - for trastuzumab and pertuzumab, last infusion date + 20,

- for trastuzumab+pertuzumab fixed dose combination, last injection date + 20,
- for tucatinib/placebo, the last dose date,
- Date of death,
- End of study date,
- Analysis data cutoff (DCO) date if the participant is still on study at the time of DCO.

Cumulative dose is defined as the sum of the actual dose amount that a participant received across all cycles.

Intended Dose Intensity (IDI) is defined as the intended dose of drug per unit of time, i.e., 600 mg/day for tucatinib/placebo.

Absolute Dose Intensity (ADI) = cumulative dose / (exposure end date – first dose date + 1).

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

For participants who received both tucatinib and placebo due to dispensing error, the duration of treatment and cumulative dose include all dosing of tucatinib and placebo.

Participants who switched regimen (Trastuzumab+Pertuzumab Fixed Dose Combination vs Trastuzumab and Pertuzumab individually) will be summarized under the regimen with the most cycles that they were on.

6.5. Efficacy Analyses

Analysis set: ITT Analysis Set

The analysis for efficacy endpoints, including the primary endpoint of PFS, the key secondary endpoint of OS, and other secondary endpoints will be conducted using the ITT analysis set, unless otherwise specified. Participants will be analyzed based on their randomized treatment arm.

For the primary analysis of PFS per INV, the randomization stratification factors per Randomization and Trial Supply Management (RTSM) system will be used as strata in stratified analysis. If the total number of participants in a level of stratification factor is less than 10% of the total population, that stratification factor will be excluded in both stratified log-rank test and stratified Cox proportional hazard regression model. For instance, if participants with diagnosis as recurrent is less than 10%, then the stratification factor of diagnosis will be excluded for the analysis.

The primary analysis of the primary endpoint (PFS) and key secondary endpoints (OS) may be analyzed by subgroups specified in Section 5.8.

6.5.1. Primary Endpoint

6.5.1.1. Progression Free Survival (PFS) by Investigator Assessment

Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression (as assessed by investigator per RECIST 1.1) or to death due to any cause, whichever occurs first.

Specifically,

$PFS = \text{Date of first documented PD or death or censoring} - \text{Date of randomization} + 1.$

PFS is defined based on below Table 3:

Table 3. PFS Event and Censoring Rules for Primary Analysis

Scenario	Progression/Censor Date	Outcome
No post-baseline tumor assessments	Date of randomization	Censored
No documented disease progression or death	Date of last tumor assessment of CR, PR, SD, NED, or non-CR/non-PD	Censored
Subsequent cancer-related therapy (systemic, radiation, or surgery) started before PD or death observed	Date of last CR, PR, SD, NED, or non-CR/non-PD on or prior to date of subsequent cancer-related therapy	Censored
Progressive disease (PD)	Date of PD	Event
Death before first PD assessment	Date of death	Event
Death or progression right after two or more consecutively missed tumor assessments	Date of last tumor assessment of CR, PR, SD, NED, or non-CR/non-PD prior to the missed visits	Censored

Note: CT, PET/CT scans are performed at baseline and every 9 weeks until documented PD or EOT, whichever is later.

The null hypothesis for the primary endpoint is that the PFS per investigator of the tucatinib arm has no difference from that of the placebo arm. To test this hypothesis, a stratified log-rank test comparing two arms in the ITT analysis set will be conducted controlling for the randomization stratification factors [i.e., diagnosis (de novo versus recurrent), hormone receptor status (positive versus negative), and presence or history of brain metastases (yes versus no)].

Kaplan-Meier curves and estimates of the median PFS time will be provided for each arm with the two-sided 95% confidence intervals (CI) using the complementary log-log transformation method ([Brookmeyer and Crowley 1982](#), [Kalbfleisch and Prentice 2002](#)). KM estimates of the 25th and 75th percentiles of PFS time and the observed minimum and maximum PFS time will also be reported. In addition, estimated probability of PFS will be reported every 3 months till the time of last PFS event.

To describe the treatment effect, a hazard ratio between the experimental arm and the control arm and its 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the stratification factors.

In addition, the proportional hazard assumption for the treatment variable will be examined using the plot of Schoenfeld residuals for the treatment variable versus time. Residuals that do not show any trend indicate the proportional hazard assumption is satisfied. Other methods may also be applied to check the proportional hazard assumption if needed.

If the results of the above-mentioned analyses suggest the proportional hazard assumption is violated, then alternative methods such as restricted mean survival time (RMST) ([Royston 2011](#); [Uno 2014](#)) may be used to describe the treatment effect. RMST is the expected survival time within a fixed follow-up interval and will be calculated as the area under the survival curve from $t=0$ up to time τ months for each treatment group.

The selection of τ should ensure that the RMST evaluation will not go beyond the maximum time point where the evaluation can be performed while also including a large period of time that is expected to provide a meaningful assessment of treatment effect. To avoid arbitrary selection of the common cutoff τ for both treatment arms, the following cutoff time will be used:

- τ_1 = min of (latest PFS event time for experimental arm, latest PFS event time for control arm),
- τ_2 = min of (latest time that $\geq 10\%$ of participants are at risk for PFS in the experimental arm, latest time that $\geq 10\%$ of participants are at risk for PFS in the control arm).

The cutoff time τ_1 and τ_2 will be rounded down to full months.

The difference in RMST between the treatment arms will be analyzed using an ANCOVA model ([Andersen 2004](#)) adjusting for the randomization stratification factors. The estimated RMST and its 95% CI will be presented.

6.5.1.2. Sensitivity Analyses

1. **Clinical progression:** To explore the potential impact of clinical progression on the analysis of PFS, a sensitivity analysis may be performed using the same censoring scheme and methods as described for the primary analysis of PFS with the exception that clinical progression will be counted as 'progression' in the analysis.
2. **Missing assessments of disease response:** To explore the potential impact of missing tumor assessments on PFS, two sensitivity analyses are planned:
 - Ignoring the missing assessments, i.e., participants who missed two or more consecutive scheduled assessments before death or PD are considered to have had an event on the date of death or progression.
 - Imputing the missing assessment, i.e., participants who missed two or more consecutive scheduled assessments before death or PD are considered to have events at the time of the first missed scheduled assessment after the last non-missing assessment.
3. **Subsequent cancer-related therapy before PD/death:** For participants who received subsequent cancer-related therapy before PD or death, three sensitivity analyses are planned:
 - Not to consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as a censoring reason;
 - Consider any subsequent cancer-related therapies (whether systemic, radiation, or other) as an event;
 - Consider systemic therapy as an event, and radiation and other therapy as a censoring reason.
4. **Mis-stratification:** In the case of $> 5\%$ inconsistency in any stratification factor between RTSM and eCRF, the hazard ratio and its 95% CI will be estimated using a stratified Cox proportional hazards regression model where the inconsistent stratification factors will be derived from eCRF.

6.5.2. Key Secondary Endpoints

6.5.2.1. Overall Survival (OS)

The primary analysis of overall survival (OS) will be based on the ITT analysis set. Overall survival is defined as the time from randomization to date of death due to any cause:

$$\text{OS} = \text{Date of death} - \text{Date of randomization} + 1.$$

In the absence of confirmation of death, OS will be censored at the last date the participant is known to be alive. If death date or the last long-term follow-up visit (which indicates participant to be alive) date were to be after DCO, then OS will be censored at DCO.

OS analysis will be performed using similar statistical methods as to evaluate the primary endpoint of PFS in the ITT analysis set. The stratified log-rank statistics and p-value will then be calculated. The Lan-DeMets O'Brien-Fleming approximation spending function will be used to obtain the alpha level at each time of OS analyses based on the actual number of OS events observed at the interim.

Kaplan-Meier curves and estimates of the median OS time will be provided for each arm with the two-sided 95% confidence intervals (CI) using the complementary log-log transformation method ([Brookmeyer and Crowley 1982](#), [Kalbfleisch and Prentice 2002](#)). In addition, KM estimates of the 25th and 75th percentiles of OS time and the observed minimum and maximum OS time will be reported. Estimated probability of OS will be reported every 6 months until the last OS event. The hazard ratio and 95% confidence interval will be estimated using a stratified Cox proportional hazards regression model controlling for the randomization stratification factors.

The proportional hazard assumption will be examined and potential RMST methods may be performed similarly as described in Section [6.5.1.1](#) for PFS.

Sensitivity Analyses

Mis-stratification: In the case of > 5% inconsistency in any stratification factor between RTSM and eCRF, the hazard ratio and its 95% CI will be estimated using a stratified Cox proportional hazards regression model where the inconsistent stratification factors will be derived from eCRF.

6.5.3. Other Secondary Endpoints

6.5.3.1. PFS by BICR

Progression-free survival by BICR is defined as the time from the date of randomization to the date of documented disease progression as determined per RECIST 1.1 by BICR or death from any cause, whichever occurs first. Participants who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, non-CR/non-PD, or SD. Details of the censoring scheme of PFS are described above in [Table 3](#).

Progression-free survival by BICR will be analyzed using the same statistical methods described in Section [6.5.1.1](#).

The concordance between BICR and investigator assessed PFS event will be summarized.

6.5.3.2. CNS-PFS

CNS-PFS is defined as the time from randomization to investigator assessed disease progression in brain (RECIST v1.1), or death from any cause, whichever occurs first. CNS-PFS will be analyzed based on below Table 4. Disease progression in brain is evaluated by applying RECIST 1.1 to assess brain lesions in isolation from other organs based on investigator assessment. In the cases where a disease progression in brain occurs due to the fact that an equivocal new brain lesion was present and later confirmed to be an unequivocal new brain lesion, the disease progression in brain date should be back dated to the date when the equivocal new brain lesion was first identified.

CNS-PFS will be evaluated by investigator assessment and performed in the ITT population.

Table 4. CNS-PFS Event and Censoring Rules

Scenario	Progression/Censor Date	Outcome
No post-baseline brain lesion assessment	Date of randomization	Censored
No documented disease progression in brain or death	Date of last evaluable (CR, PR, SD, NON-CR/NON-PD) brain lesion assessment for participants with target or non-target brain lesion Date of last brain lesion assessment for participants with neither target nor non-target brain lesion	Censored
Subsequent cancer-related therapy (systemic, radiation, or surgery) started before disease progression in brain or death observed	Date of last evaluable brain lesion assessment on or prior to date of subsequent cancer-related therapy for participants with target or non-target brain lesion Date of last brain lesion assessment on or prior to date of subsequent cancer-related therapy for participants with neither target nor non-target brain lesion	Censored
Progressive disease in brain	Date of disease progression in brain	Event
Death before first disease progression in brain assessment	Date of death	Event
Death or disease progression in brain right after two or more consecutively missed tumor assessments	Date of last evaluable brain lesion assessment prior to the missed brain lesion assessment Date of last brain lesion assessment for participants with neither target nor non-target brain lesion	Censored

Note: Contrast enhanced brain MRI is required for all participants at screening and at EOT and is to be repeated for participants with a history of, or baseline, brain metastasis every 9 weeks. For participants without a history of, or baseline, brain metastasis, contrast enhanced brain MRI is to be repeated every 27 weeks (~6 months).

6.6. Safety Analyses

Analysis sets: Safety Analysis Set

All safety endpoints will be analyzed using the Safety analysis set.

Adverse events will be coded by standard preferred terms (PT) and system organ classifications (SOC) using Medical Dictionary for Regulatory Activities (MedDRA, version 28.0 or higher).

Laboratory values will be graded using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE, version 5.0).

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug, Global 202503 or higher).

6.6.1. Adverse Events

Adverse events will be summarized by MedDRA preferred term (PT) in descending frequency of occurrence in the experimental arm (tucatinib + trastuzumab and pertuzumab) unless otherwise specified. For incidence reporting, if a participant reports more than one AE that was coded to the same SOC or PT, the participant will be counted only once for that specific SOC or PT. For summaries by severity, only the worst grade for an AE will be counted for a participant.

Treatment-emergent adverse event (TEAE) is defined as AE that is new or worsened on or after the first dose of study treatment (tucatinib/placebo, or trastuzumab, or pertuzumab) and up through 30 days after the last dose of study treatment (tucatinib/placebo or trastuzumab or pertuzumab, whichever is later).

Treatment-related AE is defined as AE assessed by the investigator as 'related' to tucatinib/placebo or trastuzumab or pertuzumab.

Summaries of TEAEs by treatment arm will include (but may not limited to):

- all TEAEs
- TEAEs by PT
- grade 3 or higher TEAEs by PT
- serious TEAEs by PT
- TEAEs leading to dose modification by PT
- TEAEs leading to drug discontinuation by PT
- TEAEs leading to death by PT
- TEAEs by SOC and PT
- treatment-related TEAEs by PT, separately for each study drug
- treatment-related grade 3 or higher TEAEs by PT, separately for each study drug
- treatment-related serious TEAEs by PT, separately for each study drug
- treatment-related TEAEs leading to dose modification by PT
- treatment-related TEAEs leading to drug discontinuation by PT
- treatment-related TEAEs leading to death by PT
- TEAEs by SOC, PT and maximum severity. At each SOC or PT, multiple occurrences of events within a participant are counted only once at the highest severity.

All adverse events will be listed.

6.6.1.1. Adverse Events of Special Interest and Other Adverse Events

Following are the protocol defined adverse events of special interest (AESIs):

- **≥ Grade 3 Diarrhea**
- **Hepatotoxicity:** either of the following types of liver enzyme elevation by laboratory criteria:
 - AST or ALT elevations that are $> 3 \times \text{ULN}$ with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin $> 2 \times \text{ULN}$, except in participants with documented Gilbert's syndrome
 - AST or ALT elevations $> 20.0 \times \text{ULN}$
 - Bilirubin elevations $> 10.0 \times \text{ULN}$

Since hepatotoxicity and diarrhea are important identified risks for tucatinib, in addition to the above criteria defined (protocol defined: Grade 3 diarrhea and Hepatotoxicity by lab parameters), these will be summarized by the below search strategy in Table 5 for all grades.

Table 5. Search strategy for AESIs and other adverse events

Identified Risk	Search Strategy
Hepatotoxicity	Drug related hepatic disorders - comprehensive search SMQ (Narrow)
Diarrhea	PT of diarrhea

Crude rates, treatment exposure-adjusted incidence rates for all grades and $\geq$ grade 3 AESIs, and time-at-risk exposure-adjusted incidence rates for all grades and $\geq$ grade 3 AESI will be reported. Treatment exposure starts from the date of the first dose of either study drug and ends on the earliest of the following:

- last dose date of either study drug + 30 days,
- data cutoff date,
- date of death
- date of end of study.

Time at risk will be calculated for each AE, starting from the date of the first dose of either study drug. The end of time at risk is:

- for participants with the specific AE, the onset date of AE;
- for participants without the specific AE, the earliest of the following:
 - last dose date of either study drug + 30 days,
 - data cutoff date,

- date of death,
- date of end of study.

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

Time to onset of an 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.

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

6.6.2. Clinical Laboratory Results

Clinical laboratory results to be collected during the study are specified in the protocol section of 7.8.3, including serum chemistry and hematology samples. The collection schedules are specified in Schedule of Events in the study protocol.

Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test by treatment. Post baseline period is defined as from the date of the first dose of study treatment to the date of last dose + 30 days.

Treatment-emergent laboratory abnormalities will also be summarized.

The incidence of liver abnormalities will be summarized by treatment arm. A liver abnormality is defined as:

- AST or ALT elevations that are $> 3 \times$ ULN with concurrent elevation of total bilirubin $> 2 \times$ the ULN (same day or within 21 days following AST and/or ALT elevations), or
- AST or ALT elevations that are $> 20 \times$ ULN, or
- Total bilirubin elevation of $> 10 \times$ ULN.

In addition, outputs will also be generated for $>3 \times$, $>5 \times$, $>10 \times$ ULN elevations of AST, ALT, and either ALT or AST.

A listing of laboratory results with CTCAE grade 3 or higher will be presented. Normal ranges will be documented and out-of-range values will be flagged.

6.6.2.1. Ejection Fraction

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

6.6.3. ECOG Performance Status

Baseline ECOG status will be listed. Shifts from baseline to the worst postbaseline score will be tabulated.

6.6.4. Vital Signs

The frequency and percentage of participants with post baseline clinically significant vital signs will be summarized. The clinically significant vital signs are defined as: Systolic blood pressure ≥ 120 mmHg or diastolic blood pressure ≥ 80 mmHg; heart rate > 100 bpm; in addition, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg will also be presented; Temperature ≥ 38.0 degrees C (100.4 F) and respiratory rate > 20 breaths per min.

For weight, the maximum percentage decrease from baseline will also be summarized.

6.6.5. Concomitant Medication/Procedure

Concomitant medication/Procedure will be summarized and listed by participant.

6.6.6. Deaths

The cause of death will be identified by MedDRA preferred term (unless otherwise specified) and summarized by treatment arm.

Death information will be listed by participant.

6.6.7. Pregnancy

Positive pregnancy test by SMQ will be listed by participant. Embryo-fetal toxicity by preferred term includes the preferred terms from: normal pregnancy conditions and outcomes SMQ (broad), pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) SMQ (broad), and termination of pregnancy and risk of abortion SMQ (broad).

6.7. Pharmacokinetic Analyses

Analysis sets: PK Analysis Set

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

Tucatinib concentrations will be summarized with descriptive statistics at each PK sampling time point.

The summary statistics for a timepoint will not be calculated if more than 50% of the results are $< \text{LLOQ}$.

6.8. Health Economics and Outcomes

6.8.1. EORTC-QLQ-C30

Analysis set: PRO Analysis Set

The EORTC QLQ-C30 scale scores will be calculated using the EORTC QLQ-C30 Scoring Manual (Fayers 2001) for Global health status / Quality of Life, functional scales, and symptom scales, symptom items and Financial Impact. The following summary will be provided for EORTC QLQ-C30 by treatment arms and by scheduled assessments:

- Completion rate and compliance rate for EORTC QLQ-C30 assessment

- CCI [REDACTED]
- Number and percentage of participants with a deterioration of ≥ 10 points from baseline in global health status/QoL scale

Completion rate is defined as the proportion of participants who completed the instrument among PRO Analysis Set.

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

6.8.1.1 Time to Deterioration

A time to deterioration (TTD) analysis will be performed for the EORTC QLQ-C30 global health status/QoL scale, and physical and role function scales. Time to deterioration is specified as the time from randomization to the date of the first meaningful deterioration of the score, where meaningful deterioration is defined as the first instance of a decrease of ≥ 10 points from baseline.

Kaplan-Meier estimates of the median TTD and its 2-sided 95% CI will be calculated. The stratified hazard ratio between 2 arms and its 95% CI will be estimated using a Cox proportional hazards regression model.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

6.9. Biomarker Analysis

The exploratory biomarker analyses will be outlined in a separate analytical document.

6.10. Additional Analyses

Analysis set: ITT Analysis

6.10.1. Subsequent Cancer-Related Therapy/Procedure

The type (and regimen, if apply) of subsequent anticancer therapy/procedure after discontinuation from study treatment will be summarized by treatment arm. Subsequent anti-cancer therapies / procedures will be listed by participants.

7. INTERIM ANALYSES

No interim analysis for the PFS primary endpoint is planned. CCI

The rejection boundaries of the interim and final OS analyses will be determined using Lan-DeMets spending functions.

8. REFERENCES

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Appendix 1. Imputation of Partial Missing Date of Disease Diagnosis

Disease diagnosis date (including initial diagnosis, earliest date disease was considered unresectable locally advanced and earliest date disease was considered distant metastatic) will be imputed as the 1st of the month if both month and year are present and only day is missing, and will be imputed as 01 January if only year is present and both day and month are missing.

Appendix 2. Imputation of Partial Missing Adverse Event Dates

For an 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, then 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, then AE start date will be imputed as the first day of the month.

AE day and month are missing.

- If the year is the same as the year of first dose of any study treatment, then 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, then AE start date will be imputed as January 1st.

AE day, month and year are missing.

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

If AE condition end date is known with a full date, and the imputed start date is after the end date, the start date will be set to the AE end date.

Incomplete AE End Date:

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

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

AE day only is missing.

AE condition end date will be imputed as the minimum of (death date, DCO date or data extraction date if without DCO, last day of the AE end date month/year, EOS date).

AE day and month are missing.

- If the year is equal to the year of the last dose date then AE end date will be imputed as the minimum of (last dose date + 30, death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).
- If the year is not equal to the year of the last dose date, then AE end date will be imputed as the minimum of (death date, DCO date or data extraction date sans DCO, December 31st of the end date year, EOS date).

AE day, month and year are missing.

AE end date will not be imputed.

Within a single record, if the imputed end date is before the start date, then the imputed end date will be set 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 3. Imputation of Partial Missing Start and End Date of Subsequent Cancer-Related Therapy, Subsequent Cancer-Related Procedure and Prior Systemic Therapy

Partial missing date will be imputed when both month and year are present and only day is missing.

- Prior therapy start date: first day of the month
- Prior therapy end date: the earlier of
 - Last day of the month and year
 - First dose date of study drug
- Subsequent therapy and hospitalization start date: the later of
 - First day of the month and year
 - First dose date of study drug
- Subsequent therapy end date: the earlier of
 - Last day of the month
 - Study end date

Appendix 4. 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 last-known-alive date.

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 fifteen of the month and year.

Appendix 5. Imputation of Partial Missing First and Last Dates of Corticosteroid Administration

Partial missing date will be imputed when both month and year are present and only day is missing.

First date of corticosteroid administration will be imputed,

- If started prior to first dose of any study treatment, as the first day of the month and year.
- If started not prior to first dose of any study treatment, as the later of the following dates
 - The date of first dose of any study treatment.
 - The first day of the month and year.

Last date of corticosteroid administration will be imputed as the earlier of the following dates,

- The last day of the month and year.
- Study end date.

Appendix 6. List of Abbreviations

Abbreviation	Term
ADI	absolute dose intensity
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BID	twice a day
CI	confidence interval
CNS	central nervous system
CR	complete response
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
CT	computed tomography
DCO	data cutoff
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality-of-life questionnaire
EOS	end of study
EOT	end of treatment
CCI	
HR	hazard ratio
HRQoL	health-related quality of life
IDI	intended dose intensity
ISRG	independent statistical reporting group
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition scan
N/A	not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	no evidence of disease
OS	overall survival

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Abbreviation	Term
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRO	patient-reported outcome
PT	preferred term
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	stable disease
SMQ	Standardized MedDRA Queries
SOC	system organ class
TEAE	Treatment-emergent adverse event
TTD	time to deterioration
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization