NOVARTIS

Clinical Development

LEE011/Ribociclib/Kisqali®

CLEE011A3201C (RIGHT CHOICE) / NCT03839823

A phase II randomized study of the combination of Ribociclib plus Goserelin acetate with Hormonal Therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer – RIGHT Choice Study

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
26-Feb-2019	Prior to FPFV	Creation of final version	N/A - First version	NA
28-Jan-2021	After Protocol amendment 1	Creation of amendment	Secondary objectives updated and included comparing 3-month treatment failure rate between two arms. [redacted]	Section 1.1
			Definition of last date of exposure was updated.	Section 2.1.1
			Dose calculation was updated and clarified.	Section 2.4.1
			Censoring for new anti cancer therapy before PFS events was updated and clarified.	Section 2.5.1
			Definitions and method of analysis were updated to include 3-month treatment failure rate as secondary endpoint.	Section 2.7
			PRO analysis updated.	Section 2.10
18-Feb-2022	After protocol amendment 2	Creation of amendment	Study design description were updated to align with protocol amendment.	Section 1.1
			Interim analysis was removed as per protocol amendment.	Section 1.1, 2.1, 2.13
			Last contact date data sources updated in Table 2-5	Section 2.1.1
			Exclusion criteria for PPS was udpated.	Section 2.2
			Last date of exposure definition updated for chemotherapy. Leuprorelin was added in definition.	Section 2.1, 2.4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			DFI defitinition was updated for clarifications and calculations based on CRF.	Section 2.3
			Protocol deviation related to COVID-19 pandemic were added.	Section 2.5
			Significance level and required number of events were updated in primary anlaysis. Sensitivity anlaysis considering COVID-19 impact was added.	Section 2.7
			Study follow-up summary was added.	Section 2.8
			Notable ECG list was updated.	Section 2.10
			PRO analysis was updated for clarification. Time to deteriation anlaysis was added.	
			Sample size calcuation updated with significance level and required number of events.	Section 2.13
23-Jun-2022	Prior to DBL	Creation of amendment	Time window for multiple assessments was updated.	Section 2.1
			Withdraw of informed consent was updated.	Section 2.2
			Subgroup of interes was updated.	Section 2.2.1
			ORR and CBR definitions were updated to clarify confirmed and unconfirmed responses.	Section 2.7.1
			Gap time calculation was added.	Section 2.7.2
			Sodium and Phosphorus will be excluded from laboratory data summary due to protocol amendment and CRF updates.	Section 2.8.3
			Baseline for PRO was updated.	Section 2.10

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List of abbreviations

AE	Adverse event
AESI	Adverse event os special interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GPT
ATC	Anatomical Therapeutic Classification
BOR	Best Overall Response
BMI	Body Mass Index
CBR	Clinical Benefit Rate
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration eCRF pages
DFS	Disease Free Interval
DI	Dose Intensity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
FACT-B	Functional Assessment of Cancer Therapy - Breast
FAS	Full Analysis Set
FPFV	First Patient First Visit
HER2	Human Epidermal Growth Factor Receptors
HLGTs	High Level Group Terms
HLT	High Level Term
HR+	Hormone Receptor Positive
IA	Interim Analysis
IRT	Interactive Response Technology
IV	Intravenous
LPFV	Last Patient First Visit
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NMQ	Novartis MedDRA queries
ORR	Overall Response Rate
OS	Overall Survival
PDI	Planned Dose Intensity
PFS	Progression-Free Survival

PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PS	Performance Status
PT	Preferred Term
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TA	Tumor Assessment
TTF	Time to Treatment Failure
TTR	Time to Response
TTP	Time to Progression
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the detailed statistical methodology to be used for the Clinical Study Report (CSR) for the analysis of study CLEE011A3201C, a phase II randomized study of the combination of Ribociclib plus goserelin acetate with hormonal therapy versus physician choice chemotherapy in premenopausal or perimenopausal patients with hormone receptor-positive/HER2-negative inoperable locally advanced or metastatic breast cancer.

CSR deliverables (shells for tables, figures, listings) and further programming specifications will be described in Tables Figures and Listings (TFL) shells and Programming Datasets Specifications (PDS) documents, respectively.

The content of this SAP is based on protocol CLEE011A3201C version 02. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a randomized, phase II, open label, multi-center trial comparing the combination of NSAI (letrozole or anastrozole) + goserelin + ribociclib versus combination chemotherapy (either of docetaxel+capecitabine, paclitaxel+gemcitabine or capecitabine+vinorelbine). Premenopausal or perimenopausal women with HR+, HER2-negative, advanced breast cancer with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and fulfill at least one of the following criteria will be considered for this study: symptomatic visceral metastases, or rapid progression of disease or impending visceral compromise, or markedly symptomatic non-visceral disease.

Approximately, 222 eligible women patients will be competitively enrolled and randomly assigned to one of the below treatment arms in 1:1 ratio:

- **Ribociclib arm:** NSAI + goserelin + ribociclib (N = 111)
- **Combination chemotherapy arm:** Either of docetaxel+capecitabine, paclitaxel+gemcitabine or capecitabine+vinorelbine based chemotherapy treatment (N = 111). The choice of which chemotherapy combination will be used on study will be decided by the study investigator; once patients initiate the treatments, switching to another combination chemotherapies will not be allowed.

Randomization will be stratified by the presence of liver metastases (present or absent), and Disease free interval (DFI) < 2 years (yes or no, de novo stage 4 is defined as DFI >2 years).

Progression free survival (PFS) as assessed by local investigator review of tumor assessments and using RECIST 1.1 criteria is the primary endpoint in this study. Secondary efficacy endpoints include overall survival (OS), time to treatment failure (TTF), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), and 3-month treatment failure rate.

Table 1-1 Study objectives and endpoints

Primary Objective:	**Primary Endpoint:**
To determine whether treatment with NSAI + goserelin+ ribociclib prolongs PFS compared to treatment with combination chemotherapy in premenopausal or perimenopausal women with HR+, HER2 negative locally advanced or metastatic breast cancer.	Progression-free survival is defined as the time from the date of randomization to the date of the first documented progression as per local review and according to RECIST 1.1 or death due to any cause.
Secondary Objectives:	**Secondary Endpoints:**
To compare time to treatment failure (TTF) between the two treatment arms.	Time to treatment failure is defined as the time from the date of randomization to the earliest of date of progression, date of death due to any cause, change to other anti-cancer therapy, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'.
To compare 3-month treatment failure rate between two treatment arms	Treatment failure rate is defined as the proportion of patients who discontinued the study treatment by 3 months due to progression disease, death due to any cause, change to other anti-cancer therapy, or discontinuation due to reasons other than protocol violation or administrative problems.
To determine whether treatment with NSAI + goserelin + ribociclib increases overall response rate (ORR), clinical benefit rate (CBR), and Time to response (TTR) compared to treatment with combination chemotherapy.	• Overall response rate (ORR) is defined as the proportion of patients whose best overall response is either CR or PR, as per local review and according to RECIST 1.1. • Clinical benefit rate is defined as the proportion of patients with a best overall response of complete response (CR), or partial response (PR) or stable disease, lasting for a duration of at least 24 weeks, as defined by RECIST 1.1. • Time to response is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be subsequently confirmed, as defined by RECIST 1.1.
To compare the overall survival (OS) between two treatment arms.	Overall survival is defined as the time from the date of randomization to the date of death due to any cause.
To evaluate the safety of ribociclib in combination with NSAI and goserelin, and combination chemotherapies	Frequency/severity of adverse events, lab abnormalities.
To compare patient reported outcomes for health-related quality of life in the two treatment arms	Change from baseline in the global health status/QOL scale score by using FACT-B questionnaires.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings. Analysis using RShiny apps might also be used as needed.

Data included in the analysis

There is one primary analysis planned for the primary efficacy endpoint and one final anlaysis planned for overall survival. An unique cut-off date will be established after the targeted number of events for the planned primary and final analyses has been documented. For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

The analysis cut-off date for the primary analysis of study data will be established after 110 targetted PFS events have been documented. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as ‘ongoing. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cutoff date for the final analysis of study data will be established at the end of the study (after 46 months from FPFV) or when OS events have been reached (80% of 222 patients have died), whichever occurs first.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables

by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group.

2.1.1 General definitions

Investigational drug and study treatment

Study (Investigational) drug is defined as LEE011 (ribociclib).

S**tudy treatment** is defined as LEE011 (ribociclib) + NSAI (Letrozole, Anastrozole) + goserelin (or leuprorelin), and combination chemotherapy is defined as docetaxel+capecitabine, paclitaxel+gemcitabine or capecitabine+vinorelbine based chemotherapy treatment. The term investigational treatment may also be referred to as ***study treatment*** which is used througouht this document.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) Electronic Case Report Form (eCRF). The date of first administration of study drug will also be referred as start of investigational drug.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as is the last date when a nonzero dose of investigational drug is administered and recorded on the DAR eCRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the Dosage Administration (e)CRF. (Example: if 1st dose of LEE011 is administered on 15-Mar-2019, and 1st dose of combination partner is administered on 12-Mar-2019, then the date of first administration of study treatment is on 12-Mar-2019).

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per Dose Administration (e)CRF. (Example: if the last LEE011 dose is administered on 24-Oct-2019, and the last dose of a combination partner is administered on 26-Oct-2019, then the date of last administration of study treatment is on 26-Oct-2019).

Last date of exposure to study drug/treatment

The last date of exposure to study treatment is derived to be the latest date of the last date of exposure to ribociclib, letrozole, anastrozole, goserelin (or leuprorelin), and chemotherapy drug (docetaxel, capecitabine, paclitaxel, gemcitabine, vinorelbine). The last date of exposure will be derived as follows:

For ribociclib, letrozole, and anatrazole, the last date for exposure is defined as the date of last administration of the corresponding medication.

For goserelin and leuprorelin, the last date of exposure is defined as the date of last administration of goserelin + 27 days. If a patient died or was lost to follow-up within date of last administration +27 days, then the last date of exposure is the date of death or last contact date, respectively.

For docetaxel and paclitaxel (175mg/m^2), the last date of exposure is defined as the date of last administration of the chemotherapy + 20 days. If a patient died or was lost to follow-up within date of last administration +20 days, then the last date of exposure is the date of death or last contact date, respectively.

For capecitabine, the last date of exposure is defined as the date of last administration of the chemotherapy + 7 days. If a patient died or was lost to follow-up within date of last administration +7 days, then the last date of exposure is the date of death or last contact date, respectively.

For gemcitabine, paclitaxel (80-90mg/m^2), and vinorelbine, the last date of exposure is defined as the date of last administration of the chemotherapy + 13 days. If a patient died or was lost to follow-up within date of last administration +13 days, then the last date of exposure is the date of death or last contact date, respectively.

The last date of exposure to study treatment is defined as the latest date among the last date of exposure to ribociclib, letrozole, anastrozole, goserelin, and chemotherapy drugs (docetaxel, capecitabine, paclitaxel, gemcitabine, vinorelbine).

If the derived last date of exposure to study drug/study treatment goes beyond the data cutoff date, it should be truncated to the date of data cutoff .

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, ECOG performance status, and patient reported outcomes (PRO)) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

'Death' is an efficacy endpoint (for OS), but it can also be included in the safety analysis. For safety, the 'study day' will be calculated relative to start of study treatment, while for efficacy overall survival will be derived relative to randomization date.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include PRO and ECOG performance status. For RECIST-based endpoints (e.g. PFS, best overall response), a window of +/-7 days for the start of study treatment will be allowed, i.e. the baseline will be considered valid if it occurs within 7 days of the treatment start date.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as 'baseline' assessment.

In case time of assessment and time of treatment start is captured , the last available assessment before the treatment start date/time is used for baseline.

For demographic and baseline summary (vital signs, ECG, etc.), the assessment on or prior to the date of randomization is taken as "baseline".

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post

treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize performance status (ECOG), PRO measures, laboratory, ECG, and vital signs collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If multiple assessments on the same date then the worst case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

The following provides an example how to define the time windows for ECOG performance status (PS).

Table 2-1 Time window for ECOG PS, ECG, vital signs and Laboratory assessments (LEE011 arm only)

Assessment	Target day of assessment	Time Interval
Baseline		≤ Day 1
Cycle 1 Day 15	15	Day 2 to day 21
Cycle 2 Day 1	29	Day 22 to day 35
Cycle 2 Day 15	43	Day 36 to day 49
Cycle 3 Day 1	57	Day 50 to day 70
Cycle k Day 1 (4≤k≤11)	d=(k-1)*28+1	Day d-14 to day d+13
Cycle 12 Day 1	309	Day 295 to day 350
Cycle 15 Day 1	393	Day 351 to day 434
Cycle k Day 1 (k=18, 21,.....)	d=(k-1)*28+1	Day d-42 to day d+41
End of Treatment		Assessment taken at the end of treatment visit

Table 2-2 Time window for ECOG PS, ECG, vital signs and Laboratory assessments (Chemotherapy arm only)

Assessment	Target day of assessment	Time Interval
Baseline		≤ Day 1
Cycle 1 Day 15	15	Day 2 to day 18
Cycle 2 Day 1	22	Day 19 to day 28
Cycle 2 Day 15	36	Day 29 to day 39
Cycle 3 Day 1	43	Day 40 to day 53
Cycle k Day 1 (4≤k≤11)	d=(k-1)*21+1	Day d-10 to day d+10
Cycle 12 Day 1	232	Day 222 to day 263

Assessment	Target day of assessment	Time Interval
Cycle 15 Day 1	295	Day 264 to day 326
Cycle k Day 1 (k=18, 21,.....)	d=(k-1)*21+1	Day d-31 to day d+31
End of Treatment		Assessment taken at the end of treatment visit

Time windows will be defined for descriptive summary of PRO data by visit and longitudinal data analysis. 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 obtained prior to visit 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 patient is treated) will be included in the time to definitive deterioration or longitudinal model analysis. Post-treatment data will be summarized separately. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

Table 2-3 Time window for PRO assessments (LEE011 arm only)

Assessment	Target day of assessment	Time Interval
Baseline		≤ Day 1
Cycle 2 Day 15	43	Study days 2 – 64
Cycle 4 Day 1	85	Study days 65 – 112
Cycle 6 Day 1	141	Study days 113 – 168
Cycle 8 Day 1	197	Study days 169 – 224
Cycle 10 Day 1	253	Study days 225 – 280
Cycle 12 Day 1	309	Study days 281 – 350
Cycle 15 Day 1	393	Study days 351 – 434
Cycle k Day 1 (k=18, 21, 24,....)	d=(k-1)*28+1	Day d-42 to day d+41
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Post treatment study day 27 - 33

Table 2-4 Time window for PRO assessments (Chemotherapy arm only)

Assessment	Target day of assessment	Time Interval
Baseline		≤ Day 1
Cycle 3 Day 1	43	Study days 2 – 64
Cycle 5 Day 1	85	Study days 65 – 112
Cycle 7 Day 15	141	Study days 113 – 168
Cycle 10 Day 8	197	Study days 169 – 224
Cycle 13 Day 1	253	Study days 225 – 280
Cycle 15 Day 15	309	Study days 281 – 350
Cycle 19 Day 15	393	Study days 351 – 434
Cycle k Day xx (k=21, 24,....)	d=(3k-1)*7+1	Day d-42 to day d+41

Assessment	Target day of assessment	Time Interval
End of Treatment		Assessment taken at the end of treatment visit
30-day safety follow-up	Post treatment study day 30	Post treatment study day 27 - 33

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-5 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or 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	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
Concomitant medication date	Non-missing medication
Date of ECG assessment	At least one non-missing parameter value
Date of PRO assessment	At least one non-missing parameter value
Cardiac imaging date	Non-missing LVEF or overall interpretation
[redacted]	
Start/End dates from antineoplastic therapy after study treatment	Non-missing medication/procedure term
Date of withdraw informed consent	No condition

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the 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. Partial date imputation is allowed for event (death)/censoring is coming from ‘Survival information’ eCRF. The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat (ITT) principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure regardless of whether or not treatment was administered. This population will be the primary population for all efficacy analyses.

Per protocol set (PPS)

The Per-Protocol Set (PPS) consists of a subset of the patients in the FAS who are compliant with requirements of the CSP.

The following list of protocol deviations will lead to exclusion of the patient from the Per-Protocol Set:

- Patient is less than 18 or greater than or equal to 60 years old at the time of informed consent (INCL01a)
- Patient did not provide informed consent (INCL01b)
- Patient does not have histologically and/or cytologically confirmed diagnosis of ER and/or PR postitive breast cancer by local laboratory (INCL02a)
- Patient does not have HER2 negative breast cancer defined as a negative in situ hybridization test or IHC status of 0, 1 or 2 (INCL03)
- Allred (Estrogen receptor) score should be greater than... or equal to 5 when ER status is positive and percentage is not provided by local laboratory testing (INCL04d)
- Estrogen Receptor (ER) percentage should be greater than 10 when ER status is positive and Allred score is not provided by local laboratory testing (INCL04e)
- Both Allred score and Estrogen receptor percentage present but Protocol inclusion criteria not met (INCL04f)
- Patient does not have at least one measurable lesion as per RECIST 1.1 criteria (INCL06d)
- Patient has received prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy, or any CDK4/6 inhibitor for advanced breast cancer) (EXCL01)
- Patient is post menopausal (EXCL05)
- Patient is concurrently using hormone replacement therapy (EXCL14)
- Patient was switched from one combination chemotherapy to another combination chemotherapy (TRT18)Patient on combination chemotherapy treatment, without disease progression and any related toxicity, switched to endocrine treatment (TRT19)
- Patient received other investigational therapy, other antineoplastic therapy while on study drug (COMD05)
- Patient received megestrol acetate while on study drug (COMD08) > 7 days

- Patient received medroxyprogesterone while on study drug (COMD09) > 7 days

A sensitivity analysis of the primary endpoint (i.e., PFS) will be performed using PPS if the primary efficacy analysis is significant and the FAS and PPS differ.

Safety

The Safety set includes all subjects who received any study treatment (i.e. at least one dose of any component of the study treatment). Subjects will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

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

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-6.

Table 2-6 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	Not applicable
Safety set	No written inform consent	No dose of study treatment
Per-protocol set	Any major protocol deviation as listed in definition of per protocol set	No dose of study treatment

Withdraw of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Analysis of biological sample(s) after a subject withdrew consent from the study is not allowed. Data containing confirmed cases of biological sample analysis after withdrawal of consent should not be transferred by the vendor to Novartis.

Patient from Malaysian and withdraw consent from study will be excluded in the analysis as per local regulation.

2.2.1 Subgroup of interest

Subgroup analyses will be performed for safety and efficacy. Subgroups will be formed using CRF data. This includes variables related to stratification factors i.e. CRF data will be used to

define these subgroups. Efficacy and safety subgroup analyses will be based on following subgroups:

- Visceral crisis status (Yes vs No)
- Disease free interval (< 2 years vs ≥ 2 years) (based on CRFdata)
- De novo (Yes vs No)
- Presence of liver metastasis (Yes vs No) (based on CRF data)
- Age (< 40 years and ≥ 40 years)
- Recurrence during or within one year of completion of adjuvant hormonal therapy (Yes vs No)
- Baseline ECOG performance status (0 vs ≥1)
- History of adjuvant endorine therapy (Yes vs No)
- History of adjubant chemotherapy (Yes vs No)
- Presence of lung and/or liver metastasis (Yes vs No)Patients eligible for inclusion criteria 4c (Yes vs No)

Efficacy

The primary efficacy endpoint will be summarized by the above mentioned subgroups to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is statistically significant.

For each of the subgroups, the following analyses will be performed:

- Kaplan-Meier estimates of the survival distribution of PFS
- Hazard ratio with 95% CI using stratified Cox proportional hazards model. For subgroups based on DFI, and presence of liver metastasis, unstratified analyses will be performed to avoid estimation issues, since these variables are related to the stratification factors.

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95%-confidence intervals will be provided.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. Key safety analyses will be repeated on safety set in the above mentioned subgroups.

The main safety analyses include:

- AEs, irrespective of causality, by primary system organ class, preferred term and maximum grade
- AEs with suspected relationship to study treatment by primary system organ class, preferred term and maximum grade
- All deaths, by primary system organ class and preferred term
- Serious AEs, irrespective of causality, by primary system organ class and preferred term – overall and grade 3 or 4

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly bserved in a subgroup of patients.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline (including disease characteristics) and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm and for all patients and listings will be reported by treatment arm to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups: <40 and ≥ 40 years, race, ethnicity, etc...) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). Body Mass Index (BMI) (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Baseline stratification factors

The number (%) of patients in each stratum (presence of liver metastases (present or absent), and DFI < 2 years (yes or no)) based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS.

DFI is defined as duration between the date of patient received curative surgery for primary breast cancer lesion to the date of most recent relapse documented < 2 years (yes or no) , de novo stage 4 disease is defined as DFI >2 years.

The date of curative surgery will be based on Prior Antineoplastic Therapy - Surgery CRF data and the date of most recent replase will be based on Diagnosis and Extent of Cancer CRF. For patients with missing surgery date, start date of prior antineoplastic therapy in adjuvant setting will be used, or data of initial diagnosis will be used if the start date of prior adjuvant therapy is missing.

Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, current disease status, histological grade, predominant histology/cytology, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to randomization (in months), stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved, HER-2/estrogen/progesterone

receptor status, estrogen/progesterone receptor percentage, estrogen/progesterone allred score, criteria met for entering the study, visceral crisis status. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Time since initial diagnosis, time since most recent relapse/progression to randomization will be summarized in months. A month is defined as 365.25/12=30.4375 days.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be summarized and listed by treatment arm. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary SOC, PT and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline such as source of patient referral will be listed.

2.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS. The number (%) of randomized patients included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized patients will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were randomized
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component)
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Phase' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the End of Post-treatment follow-up page);

- Reasons for discontinuation from the post-treatment follow-up (based on End of Post-treatment follow-up page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

In addition to the pre-defined standard PD terms, the following protocol deviations related to the COVID-19 pandemic were added and will be summarized.

- Extended screening period due to COVID-19 outbreak
- Extended period between safety or efficacy assessments due to COVID-19 outbreak
- Failure to follow drugs administration scheme due to restrictions imposed for hospital visits due to COVID-19 outbreak
- Missed patient visit due to COVID-19
- Visit done outside of study site due to COVID-19
- Assessment/procedure changed due to COVID-19
- Drug supply method changed due to COVID-19
- Discontinuation due to COVID-19
- Treatment not given due to COVID-19

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized by treatment group.

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

The Safety set will be used for the analysis below unless otherwise specified. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be presented.

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, average daily dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm, separately for each component of study treatment. The duration of treatment will also be presented for each combination arm. Duration of exposure 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 arm.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control, and any combination partner:

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

The last date of exposure to study treatment is the latest of the last dates of exposure to investigational drug or control, and any combination partner.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (<3 months; 3 to <6 months, 6 to <9 months, 9 to <12 months, etc) and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

Duration of exposure to LEE011, combination partner and chemotherapy

Duration of exposure to any single component of study treatment will be calculated as

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

The duration includes the periods of temporary interruption.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For ribociclib and letrozole, anastrozole, goserelin and leuprorelin, the cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure of ribociclib and letrozole, anastrozole, goserelin respectively.

For docetaxel (IV infusion) and paclitaxel (IV infusion), the dose is collected in mg/m^2 at cycle N and it should be obtained by the investigator as the dose administered (mg) at cycle N divided by the body surface area (BSA) at the beginning of the cycle N using the weight measured before the infusion.

For gemcitabine (IV infusion), paclitaxel (IV infusion), and vinorelbine, the dose in mg/m^2 at cycle N will be the sum of the 2 doses planned to be received at day 1 and day 8 of cycle N when applicable.

Dose intensity and relative dose intensity

Dose intensity (DI) is defined for subjects with non-zero duration of exposure. For subjects who did not take the drug, the DI is by definition equal to zero.

DI (dosing unit/unit of time) = cumulative dose (dosing unit) / duration of exposure (unit of time)

Planned dose intensity (PDI) is defined as the assigned dose by unit of time planned to be given to patients as per protocol. The PDI for each study treatment component is displayed in Table 2-7. Note that DI will also be calculated and reported in the units displayed in Table 2-7, whereas duration of exposure itself will be summarized in months.

Table 2-7 Planned dose intensity

Medication	PDI (dose unit/unit of time)
Ribociclib/placebo	600 mg/day
Letrozole	2.5 mg/day
Anastrozole	1 mg/day
Goserelin	3.6 mg/28 days
Leuprorelin	3.75 mg/28 days
Docetaxel	60 – 75 mg/m^2
Capecitabine	1600 – 2500 mg/m^2
Paclitaxel	175 mg/m^2 or 80-90 mg/m^2
Gemcitabine	1000 – 1250 mg/m^2 or 800-1250 mg/m^2
Vinorelbine	60 – 80 mg/m^2 or 25-30 mg/m^2

Relative dose intensity (RDI) is defined as:

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

DI will be summarized separately for each of the study treatment components but using the duration of exposure of each of the components. RDI will summarized for ribociclib, goserelin, leuprorelin, letrozole and anatrozole.

DI and relative dose intensity (RDI) are defined as follows :

For letrozole and anastrozole, DI is defined as

DI (mg/day) = Cumulative dose (mg) / duration of exposure to study treatment component (days)

RDI = DI (mg/day) / PDI (mg/day).

For goserelin, DI is defined as

DI (mg/28 days) = Cumulative dose (mg) / {[(date of last administration of goserelin + 27) – (date of first administration of goserelin)+1] / 28},

RDI = DI (mg/28days) / PDI (mg/28days).

For ribociclib, DI is defined as

DI (mg/day) = Cumulative dose (mg) / adjusted duration of exposure to ribociclib/placebo (days),

RDI = DI (mg/day) / PDI (mg/day)

where adjusted duration of exposure (days) to ribociclib represents the number of ribociclib dosing days a patient would be expected to have received per protocol, given their duration of exposure to ribociclib. Since ribociclib follows a 3 weeks on, 1 week off schedule, the adjusted duration of exposure to ribociclib is the duration of exposure to ribociclib minus the planned off days. The adjusted duration of exposure to ribociclib is therefore 21 x (# completed 28 day cycles) + min(21, duration of last incomplete cycle).

For example, if the duration of exposure to ribociclib is 66 (corresponding to two cycles and 10 days), then the adjusted duration of exposure to ribociclib is 21*2+10=52. If the duration of exposure to ribociclib is 108 days (corresponding to three cycles and 24 days), then the adjusted duration of exposure is 21*3+21=84 days.

Specifically, let D1 represent the duration of exposure to ribociclib. Then the adjusted duration of exposure is defined as
D=21*[D1/28]+min(21,D1-28*[D1/28]) days,

where [x] stands for the integer part of x. In this equation [D1/28] is the number of completed cycles, and D1-28*[D1/28] is the additional number of days in the last, incomplete cycle (if any). For example, if D1=30 then [D1/28]=1, D1-28*[D1/28]=2, and D=23. If D1=7 then D=7; if D1=22 then D=21; if D1=28 then D=21, etc.

DI for chemotherapy
For capecitabine,
DI (mg/ cycle) = [cumulative dose (mg/ m^2) / adjusted duration of exposure to capecitabine (days),
Where adjusted duration of expousre (days) is 14 x (# completed 21 day cycles) + min(14, duration of last incomplete cycle).
For other chemotherapy :
DI (mg/cycle) = [cumulative dose (mg/m^2) / duration of exposure (days)]*21

Dose reductions, interruptions or permanent discontinuations

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

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

Dose interruptions are captured in the eCRF following the Oncology Data standard Reference manual and CRF Completions Guidelines. Depending on the dosing administration schedule (e.g. continuous dosing, interval dosing), data would be collected in different fashion. For

instance, for continuous dosing an interruption is defined as a dose of zero in a unit of time between two non-zero dosing records. In general any rest period as part of the regimen/schedule is not considered as an interruption.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the dose change and the direction of the change.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery, or other therapies not defined by the previous categories, will be summarized by treatment arm. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy, immunotherapy etc.), setting (e.g. adjuvant, neoadjuvant etc.) and also by lowest Anatomical Therapeutic Classification (ATC) class, preferred term and treatment.

Number of lines of prior medication therapy, prior chemotherapy, and prior hormonal therapy will be summarized by treatment arm in any setting and in the metastatic setting. In addition, number of lines of prior chemotherapy in the neo-/adjuvant setting will also be summarized by treatment group.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

Anti-neoplastic medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, PT, overall and by treatment group by means of frequency counts and percentages using FAS.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

2.5 Analysis of the primary objective

The primary objective of the study is to determine whether treatment with LEE011 + NSAI + goserelin prolongs PFS compared to treatment with combination chemotherapy in premenopausal or perimenopausal women with HR+, HER2 negative locally advanced or metastatic breast cancer.

2.5.1 Primary endpoint

The primary endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. For the primary efficacy analysis, PFS will be based on local investigators review of tumor assessments and using RECIST 1.1 criteria (see Appendix 2 of the study protocol). The primary analysis will be based on FAS and will include all data observed up-to the cut-off date.

If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be censored for the primary analysis. (See Section 2.5.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the ‘End of treatment’ and ‘End of post treatment follow up’ disposition pages without supporting objective evidence satisfying progression criteria per RECIST 1.1) will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression for the primary analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups. Assuming proportional hazards for PFS, the following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 \geq 1 \quad \text{vs.} \quad H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (ribociclib + NSAI + goserelin arm vs combination chemotherapy arm). The analysis to test this hypothesis will consist of a stratified log-rank test at an overall one-sided 10% level of significance. Stratification will be based on the randomization stratification factors: presence of liver metastases (present or absent), and DFI < 2 years (yes or no, de novo stage 4 is defined as DFI < 2 years).

The primary efficacy variable, PFS will be analyzed once 110 PFS events are observed. The survival distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically by treatment arm. The median, 25th and 75th percentiles of PFS along with 95% confidence intervals will be presented by treatment group. The survival probabilities at 2-month intervals, and the associated 95% confidence intervals will be summarized by treatment arm. Kaplan-Meier estimates will be obtained using PROC LIFETEST with method=KM option in SAS. The loglog option available within PROC LIFETEST will be used to compute the confidence intervals.

A stratified Cox regression will be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence interval using the same strata information as the primary efficacy comparison. SAS PHREG procedure with ties=EXACT option will be used to carry out this analysis in which the model statement will include treatment arm variable as the only covariate and the STRATA statement will include the stratum information as obtained via IRT.

2.5.3 Handling of missing values/censoring/discontinuations

This is an event-driven trial and the final analysis for PFS will be performed after approximately 110 PFS events have been documented based on local investigators review of tumor assessments.

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event is observed prior to the analysis cut-off date.

PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be censored on the date of the last adequate tumor assessment before the start of new anticancer therapy if no PFS event is observed prior to the start of new antineoplastic therapy.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or stable disease (SD) or non-CR/non-PD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The

term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-8 for censoring and event date options and outcomes for PFS.

Table 2-8 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Date of last adequate assessment prior to new anticancer therapy	Censored
Death before first PD assessment	Date of death	Progressed

2.5.4 Supportive analyses

As a sensitivity analysis to assess the impact of stratification, the two treatment groups will be compared using the unstratified log-rank test. The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model will also be presented.

The primary analysis will be repeated using the PPS if the primary efficacy analysis is statistically significant and if the number of patients in the FAS and PPS differ by more than 10 percent.

The following will be provided:
Kaplan-Meier estimates, estimate of the median PFS along with 95% confidence interval, and hazard ratio obtained using the Cox proportional hazards model.

- using the primary analysis source (i.e., investigator assessment) on the FAS and including events whenever it occurs, even after two or more missing tumor assessments. In the summary tables, this approach is referred as 'actual event PFS sensitivity analyses.
- using the primary analysis source (i.e., investigator assessment) on the FAS and backdating of events occurring after missing one or more tumor assessments. In the summary tables, this approach is referred as 'backdating PFS sensitivity analysis'.
- using the primary analysis source (i.e., investigator assessment) on the FAS and including PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) for the primary analysis provided tumor assessments continue after initiation of new cancer therapy. . In the summary tables, this approach is referred to as 'new anticancer therapy PFS sensitivity analysis'.
- using the primary analysis source (i.e., investigator assessment) on the FAS and considering treatment discontinuation due to 'Disease progression' without documented progression as event. In the summary tables, this approach is referred to as 'clinical PD sensitivity analysis'.
- using the primary anlaysis source (i.e., investigator assessment) on the FAS and considering impact of COVID-19 pandemic. For patients who discontinued due to COVID-19 pandemic reasons, PFS will be censored at the date of last adequate assessment prior to discontinuation of treatment due to COVID-19 pandemic. For death due to COVID-19, PFS will be censored at the date of the last adequate assessment prior to death due to COVID-19. In the summary tables, this approach is referred to as 'COVID-19 sensitivity analysis'.

Further supportive analyses will include:

- Number of patients and number of events by treatment arm within each stratum will be presented along with the hazard ratio for treatment effect obtained using the Cox proportional hazards regression with corresponding confidence intervals. No p-values will be presented for this analysis. Kaplan-Meier plots of survival distributions will be presented by stratum.

Subgroup analyses for the primary endpoint

If the primary efficacy analysis is statistically significant, the primary endpoint of PFS will be summarized for the subgroups specified in Section 2.2.1 and using the same conventions as for the primary analysis.

For each of the subgroups, the following analyses will be performed:

- Kaplan-Meier estimates of the survival distribution of PFS
- Hazard ratio with 95% CI using stratified Cox proportional hazards model.

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. Forest plot (including sample size/number of events and HR with 95% CI) will

be produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-values) will be produced for the subgroups.

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment arm based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments:

1. Analysis cut-off date,
2. Start date of further anti-neoplastic therapy,
3. Date of consent withdrawal,
4. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. ‘Ongoing’,
2. ‘New cancer therapy added’,
3. ‘Withdrew consent’,
4. ‘Lost to follow-up’,

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed then the PFS censoring reason will always default to ‘Adequate assessment no longer available’. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced for PFS by investigator assessment. The censoring patterns will be compared between treatment arms.

2.6 Analysis of the key secondary objective

There is no key secondary objective in the study.

2.7 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- compare the two treatment arms with respect to overall survival (OS)
- compare 3-month treatment failure rate between the two treatment arms
- evaluate the two treatment arms with respect to overall response rate(ORR) and clinical benefit rate (CBR)
- describe time to response (TTR) and time to treatment failure (TTF) in each treatment arm

2.7.1 Secondary endpoints

For detailed information on guidelines of the below secondary efficacy endpoints, please refer to protocol Section 16.2.

Overall survival (OS)

OS is defined as the time from date of randomization to date of death due to any cause. A cut-off date will be established for analysis of OS. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the last contact date.

Overall response rate (ORR)

ORR with confirmation is defined as proportion of patients with best overall response (BOR) of confirmed CR or confirmed PR according to RECIST 1.1. ORR without confirmation is the proportion of patients with best overall response (BOR) of CR or PR without confirmation according to RECIST 1.1. Both ORR with confirmation and without confirmation will be calculated based on the FAS using investigators' review of tumor assessment data. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a complete response was observed.

Clinical benefit rate (CBR)

CBR with confirmation is defined as the proportion of patients with a BOR of confirmed CR or PR, or SD lasting 24 weeks or longer, according to RECIST 1.1 criteria. CBR without confirmation is defined as the proportion of patients with a BOR of CR or PR without confirmation, or SD lasting 24 weeks or longer, according to RECIST 1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 24-1=23 weeks or later from randomization, allowing for the ±1 week visit window for tumor assessments. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if they achieve a complete response or have a 'Non-CR/Non-PD' response at 23 weeks or more after randomization. CBR will be calculated using the FAS based on the investigators' tumor assessments.

Time to response (TTR)

Time to response (CR or PR) is the time from date of randomization to first documented response of CR or PR (which must be confirmed subsequently) using local investigator's review of tumor assessment data and according to RECIST 1.1. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. LPLV - FPFV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

Time to treatment failure (TTF)

Time to treatment failure (TTF) is defined as the time from the date of randomization to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'protocol violation' or 'administrative problems'.

The following discontinuation reasons will be considered as events for TTF: Adverse event, Death due to any reasons, Lost to follow-up, Physician decision, Pregnancy, Progressive disease, Subject decision and New therapy for study indication.

Treatment failure rate (TFR)

TFR is defined as the proportion of patients who discontinued the study treatment by 3 months due to progression disease, death due to any cause, change to other anti-cancer therapy, or discontinuation due to reasons other than 'protocol violation' or 'administrative problems'. All patients in the FAS will be included in 3-month TFR.

2.7.2 Statistical hypothesis, model, and method of analysis

Overall Survival

The analysis of OS will be based on FAS population according to the randomized treatment group assigned at randomization. The survival distribution of OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals [Brookmeyer and Crowley 1982] of the medians intervals will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Study follow-up will be summarized using the following methods:

Summary of duration between randomization and cut-off date, and follow-up times for PFS/OS, which are defined as follows:

- Randomization (recruitment) period = (Date of last patient randomized - Date of first patient randomized + 1) / 30.4375 (months)
- Duration between randomization and data cut-off date = (Cut-off date – Date of randomization + 1) / 30.4375 (months)..
- Follow-up time = (Date of event or censoring – Date of randomization + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date for OS.

All summaries will be reported in months. The calculations for PFS will be based on local assessment. Date of censoring is the same as defined for the PFS and OS analysis.
The time from PFS and OS censoring date to data cut-off date will be summarized by time intervals in months: <3, 3 - < 6, 6 - < 12, 12 - < 18, 18 - <24 and by 12 month intervals thereafter if necessary. The gap time is calculated as (analysis cut-off date – censoring date +1)/30.4375.

Treatment failure rate (TFR)

3-month TFR will be compared between two treatment. The stratification will be based on the randomization stratification factors: presence of liver metastases (present or absent), and DFI < 2 years (yes or no, de novo stage 4 is defined as DFI < 2 years).

3-month TFR will be summarized using descriptive statistics by treatment arm along with standard Wald asymptotic (i.e. normal approximation) 95% confidence intervals.

Overall response rate

ORR will be compared between two treatment arms. The stratification will be based on the randomization stratification factors: presence of liver metastases (present or absent), and DFI < 2 years (yes or no, de novo stage 4 is defined as DFI < 2 years).

ORR will be summarized using descriptive statistics by treatment arm along with standard Wald asymptotic (i.e. normal approximation) 95% confidence intervals.

Clinical benefit rate

CBR will be compared between two treatment. The stratification will be based on the randomization stratification factors: presence of liver metastases (present or absent), and DFI < 2 years (yes or no, de novo stage 4 is defined as DFI < 2 years).

ORR will be summarized using descriptive statistics by treatment arm along with standard Wald asymptotic (i.e. normal approximation) 95% confidence intervals.

Time to response and Time to treatment failure

TTR and TTF data will be listed and summarized by treatment arm. The distribution of TTR and TTF will be estimated using the Kaplan-Meier method and the median time to response/failure will be presented along with 95% confidence interval. No inferential analysis that compares the two treatment arms will be performed.

ECOG performance status

The ECOG PS scale (Table 2-9) will be used to assess physical health of patients, ranging from 0 (most active) to 5 (least active):

Table 2-9 ECOG Performance 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

Score	Description
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

Frequency counts and percentages of patients in each score category will be provided by treatment arm and time point based on the windows defined in Section 2.1.

2.8 Safety analyses

The assessment of safety will be based mainly on the frequency of AE and on the number of laboratory/ECG values that fall outside of pre-determined ranges. Other safety data (e.g. vital signs and special tests) will be considered as appropriate.

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Safety summary tables will include only 'on-treatment' events/assessments. The AEs started before the first dose but worsening during the treatment period are also considered as 'on-treatment' events. All safety events/assessments will be listed and those collected outside of the on-treatment window will be flagged.

If dates are incomplete in a way that clear assignment to pre-, on-, or post-treatment period cannot be made, then the respecctive data will be assigned to the on-treatment period.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. Additional sumaries will be displayed to report all AEs, AEs related to study treatment, all SAEs. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary SOC and for each (PT using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple Common Terminology Criteria for Adverse Events (CTCAE) grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the investigational arm.

The following AE summaries will be produced by treatment arm: overview of AE and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions, leading to treatment discontinuation), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to

treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

For clinicaltrials.gov and EudraCT site reporting, tables on on-treatment AE which are not serious with an incidence greater than and equal to 5%; on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and PT on the safety set.

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.

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) during the on-treatment period will be tabulated.

A Case Retrieval Sheet (CRS; an Excel file) with the exact composition of the AE groupings is to be used to map reported AE to the AESIs groupings (termed Specific Event Categories (SECs) in the CRS). This file may be updated (i.e. it is a living document) based on review of accumulating trial data.

Data analysis of AESIs

An AESI interest is a grouping of AE that are of scientific and medical concern specific to ribociclib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLTs (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 patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.).

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by treatment arm, SOC and PT.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) CTCAE v4.03. 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.

On analyzing laboratory, data from all sources will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

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

- 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 on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Sodium and Phosphorus will be excluded from laboratory data summary. Sodium and Phosphorus were removed in Protocol amendment 1 and therefore the data is incomplete; data fields are hidden due to CRF updates.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
    - TBL > 2xULN
    - TBL > 3xULN
    - ALT or AST > 3xULN & TBL > 2xULN

- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN *(potential Hy's law)*

Potential Hy's Law events are defined as those subjects with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastates, liver function at baseline etc.

2.8.4 Other safety data

2.8.4.1 ECG data

Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced by treatment group.

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

12-lead ECGs including QTcF and intervals will be obtained for each subject during the study. ECG data will be read and interpreted locally.

The number and percentage of subjects with notable ECG values will be presented by treatment arm.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- PR
  - New PR > 200 ms
  - Increase > 25% and PR > 200 ms
- QRS
  - New QRS >110 ms
  - Increase QRS > 25% and QRS >110 ms
- HR
  - Increase from baseline >25% and HR > 100 bpm
  - Decrease from baseline > 25% and HR < 50 bpm

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable ECG values may also be produced. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg), and body surface area.

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-10 below.

Table 2-10 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. A separate listing of only the subjects with notable vital sign values may also be produced. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 Patient-reported outcomes

The FAS will be used for analyzing PRO data unless specified differently. The PRO Analysis Set will be used for analyzing PRO data unless specified differently. The FACT-Breast (FACT-B) quality of life questionnaire (see Appendix 2 of the protocol) will be used to explore patient-

reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects.

The baseline is defined as the last PRO assessment on or prior randomization. Collection of FACT-B PRO have a ±3 days window unless otherwise indicated.

No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied. Descriptive statistics will be used to summarize the subscale and overall scores at each scheduled assessment time point as given in Table 8-1 of the protocol.

Scores from the FACT-B will be displayed as mean profiles, presented over time using time windows as described in Section 2.1. Change from baseline in the scores at the time of each assessment will also be summarized for overall FACT-B scores, physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

Compliance to the schedule of administration of PRO will be summarized, for baseline and post-baseline on treatment scheduled assessments (the number of ongoing patients will be used as denominator). The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes, fully completed
2. yes, partly completed
3. no.

If more than 50% of the items are missing in a scale or subscale, the score for this scale or subscale will be considered missing for this assessment. Otherwise, the average of the non-missing items in the scale or subscale will be used to impute for the missing items when calculate the score for the scale or subscale.

The following time to event analyses will be summarized for FACT-B total scores:

- Time to first occurrence of a clinically relevant deterioration, defined as a $\geq$ 5 points decrease in FACT-B total scores with no subsequent observation of a <5 points decrease
- Time to first occurrence of a clinically relevant deterioration, defined as a $\geq$ 7 points decrease in FACT-B total scores with no subsequent observation of a <7 points decrease
- Time to first occurrence of a clinically relevant deterioration, defined as a $\geq$ 10% decrease in FACT-B total scores with no subsequent observation of a <10% decrease

The following symptoms will be summarized:

- Pain (Question GP4: I have pain), time to first occurrence of a clinically relevant deterioration, defined as a $\geq$ 10% decrease with no subsequent observation of a <10% decrease
- Nausea (Question GP2: I have nausea), time to first occurrence of a clinically relevant deterioration, defined as a $\geq$ 10% decrease with no subsequent observation of a <10% decrease

Time to deterioration is the number of days between the date of randomization and the date of the assessment at which deterioration is seen. If a patient has not had an event prior to analysis cut-off, end of treatment, start of new anti-neoplastic therapy, lost to follow-up, or withdrawal of consent, the time to deterioration will be censored at the date of the last evaluation on or before the earliest of these times. Only assessments collected while the patient is on treatment and on or before the end of treatment visit will be included in the PRO time to deterioration analysis.

If deterioration is observed after two or more missing assessments, time to deterioration will be censored at the date of the last assessment prior to the deterioration.

Time to deterioration in the PRO scales will be compared between the two treatment arms using a stratified logrank test (strata based on IRT data) at one-sided 5% level of significance. The survival distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions will be determined, including the median time to 10% deterioration. Both point estimates and 95% CIs will be presented.

[redacted]

2.13 Interim analysis

Not interim analysis is planned.

3 Sample size calculation

3.1 Primary analysis

The sample size calculation is based on the primary analysis of PFS.

Based on published available data (O'Shaughnessy et al 2002, Albain et al 2008, Jassem et al 2001), the median PFS in the combination chemotherapy arm is expected to be approximately 8 months. It is expected that treatment with ribociclib arm will result in a 33% reduction in the hazard rate for PFS, i.e., an expected hazard ratio of 0.667 (which corresponds to an increase in median PFS to 12 months under the exponential model assumption).

Then in order to ensure 80% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.667, it is calculated that a total of 110 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 10% level of significance, patients randomized to the two treatment arms in a 1:1 ratio. Considering that enrolment will continue for about 30 months, 3 patients for 0-6 months, 10 patients for 7-17 months and 6 patients thereafter, a total of 200 patients will be needed to observe the targeted 110 PFS events at about 4 months after the randomization date of the last patient. Assuming 10% drop-out, a total of 222 patients will be needed. The sample size of 222 patients will be randomly assigned to each treatment arm in a 1:1 ratio (111 patients in the experimental arm, 111 patients in the control arm). These calculations were made using the software package East 6.4.

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

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

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

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

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

Use last day of the Month (mm)

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

Patients 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.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  o Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  o Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the CTCAE version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE 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 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI 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. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

5.4.1 Primary analysis

Analysis of time to events Data

Hypothesis and test statistic

The null hypothesis stating that PFS survival distributions of the two treatment groups are equivalent will be tested against one-sided alternative.

Assuming proportional hazards for PFS, the following statistical hypotheses will be tested:

$$H_{01}: \theta_1 \geq 1 \quad \text{vs.} \quad H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (ribociclib arm vs combination chemotherapy arm).

Stratified log-rank test adjusting for the strata used in the randomization will be implemented as follows: In each of the K strata separately, the LIFETEST procedure with STRATA statement including only the treatment group variable and with the TIME statement will be used to obtain the rank statistic S_k and variance var(S_k) where k=1, 2, …, K. The final test statistics will then be reconstructed as follows:

$Z=[S_1 + \cdots + S_K] / \sqrt{[var(S_1) + \cdots + var(S_k)]}$.

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Hazard ratio

Hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s).

Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

Treatment of ties

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

Checking proportionality of hazard assumption

Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazard assumption.

- SURVIVAL plots estimated survivor functions. The shape of the curves should be basically the same if hazards are proportional.
- LOGSURV plots the cumulative hazard functions The larger cumulative hazard should be a multiple of smaller if hazards are proportional
- LOGLOGS plots log (cumulative hazard). The LOGLOG plot will show parallel curves if hazards are proportional.

Analysis of Binary Data

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1-\alpha)\%$ confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Audit-based BIRC assessment of PFS

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

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