NOVARTIS

Clinical Development

RAD001(everolimus)

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A randomized, double-blind, placebo controlled, phase II study of Everolimus in combination with Exemestane in the treatment of Chinese postmenopausal women with estrogen receptor positive, HER-2 negative, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole

Statistical Analysis Plan (SAP) for Final CSR

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List of abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
ASCO	American Society of Clinical Oncology
BC	Breast Cancer
BIRC	Blinded independent review committee
CBR	Clinical Benefit Rate
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Concentration
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EOT	End of Treatment
ER	Estrogen receptor
EU	European Union
FAS	Full Analysis Set
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2 negative
HER2+	Human epidermal growth factor receptor 2 positive
HR	Hazard ratio
INR	International Normalized Ratio
IRT	Interactive Response Technology
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
N	Sample size
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable disease
UNK	Unknown

ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This document describes the detailed statistical methodology of the Statistical Analysis Plan (SAP) for the final Clinical Study Report (CSR) at the end of CRAD001Y2202: A randomized, double-blind, placebo controlled, phase II study of Everolimus in combination with Exemestane in the treatment of Chinese postmenopausal women with estrogen receptor (ER) positive, HER-2 negative, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole. The data will be analyzed by Novartis. It is planned that data from all centers that participate in this study will be used. This document refers to the study protocol Version 1.0 dated May 23 2017. The the indication of "Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole" has been approved by the Chinese Health Authorities February 09 2022.

1.1 Study design

This is a multicenter, double-blind, randomized, placebo-controlled, phase II study evaluating treatment with everolimus (10 mg daily) versus placebo in combination with exemestane (25 mg daily) in Chinese postmenopausal women with locally advanced, recurrent or metastatic ER positive HER2-negative breast cancer refractory to non-steroidal aromatase inhibitors.

Approximately 160 subjects will be randomized in 1:1 ratio to receive either everolimus or matching placebo in a blinded manner in addition to open label exemestane (25 mg daily tablets).

All eligible subjects will be randomized within 7 days before Cycle 1 Day 1 to one of the two treatment arms: everolimus plus exemestane arm or placebo plus exemestane arm. Randomization will be stratified according to the presence of visceral disease and sensitivity to prior hormonal therapy status. Visceral refers to lung, liver, brain, pleural and peritoneal involvement.

Randomized subjects will start the study treatment at Cycle 1 Day 1. Subjects will receive everolimus/placebo (10 mg daily oral tablets) in addition to exemestane (25 mg daily oral tablets) continuously.

Subjects will receive treatment until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from treatment for any other reason. Tumor assessments will be performed every 8 weeks after randomization until radiological progression per local assessment.

There won't be any interim analysis for this study.

1.2 Study objectives and endpoints

The primary objective is to assess the progression-free survival (PFS) as determined by investigator assessment of everolimus plus exemestane and of placebo plus exemestane.

The secondary objectives are:

- To assess PFS in the two treatment arms as determined by a Blinded Independent Review Committee (BIRC)

- To assess overall survival (OS) in the two treatment arms
- To assess the following efficacy endpoints in the two treatment arms based on both local investigator's assessment and BIRC
  - Overall response rate (ORR)
  - Clinical benefit rate (CBR)
  - Time to response and duration of response
- To assess time to deterioration of ECOG Performance Status (PS)
- To characterize the safety and tolerability of everolimus and exemestane versus placebo and exemestane
- Characterize the pharmacokinetics of everolimus pre-dose concentration (C_{min}) and concentration at 2 hours post dose (C_{2h}) when administered in combination with exemestane
- Compare the two treatment arms with respect to pre-dose concentration (C_{min}) and concentration at 2 hours post dose (C_{2h}) of exemestane and to compare the two treatment arms with respect to estradiol (E2) changes from baseline.

For secondary objectives with regards to BIRC assessment and PK analyses, the analysis will not be repeated for the final CSR as per protocol. The results were addressed in the primary CSR (DCO:19-May-2020).

2 Statistical methods

2.1 Data analysis general information

Novartis and/or a designated CRO will perform all the analyses. Any additional data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation. The end of study is defined as the earliest occurrence of one of the following:

- All patients have died or discontinued from the study
- Another clinical study or patient support programs becomes available that can continue to provide Afinitor in this patient population and all patients ongoing are eligible to be transferred to them
- Afinitor has been approved for this indication in combination with Exemestane

The final analysis for safety and efficacy will be conducted at the end of the study. All available data from all patients up to this cutoff date will be analyzed per protocol.

SAS® version 9.4 or later will be used in all analyses.

2.1.1 General definitions

Study drug is defined as everolimus, or matching placebo. ***Study treatment*** is defined as everolimus + exemestane or placebo + exemestane.

2.1.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a non-zero dose of study drug is administered and recorded on the dose administration record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as the start of study drug.

2.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR eCRF.

2.1.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of any component of study treatment is administered and recorded on the DAR eCRF. For the sake of simplicity, the date of first administration of study treatment will also be referred to as the start of study treatment.

2.1.5 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of any component of study treatment was administered and recorded on the DAR eCRF.

2.1.6 Study day

The study day for safety assessments (e.g., adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, etc.) will be calculated as the difference between the date of the assessment and the start of study treatment plus 1. (Note: except in the case when the assessment is before start of study treatment in which case study day is calculated as the difference between the date of the assessment and the start of study treatment. In this particular case, the study day displayed on the listing will be negative.)

The study day for all other, i.e., non-safety assessments (tumor assessment, death, disease progression, tumor response, ECOG performance status) will be calculated as the difference between the date of the event and the randomization date plus 1. In other words, all efficacy time-to-event variables (e.g., progression-free survival, overall survival, time to response) will be calculated from date of randomization. (Example: if randomization date is 02JAN2007, start of study drug is on 05JAN2007, and the date of death is 09JAN2007, then the study day when death occurred is 8.)

The study day will be displayed in data listings.

2.1.7 Baseline

Baseline value(s) is (are) the result of an investigation describing the “true” uninfluenced state of the subject.

For ***efficacy evaluations***, the last available assessment before or at the date of randomization is taken as ‘baseline’ value or ‘baseline’ assessment. In the context of the definition of baseline,

efficacy evaluations also include the ECOG performance status, subject-reported outcome measures and clinical measurements included in the stratification.

For ***safety evaluations*** (i.e., laboratory and vital signs), the last available assessment before or at the date of the start of study treatment is taken as 'baseline' assessment.

2.1.8 On-treatment assessment/event

On-treatment assessment/event is defined as any assessment/event obtained in the time interval:[date of first administration of study treatment; date of last administration of study treatment + 30 days], i.e., including the lower and upper limits. (Note: The calculation of study treatment duration, however, may use different rules as specified in Section 2.4.1.)

2.1.9 Last contact date

The last contact date will be derived for subjects not known to have died at the final analysis cut-off using the sources presented in Table 2-1 below:

Table 2-1 Last contact date data sources

Source data	Condition
Last contact date/last date subject was known to be alive from survival follow-up page	Subject status is reported to be alive. **Do not use if subject status is reported unknown.**
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation is marked as 'done'.
Laboratory collection dates	Sample collection marked as done.
Vital signs date	At least one non-missing parameter value.
Performance status date	Non-missing performance status.
Start/End dates of AE	Non-missing verbatim term.

The last contact date on or before the data cut-off date should be used; the cut-off date should not be used as the censoring date (even in presence of post cut-off data) unless the subject was seen or contacted on the cut-off date.

Imputed dates (e.g., analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partially imputed dates (i.e., only day or day and month imputed) are allowed to be used for last contact date only if coming from Survival Follow-up page.

The last contact date will be used for censoring of subjects in the analysis of overall survival.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The Safety Set (SAF) consists of all subjects who received at least one dose of study treatment. Subjects will be analyzed according to treatment actually received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The actual treatment received corresponds to:

- the randomized treatment if subjects took at least one dose of that treatment
- the first treatment received if the randomized treatment was never received

2.2.1 Subgroup of interest

Not Applicable.

2.3 Subject disposition, demographics and other baseline characteristics

Subjects who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure Subjects.A summary of the demographic, baseline disease characteristics and prior antineoplastic therapy of the study population was provided in the primary CSR [Study Y2202-Section 10.4].

2.3.1 Subject disposition

The Full Analysis Set will be used for subject disposition summaries. Based on the two eCRF pages ‘End of Treatment’ and ‘End of Post Treatment Disposition eCRF page’ there will be one combined summary, stratified by treatment, showing:

- Number (%) of subjects who discontinued the study treatment (based on the ‘End of Treatment’ page);
- Reasons for study treatment discontinuation (based on the ‘End of Treatment’ page).
- Number (%) of subjects who entered the post-treatment evaluation phase (based on the ‘End of Treatment’ page);
- Number (%) of subjects who discontinued from the post-treatment evaluations (based on the ‘End of Post Treatment Disposition eCRF page’ page);
- Reasons for discontinuation from the post-treatment evaluations phase (based on the ‘End of Post Treatment Disposition eCRF page’ page).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of study treatment exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment. In addition, the duration of exposure to study treatment will be categorized into time intervals; frequency counts and percentages will be presented for the number of subjects in each interval. The number of subjects, who have dose reductions or interruptions, and the reasons, will be summarized by treatment.

Listings of all doses of the study treatment along with dose change reasons will be produced.

The Safety Set will be used for all summaries and listings of study treatment.

2.4.2 Duration of study treatment exposure

The following algorithm will be used for everolimus and exemestane to calculate the duration of study treatment exposure for subjects who took at least one dose of any of the components of the study treatment:

Duration of exposure (days) = (date of last administration of study treatment) – (date of first administration of study treatment) + 1.

Total duration of exposure will be derived as the sum of the cycle duration of exposure.

The duration includes the periods of temporary interruption (of any component of the study treatment for any reason).

Duration of exposure to each component of the study treatment will also be calculated.

2.4.3 Cumulative dose

Cumulative dose is defined as the total dose given during the study treatment exposure period and will be summarized for each of the study treatment components separately. For subjects who do not receive any drug, the cumulative dose will be set to zero.

2.4.4 Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

DI (dosing unit / unit of time) = Cumulative dose (dosing unit) / Duration of exposure (unit of time).

For subjects who do not receive any drug, the DI will be set to zero.

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to subjects as per protocol in the same dose unit and unit of time as that of the Dose Intensity.

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

DI and RDI will be summarized separately for each of the study treatment components, but using the duration of the study treatment exposure, not the duration of exposure to each of the components.

2.4.5 Dose reductions or interruptions

The number of subjects, who have dose reductions or interruptions, and the reasons for such reductions/interruptions, will be summarized separately for each of the study treatment components.

An interruption is defined as a 0 mg dose given on one or more days. However, for last records, it will be counted as an interruption only if there are 2 or more last records with 0 mg dose.

If a subject moves from a dose level that is higher than the studied dose under the protocol to the dose level that is being studied in the protocol, such changes will not be counted as reductions. However, if any subject moves directly from a higher than studied dose down to a lower than protocol-studied dose, or to the dose level being studied under the protocol but on a less frequent regimen, such changes will be counted as reductions. If first dose is lower than the studied dose under the protocol, it will be counted as a dose reduction.

For everolimus and exemestane, reductions count should be based on the actual total daily dose (mg).

If one drug is permanently discontinued (before a protocol-planned discontinuation date) while the other is ongoing, such discontinuations will be classified as interruptions.

Dose reductions and interruptions will be tabulated both separately and in a combined fashion. In the combined summary, dose interruptions will be considered as dose reductions to 0 mg, and therefore all reductions/interruptions will be labeled as reductions and tabulated in one table.

2.4.6 Prior, concomitant and post therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study treatment that were administered to a subject, preceding or coinciding with the study assessment period (within 28 days prior to the study treatment through 30 days after the last dose of study treatment).

Concomitant medications entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs will be classified according to their ATC classification in order to present and compare how they are being utilized.

Concomitant medications and significant non-drug therapies taken concurrently with the study drug(s) will be listed and summarized by ATC class, preferred term and treatment arm by means of frequency counts and percentages. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment were summarizedsummarized in the primary CSR and will not be repeated for the final CSR.

The Safety Analysis Set will be used for all concomitant medication tables and listings.

2.4.7 Inducers, inhibitors and substrates of CYP3A

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Therefore:

- Co-administration with strong inhibitors of CYP3A4 or PgP should be avoided;
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution;
- Seville orange, star fruit, grapefruit and their juices affect CYP3A4 and PgP activity concomitant use should be avoided.

Please refer to Table 6-8 of the protocol for the list of relevant inducers and inhibitors of CYP3A and to Table 6-9 of the protocol for the list of relevant substrates, inducers, and inhibitors of PgP. Despite the fact that some of these drugs should be avoided completely and some used with caution, there may be subjects who took these drugs during the study. In that case, the concomitant medications need to be identified and classified as protocol deviations (review to be performed by a Clinical Pharmacologist) and then tabulated and/or listed in the Clinical Study Report as appropriate.

2.4.8 Further anti-neoplastic therapy

Anti-neoplastic therapy regimen received between EOT and progression will also be collected as well as the first regimen received after progression. Additionally, the tumortumor response classification was described in Table 14-5 of the protocol after the start of anti-neoplastic drugs. For details on the censoring rules, see [Appendix 1 of the study protocol].

Clinical review of study data will be performed to identify anti-neoplastic medications that are not allowed during study treatment.

Anti-neoplastic therapies since discontinuation of study drug will be listed and summarized by ATC class, preferred term and treatment arm by means of frequency counts and percentages in separate summaries using the Full Analysis Set.

2.5 Analysis of the primary objective

The primary objective in this study is to assess PFS based on investigator's assessment on the combination treatment of everolimus + exemestane and placebo + exemestane in Chinese postmenopausal women with estrogen receptor positive, HER2-negative, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole. The primary analysis for efficacy was conducted when approximately 110 PFS events have been documented，the corresponding results for the PFS are provided in the primary CSR [Study Y2202-Section 11.1] (DCO: 19 May-2020).

2.5.1 Primary endpoint

Progression-free survival (PFS) derived from an investigator's assessment of radiology data will be used as the primary efficacy variable. Disease progression for primary efficacy endpoint derivation will be assessed using the local (treating center's radiologist's) investigator's tumor assessment per RECIST 1.1.

The PFS is defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurs first. If a subject has not progressed or died at the analysis cut-off date, or if she receives any further anti-cancer therapy, PFS will be censored at the time of the last adequate tumor assessment before the cut-off date or the anti-cancer therapy date, whichever occurs first. Disease progression for primary efficacy endpoint derivation will be assessed using the local (treating center's radiologist's) investigator's tumor assessment. Definitions and further details on PFS can be found in Appendix 1 of the protocol.

Discontinuation due to disease progression (collected on the "End of treatment" and "End of Post Treatment Disposition eCRF page" page) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered a progressive disease.

Data included in efficacy analyses

Thefinal analysis for safety and efficacy will be conducted closeout at the end of the study. Efficacy analyses will include all data observed in subjects from the FAS regardless of whether the data were observed on-treatment or after the study treatment discontinuation until the analysis cut-off date. In particular, the "30 days" rule applied to all safety analyses will NOT be used for efficacy analyses.

2.5.2 Statistical hypothesis, model, and method of analysis

No hypothesis testing will be performed and the primary objective of this study is to estimate hazard ratio of everolimus in combination with exemestane compared to placebo plus exemestane.

Thefinal analysis of PFS will be based on data from investigator/local radiology review. The analysis will be performed on the FAS following the intention-to-treat (ITT) principle, i.e., subjects will be analyzed according to the treatment group they were randomized and the stratum they were assigned to at baseline. The analysis will use the default censoring and event date definitions from Table 14-5 of Appendix 1 of the study protocol, i.e. A(1), B(1), C1(1), C2(1), D(1), E(1), and F(1). In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of a PFS event; a PFS event occurs after a new anticancer therapy is given; a PFS event occurs after two or more missing tumor assessments. Discontinuation of study treatment (for any reason) will not be considered as a reason for censoring.

Kaplan-Meier estimates

The Kaplan-Meier (KM) estimate of the progression-free survival function will be computed for each treatment group. The results will also be plotted graphically (Kaplan-Meier curves) by

treatment and by randomization strata as assigned through IRT. The plots will display the number of subjects at risk at equidistant time points.

The estimated median PFS for each treatment group will be provided along with the approximate 90% confidence intervals (Brookmeyer and Crowley, 1982). Additionally, the 25th and 75th percentiles will also be computed. The log-log will be used to compute the confidence intervals.

Hazard ratio estimate

The hazard ratio estimate of a PFS event comparing the everolimus + exemestane combination therapy with placebo + everolimus, along with the two-sided 90% confidence interval, will be obtained from the stratified Cox proportional hazards model using the stratification information obtained through IRT. The model will include the indicator of assignment to the everolimus + exemestane arm or placebo + exemestane arm as the covariate. The baseline hazard function will be allowed to vary across strata. As this is an estimation based approach, no p-value will be provided.

2.5.3 Handling of missing values/censoring/discontinuations

PFS will be censored if no PFS event is observed before the cut-off date or before the start date of a new anticancer therapy or another investigational treatment, whichever occurs earlier.

The censoring date will be the date of last adequate tumor assessment before either of these two dates. If a PFS event is documented after two or more missing assessments or nonadequate tumor assessments, then the date of PFS will be censored at the date of the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

2.5.4 Sensitivity and other supportive analyses

No sensitivity analysis will be performed for final CSR.

2.6 Analysis of the key secondary objective

Not applicable. There is no key secondary endpoint in this study.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives in this study are the two treatment groups with respect to OS, ORR, deterioration in the ECOG PS, and CBR.

Additionally, ORR, deterioration in the ECOG PS, CBR, time to response and duration of response will be summarized between the treatment groups in the final CSR. The analysis results for the other secondary efficacy endpoints were provided in the primary CSR [Study Y2202-Section 11]. The analysis of all secondary efficacy endpoints (mentioned below) will be performed on the FAS.

Overall survival (OS)

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. If the subject is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date. Only one OS analysis will be performed at the end of the study. The OS analysis will be based on data from the FAS on the ITT basis, i.e., according to the treatment group subjects are randomized to at baseline.

Overall response rate (ORR)

Overall response rate (ORR) is defined as the proportion of subjects with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 (Appendix 1 of the protocol). ORR will be calculated based on the FAS according to the ITT principle, using local radiologist's/investigator's tumor assessment. Subjects with bone lesions only at baseline will be included in the numerator if they achieve a complete response.

Clinical benefit rate (CBR)

Clinical benefit rate (CBR) is defined as the proportion of subjects with best overall response of CR, PR, or overall lesion response of stable disease (SD for measurable disease and non-CR/non-PD (NCRNPD) for non-measurable disease) with duration of 24 weeks or longer. A subject will be considered to have a SD/NCRNPD for 24 weeks or longer if SD/NCRNPD is recorded at 24 weeks or later after randomization. Taking into account the allowed time window for tumor assessment visits, the SD/NCRNPD response has to be recorded at 23 weeks or later after randomization to be included in the CBR calculation. Best overall response of CR, PR and overall lesion response of SD/NCRNPD are defined according to RECIST 1.1 (see Appendix 1). CBR will be calculated based on the FAS according to the ITT principle, using local radiologist's/investigator's tumor assessment. Subjects with non-measurable disease only at baseline will be included in the numerator if they achieve a complete response.

Time to response (TTR)

Time to overall response (TTR) of CR or PR is defined as the time from randomization to first documented response (CR or PR, which must be confirmed subsequently) for subjects with a confirmed CR or PR. It will be summarized using local radiologist's/investigator's tumor assessment.

Duration of Response (DOR)

Among subjects with a confirmed response (PR or CR) per RECIST 1.1 by investigator, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. It will be summarized using local radiologist's/investigator's tumor assessment.

ECOG performance status

ECOG performance status (PS) scale will be used to assess physical health of subjects, ranging from 0 (most active) to 5 (least active) given in Table 2.2.

ECOG PS will be evaluated at the following visits:

- Baseline (≤ 7 days prior to administration of the study drugs)
- Cycle 1 Day 1 (prior to administration of the study drugs)
- Every 2 Cycles after Cycle 1 Day 1(Cycle 3 Day 1, Cycle 5 Day 1 and etc)
- End of treatment

Table 2-2 ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG performance status will be assessed and recorded at baseline, and every two cycles thereafter as well as at discontinuation from the study treatment (within one week after discontinuation).

2.7.1 Secondary endpoints

Overall survival (OS), Objective Response Rate (ORR), Clinical Benefit Rate (CBR), Time to overall response（TTR) and Duration of Response (DOR), Time to deterioration of ECOG Performance Status.

2.7.2 Statistical hypothesis, model, and method of analysis

Overall Survival

Distribution of OS in each of the two treatment arms will be assessed using the Kaplan-Meier (KM) estimation method, and the treatment-specific KM curves will be graphically displayed. The estimated median OS and probability of surviving at the estimated median OS, along with 90% confidence intervals, will be presented for the two treatment arms. Stratified Cox regression models will be used to estimate the hazard ratio (HR) of death from any cause, along with the associated 90% confidence interval, comparing the everolimus + exemestane combination therapy with placebo + everolimus therapy where the stratification information will be obtained through IRT and the baseline hazard functions will be allowed to vary across strata.

Overall Response Rate

ORR estimates will be presented by treatment group along with exact 90% confidence intervals (Clopper and Pearson 1934). The estimation procedure will be repeated based on data for a subset of subjects in the FAS with measurable disease only at baseline.

Clinical Benefit Rate

CBR estimates will be presented by treatment group along with exact 90% confidence intervals.

Time to response

TTR will be summarized in 3-month intervals using descriptive statistics: mean, median, q1, q3, minimum and maximum. The analysis will be performed based on investigator assessment.

Duration of response

DOR will be summarized using descriptive statistics (count, mean, median, standard deviation, first and third quartile). The analysis will be performed based on investigator assessment.

ECOG performance status

Time windows will be defined for summaries of ECOG data. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment with the worst value will be considered. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. Note that only data collected under treatment (i.e. while the subject is treated and up to 7 days after last dose intake) will be included in the time to deterioration analysis. Post-treatment data will be summarized separately. The end of treatment assessment will be included if collected within 7 days of the last dose intake.

Time Window	Planned visit timing	Time Window Definition
Baseline	On or before Study Day 1	<= Study Day 1
Cycle 1 Day 1	Study Day 1	Study Days 1-8
Cycle 3 Day 1	Study Day 57	Study Days 50-64
Cycle 5 Day 1	Study Day 113	Study Days 106-120
Every 2 Cycles thereafter, Cycle X Day 1; X>1	Study Day ((X-1)*4)*7+1	Study Days ((x-1)*4)*7-6 to ((x-1)*4)*7+8 Note: EOT data visit are included if obtained within 7 days of last non-0 dose intake.
Study Day 1 = randomization date		

Frequencies of subjects with ECOG PS values of 0, 1 or >=2 will be used to summarize the ECOG PS data at each time window.

An analysis of the time to definitive deterioration of the ECOG PS by at least one category of the score from baseline will be performed. A deterioration will be considered definitive if no improvements in the ECOG PS are observed at subsequent measurement times during the treatment period following the time point at which the deterioration is observed. (Example 1: if the score is 1 at baseline and then 1, 2, 1, 2, 3 at study days 28, 57, 83, 115, 150, respectively, then the time to definitive worsening is 115 days. Example 2: if the score is 1 at baseline and then 1, 1, 2 at study days 28, 57, 83, respectively, with no assessment of the ECOG performance status after day 83, then the time to definitive worsening is 83 days.)

Death will be considered as worsening of the ECOG PS if it occurs close to the last available assessment where "close" is defined as being within twice the planned period between two assessments. Subjects who die after more than twice the planned period between two assessments will be censored at the date of their last assessment before the cut-off. This avoids overestimating the time to definitive worsening in subjects dying after an irregular assessment scheme. For example, if the last assessment is at week 6 and the subject dies at week 16, the definitive deterioration date will be week 16. On the other hand, if the last assessment is at week 6 and the subject dies at week 22, which is after more than twice the planned period between two assessments (6 weeks) since the last assessment (at week 6), then the subject is censored for definitive deterioration and the censoring date will be week 6. Subjects receiving any further anti-neoplastic therapy prior to definitive worsening will be censored at their date of last assessment prior to the start of therapy. Subjects that have not worsened at the data cut-off point will be censored at the date of last assessment prior to the cutoff.

The Kaplan-Meier estimation method will be used to assess the distribution of time to definitive worsening in the ECOG PS score, stratified by treatment. The estimated treatment-specific median times to definitive worsening will be presented along with 90% confidence intervals. The stratified Cox regression model will be used to estimate the hazard ratio of a definitive worsening in the ECOG PS score, along with the associated 90% confidence interval, comparing the everolimus + exemestane combination therapy with placebo + everolimus therapy.

2.7.3 Handling of missing values/censoring/discontinuations

The same statistical principles will be applied, and supportive analyses conducted as described in Section 2.5.3 for the handling of missing values/censoring/discontinuations.

The partial missing death date will be imputed following the rules in Section 5.4.4, but the complete missing death date won't be imputed. For the purpose of analysis, the patient with a complete missing death date will be censored at the last contact date.

2.8 Safety analyses

For all safety analyses, the safety set will be used. The assessment of safety will be based on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges.

The overall observation period will be divided into three mutually exclusive segments:

- pre-treatment period: from day of subject's informed consent to the day before first dose of study treatment
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study treatment
- post-treatment period: starting on day 31 after last dose of study treatment.

Safety summary tables will only include on-treatment events/assessments, i.e., those collected no later than 30 days after the date of the last study treatment administration. All safety events/assessments will be listed and those collected in the pre- and post-treatment period will be flagged.

2.8.1 Adverse events (AEs)

2.8.1.1 Coding of AEs

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 25.0.

2.8.1.2 Grading of AEs

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 AE is not necessarily twice as severe as a grade 1 AE).

If CTCAE grading is not available for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding to Grades 1 - 5, respectively, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form and "End of Post Treatment Disposition eCRF page".

2.8.1.3 General rules for AE Reporting

AE summaries will include all AEs starting on or after study day 1 (i.e., on or after the day of the first intake of study treatment) and starting no later than 30 days after the last treatment/exposure date. All AEs, deaths and serious adverse events will be listed. AEs starting prior to study day 1 and AEs starting later than 30 days after the last treatment/exposure date will be flagged in the listings.

AEs will be summarized by presenting the number and percentage of subjects having at least one AE and having at least one AE in each body system/primary system organ class, and for each preferred term using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade. A subject with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTC gradable or not, i.e., regardless of whether the question "CTC AE" on the Adverse Events eCRF is answered 'Yes' or 'No'.

The frequency of CTC grade 3 and 4 AEs will be summarized separately as well as summaries of all deaths and on-treatment deaths.

Any information collected (e.g., CTC grades, relatedness to study drug, action taken, etc.) will be listed as appropriate.

2.8.1.4 AE summaries

The following adverse event summaries will be produced:

- Adverse events, regardlessd of study drug relationship by primary system organ class, preferred term and maximum CTC
- Adverse events with suspected relationship to study drug by primary system organ class, preferred term and maximum CTC
- Adverse events with an overall incidence rate of 5% or more in either treatment arm, regardless of study drug relationship by primary system organ class and preferred term
- CTC grade >=3 adverse events, regardless of study drug relationship by primary system organ class and preferred term
- CTC grade >=3 adverse events with suspected study drug relationship by primary system organ class and preferred term
- Deaths, by primary system organ class and preferred term
- On-treatment deaths, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events with suspected study drug relationship, by primary system organ class and preferred term
- Serious adverse events with fatal outcome
- Non-Serious AEs (threshold>=5%), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation, with suspected study drug relationship, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term

- Adverse events requiring additional therapy, regardless of study drug relationship, by grade, primary system organ class and preferred term

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.5 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound everolimus. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on treatment period will be summarized by treatment arm. Time to first occurrence of AESI by variable was provided in the primary CSR (DCO: 05-May-2020) and hence will not be repeated in the report. The updated information will be provided in the listings.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI groupings. This file may be updated (i.e. it is a living document) based on review of accumulating trial data, and therefore the groupings are also subject to potential change. Table 2-3 provides the latest groupings at the time of the finalization of the SAP. The most up-to-date version of the CRS will be used at the time of the analysis.

Table 2-3 AESI groupings

AESI grouping	MedDRA category
Wound healing complications	CMQ

Thrombotic and embolic events	CMQ
Stomatitis	CMQ
Severe infections	SOC
Pre-existing infection (reactivation, aggravation, or exacerbation)	CMQ
Muscle wasting / Muscle loss	CMQ
Renal failure	CMQ
Hypophosphatemia	SMQ
Hyperglycemia/ new onset of diabetes mellitus	SMQ
Haemorrhages	SMQ
Dyslipidemia	SMQ
Cytopenia	CMQ
Cardiac failure	SMQ
Hypersensitivity (anaphylactic reactions)	SMQ
Non infectious pneumonitis	SMQ

2.8.2 Deaths

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT. Summaries of all deaths and on-treatment deaths will be provided.

2.8.3 Laboratory data

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTCAE).

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 events (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious adverse event.

A listing of laboratory values will be provided by laboratory parameter, subject, and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by parameter and treatment group.

Laboratory data summaries will include all laboratory assessments collected no later than 30 days after the last treatment/exposure date. All laboratory assessments will be listed and those collected later than 30 days after the last treatment/exposure date will be flagged in the listings.

Laboratory data will be classified (by Novartis biostatistics/SAS programming) into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A severity grade of 0 will be assigned when the value is within normal limits. In the case when a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.

The following rules will be applied:

- Conflict between normal range and grade definition: because many institutions have differences for normal ranges of metabolic laboratory and hematology values, the CTCAE often uses the terms 'Upper Limit of Normal (ULN)' and 'Lower Limit of Normal (LLN)' in lieu of actual numerical values. In some cases, an institution's LLN might be beyond the range specified for a grade. In this case, the institutional limits of normal should take precedence over the CTCAE values: the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.
- For the few parameters having comparison to baseline in CTCAE grading definition (Fibrinogen, INR, Hemoglobin, Creatinine), the highest grade will be retained. In other words, in the particular case when a value is grade x as per CTC grade definition based on threshold/ranges and grade x+1 when comparing to baseline, grade x+1 is retained.
- Grade values will be integers from 1 to 4. Grade 5 will only be used if the laboratory abnormality results in Death.
- For calcium, CTCAE grading is based on Corrected Calcium and not on Calcium. Corrected Calcium (CALC) will be calculated from Albumin and Calcium: Corrected Calcium (mg/dL) = Calcium (mg/dL) ‑0.8 [Albumin (g/dL)-4].
- For creatinine clearance (CRCLCG parameter), no calculation of CTC grade will be done.

The following summaries will be produced for the laboratory data (by laboratory parameter and treatment):

- Number and percentage of subjects with worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

The following listings will be produced for the laboratory data:

- Listing of subjects with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.
For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.
The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges
- Listing of notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities)

For laboratory tests where grades are defined by CTCAE v4.03.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where grades are not defined by CTCAE v4.03, shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

2.8.4 Other safety data

Data from other tests (e.g., electrocardiogram) will be summarized and listed, notable values will be flagged, and any other information collected will be listed as appropriate.
All assessments collected later than 30 days after the last treatment/exposure date will be flagged in the listings.
Any statistical tests performed to explore the data will be used only to identify any interesting comparisons that may warrant further consideration.

2.8.4.1 Vital signs

Vital sign assessments will be performed in order to characterize basic body function. The parameters expected to be collected include height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- body temperature: ≥ 39.1°C

- weight: increase from baseline of ≥ 10%
- pulse rate: ≥ 120 bpm with increase from baseline ≥ 15 bpm

Clinically notable below normal values

- systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- body temperature: ≤ 35°C
- weight: decrease from baseline of ≥ 10%
- pulse rate: ≤ 50 bpm with decrease from baseline ≥ 15 bpm.

The following summaries will be produced for each vital sign parameter:

- summary statistics for change from baseline to the worst post-baseline value (in both directions, i.e., from baseline to the highest post-baseline and from baseline to the lowest post-baseline value)
- number and percentage of subjects with at least one post-baseline vital sign abnormality (in both directions, i.e., both elevated and below normal values).

In addition, the following two listings will be produced by treatment group:

- subjects with clinically notable vital sign abnormalities
- all vital sign assessments will be listed by subject and vital sign parameter.

In both listings, the clinically notable values will be flagged and also the assessments collected later than 30 days after the last treatment/exposure date will be flagged.

2.9 Interim analysis

Not applicable.

3 Sample size calculation

Refer to CRAD001Y2202 SAP Addendum 1 for details.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Baseline comparability

Appropriate descriptive statistics of baseline variables will be provided as in-text tables in the core CSR and also in Section 14 in the post-text tables. The summaries will be presented by treatment group, but no p-values will be provided.

5.2 Time-to-event analyses

The following sections present a general methodology to be used to analyze the following time-to-event variables:

- Progression-free survival
- Overall survival
- Time to definitive deterioration in the ECOG score by one category of the score from baseline

5.2.1 Analysis of time to event data with ties

The STRATA statement in the SAS LIFETEST procedure will be used to analyze time-to-event data with ties. The SAS PHREG procedure with option TIES=EXACT will be used to fit the Cox proportional hazards model.

5.2.2 Kaplan-Meier survival function estimation

The survival function in each treatment group will be estimated using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST (see Figure 4-2 below). In each treatment group, the estimated median PFS time, along with the approximate 90% confidence interval, will be obtained from the PROC LIFETEST output. The log-log transformation option available within PROC LIFETEST will be used to compute the confidence intervals. The Kaplan-Meier graphs will be obtained from the SAS software. The hazard ratio point and interval estimates will be displayed in the figures.

5.2.3 Hazard ratio estimation

The hazard ratio as a measure of treatment effect will be derived from the ***Cox proportional hazards model*** using SAS procedure PHREG with TIES=EXACT option in the MODEL statement. The ***stratified unadjusted Cox model*** will be used (where the baseline hazard function is allowed to vary across strata) for the primary andandsecondaryandandsecondary analyses, i.e., the MODEL statement will include the indicator of assignment to the everolimus + exemestane arm as the only covariate, and the STRATA statement will include the stratification variable obtained through IRT.

The two-sided 90% asymptotic confidence interval for the hazard ratio will be based on ***the Wald test***.

5.3 Median follow-up of the study

Median study follow-up (in months) in this study will be calculated as

([analysis cut-off date] - [median randomization date] + 1)/30.4375, where 30.4375 is the average duration of a month in days: 365.25/12 ≈ 30.4375.

The median randomization date is obtained by first sorting all subjects in the FAS by the randomization dates, respectively, and then taking the date of the median subject (i.e., the subject in the middle of the sorted list in case of an odd number of subjects or the average between the two subjects in the middle of the sorted list in case of an even number of subjects).

The time from last contact date to data cut-off date will be summarized by time intervals in increments of 6 weeks.

The number of subjects at risk of death and the number of deaths in intervals of time with increments of 6 weeks will be summarized during the course of the trial using the life table method. The Kaplan-Meier estimates of survival probabilities and associated standard errors will be provided.

5.4 Imputation rules

5.4.1 Study drug

The following rule should be used for the imputation of date of the last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the dose end date. The scenario is only used for interim analysis.

Scenario 2: If the date of last administration is completely or partially missing and the EOT page is available:

Case 1: The date of last administration is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the date of last administration is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the date of last administration sis available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

Case 5: Both Year (yyyy) and Month(mm) are available for the date of last administration, and yyyy = the year of EOT and mm = the month of EOT date, use EOT date if day of EOT not missing or use the first day of month if date of EOT missing.

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.4.2 AE date imputation

No imputation of missing or incomplete data will occur except for AE start dates in the determination of treatment emergence as described below:

If the date is completely missing, then it will be set to the first dose date.

If the day is missing, then the first day of the month will be used. If this date is before the first dose date and the months are the same, then the first dose date will be used.

If the day and month are missing, then the first day of the year will be used. If this date is before the first dose date and the years are the same, then the first dose date will be used.

If the imputed AE onset date is after the AE stop date, then the AE stop date will be used.

The original partial or missing dates rather than the imputed dates will be presented in data listings. Missing AE start times will not be imputed.

5.4.3 Concomitant medication date imputation

5.4.3.1 Prior therapies date imputation

For prior or concomitant medications, including rescue medications, incomplete (ie, partially missing) start dates and/or stop dates will be imputed. When the start date and stop date are both missing start dates and/or stop dates will be imputed. When the start date and stop date are both incomplete for a subject, impute the start date first.

Incomplete Start Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the incomplete start date, assuming year is available. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing Day and Month

If the year of the incomplete start date is the same as the year of the date of the first dose of study treatment, then the day and month of the date of the first dose of study treatment will be assigned to the missing fields.

If the year of the incomplete start date is before the year of the date of the first dose of study treatment, then December 31 will be assigned to the missing fields.

If the year of the incomplete start date is after the year of the date of the first dose of study treatment, then January 1 will be assigned to the missing fields.

Missing Month Only

The day will remain the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study treatment, then the day of the date of the first dose of study treatment will be assigned to the missing day.

If either the year is before the year of the date of the first dose of study treatment or if both years are the same but the month is before the month of the date of the first dose of study treatment, then the last day of the month will be assigned to the missing day.

If either the year is after the year of the date of the first dose of study treatment or if both years are the same but the month is after the month of the date of the first dose of study treatment, then the first day of the month will be assigned to the missing day.

Incomplete Stop Dates

If the field of year is missing, then no value will be imputed. The following rules will be applied to impute the missing numerical fields, assuming year is available. If the date of the last dose of study treatment is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the stop date will be imputed using the start date.

Missing Day and Month

If the year of the incomplete stop date is the same as the year of the date of the last dose of study treatment, then the day and month of the date of the last dose of study treatment will be assigned to the missing fields.

If the year of the incomplete stop date is before the year of the date of the last dose of study treatment, then December 31 will be assigned to the missing fields.

If the year of the incomplete stop date is after the year of the date of the last dose of study treatment, then January 1 will be assigned to the missing fields.

Missing Month Only

The day will be the same as observed and the month will be replaced according to the procedure in the preceding subsection.

Missing Day Only

If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study treatment, then the day of the date of the last dose of study treatment will be assigned to the missing day.

If either the year is before the year of the date of the last dose of study treatment or if both years are the same but the month is before the month of the date of the last dose of study treatment, then the last day of the month will be assigned to the missing day.

If either the year is after the year of the date of the last dose of study treatment or if both years are the same but the month is after the month of the date of the last dose of study treatment, then the first day of the month will be assigned to the missing day.

5.4.3.2 Post therapies date imputation

The date imputation method will be similar to the above section.

5.4.4 Death date imputation

If the day is missing, then a) if the year and month of EOT is the same as year and month of death, then use the EOT date; b) if the year of death is later than year of EOT, then use the first day of the first month in this year; c) if the year of the death is the same as year of EOT and month is later than month of EOT, then use the first day of the month. If the month and day are missing, then a) if the year of EOT is the same as year of death, then use the EOT date; b) if the year of death is later than the year of EOT, then use the first day of the first month in this year (JAN01).

5.5 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v4.03 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 AE is not necessarily twice as severe as a grade 1 AE).

If CTCAE grading is not available for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding to Grades 1 - 5, respectively, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

5.6 Laboratory parameters derivations

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTCAE).

A listing of laboratory values will be provided by laboratory parameter, subject, and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by parameter and treatment group.

Laboratory data summaries will include all laboratory assessments collected no later than 30 days after the last treatment/exposure date. All laboratory assessments will be listed and those collected later than 30 days after the last treatment/exposure date will be flagged in the listings.

Laboratory data will be classified (by Novartis biostatistics/SAS programming) into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A severity grade of 0 will be assigned when the value is within normal limits. In the case

when a local laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.

3 Reference

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