NOVARTIS

Oncology Clinical Development

Ribociclib (LEE011)

Protocol CLEE011XUS29 / NCT02732119

TRINITI-1: A Phase I/II, single arm, open-label study of Ribociclib in Combination with Everolimus + Exemestane in the Treatment of Men and Postmenopausal Women with HR+, HER2- Locally Advanced or Metastatic Breast Cancer Following Progression on a CDK 4/6 Inhibitor

Triplet with Ribociclib, AfINitor® and AI posT CDK 4/6 Inhibitor

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List of abbreviations

aBC	Advanced Breast Cancer
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
IRC	Independent Review Committee
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CCND1	Cyclin D1
CDK4/6	Cyclin-Dependent Kinases 4 and 6
Cmax	Peak blood concentration
Cmin	Minimum concentration
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOT	End of Treatment
ER	Estrogen Receptor
FAS	Full Analysis Set
FFPE	Formalin-Fixed, Paraffin-Embedded
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus

[redacted]

HR+	Hormone Receptor Positive
IB	Investigator Brochure
IC50	Inhibitory Concentration, where 50% inhibition is observed
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MBC	Metastatic Breast Cancer
MTD	Maximum Tolerated Dose
MUGA	Multiple Gated Acquisition
NCRNPD	Non-Complete Response Non-Progressive Disease
NSAI	Nonsteroidal Aromatase Inhibitors
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
Pd	Pharmacodynamics
PD	Progressive Disease
PFS	Progression free survival
P-gP	Permeability-glycoprotein
PgR	Progesterone receptor
PHI	Protected Health Information
PK	Pharmacokinetics
PPS	Per Protocol Set
PR	Partial Response
pRb	Retinoblastoma Protein
PS	Performance Status
PT	Prothrombin time
QD	Quaque Die (every day)
RAP	Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RDE	Recommended dose of expansion

[redacted]

REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SC	Steering Committee
SD	Stable Disease
SEC	Safety Event Categories
SERM	Selective ER Modulators
S-ICF	Study ICF
SMT	Novartis Safety Management Team
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	The elimination half-life associated with the terminal slope (z) of a semi logarithmic concentration-time curve (time).
TBIL	Total Bilirubin
ULN	Upper Limit of Normal

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when a patient permanently discontinues study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.

[redacted]

Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

[redacted]

Amendment 3

Study CLEE011XUS29 (TRINITI-1) was initiated in June 2016. As of 14-Nov-18, a total of 104 patients have been enrolled in the study (25 patients in Phase I, 79 patients in Phase II).

The purpose of this amendment is to:

(i) Update the dose adjustment and management recommendations for QTcF prolongation. Analyses of preclinical and clinical data with ribociclib have demonstrated that ribociclib prolongs the QT interval in a concentration-dependent manner. Moreover, based on the ribociclib exposure-ΔQTcF relationship and the clinical experience in studies CLEE011A2301 (MONALEESA-2), CLEE011F2301 (MONALEESA-3) and CLEE011E2301 (MONALEESA-7), ribociclib dose reduction is an effective strategy for managing ribociclib therapy in patients experiencing QTcF prolongation. Therefore, in order to reduce the risk of subsequent QTcF prolongation in patients experiencing a QTcF between 481-500 msec, ribociclib dosing should be reduced by 1 dose level with the first occurrence of QTcF $\geq$ 481 msec. As a result, this amendment includes an update to the dosage management guidance for patients who experience QTcF prolongation.

(ii) Update the prohibited concomitant medications based on drug-drug interaction and comedication considerations.

(iii). Update End of Study to be defined as 15 months follow up from the last patient enrolled in the study

(iv). Minor additional updates as summarized below

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Section 4.1 and 6.2.4: RP2D for Phase II Group 2 was added
- Section 4.1.3: Updated treatment discontinuation to follow patients through progression or follow up for up to 15 months after last patient enrolled in the study
- Section 4.3: Updated definition of end of study to follow up for at least 15 months after last patient enrolled in the study
- Section 4.4: updated the language regarding the reasons why the study may be terminated early by the sponsor and what actions are needed in that case
- Section 5.1: updated inclusion criteria to add estimated glomerular filtration rate
- Section 6.2.4.1 and 6.5.2: updated to clarify that herbal or dietary supplements with a known risk of QT prolongation are not permitted
- Section 6.5.1.4: added to include guidance on use of antiemetic medications

[redacted]

- Section 6.5.3: clarified the information provided regarding renal transporters MATE1, OCT2 and BCRP.
- Section 6.5.3.1: added to include guidance on use of corticosteroids with caution
- Section 7.1.5: updated language regarding actions needed when a patient withdraws their consent to participate in the trial
- Section 7.1.7 and 7.1.8: updated to define end of follow up
- Table 6-4: updated with instructions on how to define hepato-biliary criteria for Dose Limiting Toxicities
- Table 6-9: updated with instructions on how to manage QTcF prolongation
- Table 14-1: updated with the most current prohibited medications
- Table 14-2: updated with the most current medications to be used with caution

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2

Amendment 2 rationale

Study CLEE011XUS29 (TRINITI-1) was initiated in June 2016. As of 22-May-17, a total of 63 patients have been enrolled in the study (18 patients in Phase I, 45 patients in Phase II).

The current amendment is intended to update the trial design to remove the Simon Two-Stage analysis of the phase II since cohort A, of Phase 1 demonstrated a CBR of 50% at 6 months in the patients that progressed on a CDK 4/6 inhibitor and a CBR of 100% at 6 months in those patients that were CDK 4/6 naïve (based on local assessment). One interim analysis was done after the completion of the phase I portion of this trial, and one final analysis will be done after the completion of the phase II portion.

Additionally this amendment will re-open the phase I portion of this trial to introduce a dose de-escalation in efforts to explore a new dosing regimen that would be safe and better tolerated with maximum exposure of everolimus. This will be referred to as Cohort C. Cohort C will be a 3+3 design to determine safety and tolerability. If proven safe and tolerable, an expansion phase will be added to phase II, referred to as Group 2 to look at Clinical Benefit Rate at 24 weeks.

The current phase II expansion phase (300mg qd + 2.5mg qd +25mg qd, will be referred to as Group 1).

A summary of the key changes proposed in this amendment is listed below:

- Removed the Simon Two-stage design from the phase II portion of this trial.
    - The phase II will now move forward with a standard phase II design and analysis.
    - The initial study design required approximately 39 evaluable patients for this Phase of the study. Now retaining the same assumptions using a one-sided alpha level of 0.05% to detect a power of at least 80%, a minimum of approximately 60 evaluable patients are required for the study, (30 evaluable patients per group, Group 1 & Group 2)
- Phase II sample size increased to 60 evaluable patients. Accounting for 10% drop out rate, approximately 66 patients will be enrolled, (33 patients per group, group 1 & group 2)
    - 8 or more patients need to show clinical benefit at 24 weeks for group 1 and 8 patients in group 2 of the phase II part of this study to be considered a success based on the statistical changes.
- Removed the term “key” from secondary endpoints for the phase II portion of this trial
- Inclusion criteria #15 was updated to allow any endocrine therapy for up to 28 days prior to enrollment, rather than only allowing exemestane, so long as the patient does not progress on this therapy.

[redacted]

- Exclusion Criteria #9 was updated to further clarify drugs with overlapping toxicities and better define the washout period.
- Exclusion Criteria #16 was updated to remove: "Clinically and radiographically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases." This change was based on supporting preclinical data demonstrating that ribociclib crosses the blood brain barrier.

Amendment 02 also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Throughout the document: Language stating, or relating to the Simon Two-Stage design was removed.
- Section 1.2.5.1.1: Safety data from the interim analysis of TRINITI-1 was added
- Section 3.2: Removed the term "Key" from Secondary Endpoints so all Secondary endpoints are looked at equally.
- Section 4.1: Updated to reflect new trial design
- Figure 4.1: Updated to reflect new trial design
- Section 5.2: Inclusion Criteria #15 was updated to allow any endocrine therapy for up to 28 days prior to enrollment, rather than only allowing exemestane.
- Section 5.3: Exclusion Criteria #9 was updated to further clarify drugs with overlapping toxicities to include CDK 4/6 inhibitors and to better define the washout period.
- Section 5.3: Exclusion Criteria #16 was updated to allow patient with clinically and radiographically unstable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
- Section 5.3: Exclusion Criteria #25 was updated to exclude medication that cannot be discontinued within five half-lives.
- Section 6.1: Updated to include cohort C treatment regimen.
- Table 6-3: Added to explain dose de-escalation dosing levels.
- Section 6.2.1: Updated to include dose de-escalation guidelines.
- Table 6-4: Modified to explain dose escalation dose modifications.

[redacted]

- Table 6-5: Modified to explain dose de-escalation dose modifications.
- Table 6-6: Updated to state: If toxicity recurs at grade 3: temporary dose interruption of ribociclib and everolimus until recovery to grade ≤1 and reduce to the next lower dose level, or continue at same dose with growth-factor support at the discretion of the treating investigator.
- Table 6-6: Modified to explain dose modifications if everolimus held more than 3 weeks.
- Section 10.1.5: updated to state "A subset of Full Analysis Set (FAS) excluding major protocol violations".
- Section 10.4.1: Updated to reflect new statistical analysis plan for the phase II portion of the trial.
- Section 10.5.1: Updated to reflect new statistical analysis plan for the phase II portion of the trial.

[redacted]

Amendment 1

Amendment 1 rationale

Study CLEE011XUS29 (TRINITI-1) was initiated in June 2016. As of 4-Jan-17, a total of 18

Patients have been enrolled in the study.

The current amendment is intended to update the existing information about ribociclib, clarify specific aspects of the original protocol and remove inclusion criteria number 4 which required evaluation of total RB1. In addition the recommended phase II dose (RP2D) for this study has been determined to be 300mg Ribociclib (daily) + 2.5mg Everolimus (daily) + 25mg Exemestane (daily).

A summary of the key changes proposed in this amendment is listed below:

- Ribociclib information was updated based on the data available in the current IB version (v10, release date: Oct-10-2016; safety cut-off date: Jul-5-2016)
- Detailed information from the pivotal study CLEE011A2301 (MONALEESA-2) supporting the use of ribociclib + letrozole in aBC has been included to strengthen the study rationale.
- Remove inclusion criteria #4: Intact retinoblastoma protein (pRB). Confirmation of RB1status by IHC or an equivalent test required based on most recent tumor biopsy following progression on a CDK 4/6 inhibitor. If no tissue is available, most recent archival tissue should be tested for RB staining from metastatic site. This tissue sample should be tested locally for RB1 status.
    - After central evaluation of total RB1of patients enrolled into the phase I, dose escalation portion on the trial, it was determined by Novartis, and the Steering Committee that the inclusion criteria could be removed. [redacted]

Amendment 01 also includes minor editorial changes and additional clarifications to address investigators' questions as described in the list of changes below.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Throughout the document: Addition of language to refer to most recent version of the LEE011 Investigator's Brochure and minor text editorial changes
- Throughout the document: Typographical and grammatical corrections

[redacted]

- Throughout the document: the term “randomization” was replaced with “start of/starting study treatment” as this is an open label trial that is not randomized
- Section 1.1.2: Updated to include data on clinical benefit of AIs in combination with ovarian function suppression (OFS) in premenopausal patients with breast cancer in neoadjuvant, adjuvant and advanced settings; Rationale for inclusion of male patients is further clarified.
- Section 1.2.1.4 Updated based on new data from ongoing and completed trials with LEE011
- Section 1.2.2: Added to provide CLEE011A2301 (MONALEESA-2) trial key efficacy and safety results of pre-planned interim analysis.
- Section 4.1: Updated to include the RP2D determined from the phase I dose escalation portion of the trial. (300mg ribociclib (daily) + 2.5mg everolimus (daily) + 25mg exemestane (daily)
- Section 5.2: Inclusion Criteria #4 was removed based on the finding from data generated in the phase I dose escalation portion of the trial
- Section 5.2: Inclusion Criteria #9 corrected to say patients must have progressed on only one CDK 4/6 inhibitor
- Section 5.2: Inclusion Criteria #12 was updated to define bone disease as “Evaluable disease”, for clarity
- Section 5.2: Inclusion Criteria #13 was updated to include alanine aminotransferase (ALT) limits
- Section 5.3: Exclusion Criteria #8 was updated to exclude patients who have progressed more than once on the same CDK 4/6 inhibitor
- Section 5.3: Exclusion Criteria #25 was updated to remove exclusion of the use of corticosteroids.
- Table 6-1: Updated to remove the 1mg and 5mg doses of everolimus as they are not being used or provided. The size of the dexamethasone bottle (500mL) was also added for clarity
- Table 6-2: Updated to provide clarity on what the dose levels of each cohort is
- Section 6.2.1: Updated to state the RP2D to be used if unable to be determined in the phase I dose escalation
- Section 6.2.4: Updated to state the RP2D for the phase II portion of this trial
- Section 6.3: Updated for clarity around dexamethasone use
- Section 6.4: Updated language to clearly state there are no dose reductions permitted for everolimus
- Table 6-4: Updated for clarity and to state the RP2D for the phase II portion of this trial
- Table 6-11: Added consideration of using flovent for pneumonitis
- Section 8.4: Updated as there was/is no interim analysis planed

[redacted]

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[redacted]

Synopsis

Title	A Phase I/II, single arm, open-label study of Ribociclib in Combination with Everolimus + Exemestane in the Treatment of Men and Postmenopausal Women with HR+, HER2 Negative Locally Advanced or Metastatic Breast Cancer Following Progression on a CDK 4/6 Inhibitor
Sponsor and Clinical	Novartis- Region US
Phase	Phase I run in followed by Phase II
Investigation/Study Type	Drug/Interventional
Purpose	To assess safety, tolerability and efficacy of ribociclib+ everolimus + exemestane in patients that progressed on CDK4/6 inhibitor based therapy.
Number of Subjects	Phase I: 9-24; Phase II : approximately 60 evaluable
Estimated time of Enrollment	Phase 1: 4 months, Phase 2 :12 months
Estimated Duration	Estimated 30 months
Number of sites	Approximately 30 sites (total Phase I and II)
Rationale	Hormone receptor-positive breast cancer is the most common form of breast cancer with endocrine therapy being the cornerstone of treatment. Unfortunately, endocrine resistance eventually develops resulting in the progression of disease and ultimately death for these patients. Disruption of the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway and cyclin D–CDK4/6–INK4–Rb pathway has been implicated in resistance to endocrine therapy and disease progression. Activation of this pathway can result in increased levels of CCND1 leading to upregulation of this pathway. Cyclin-dependent kinase (CDK) 4/6 inhibitors are believed to be critical mediators of this pathway as it acts downstream of the PIK3CA/Protein Kinase B (AKT)/mTOR axis. The addition of everolimus to exemestane significantly improves progression-free survival of patients with endocrine resistant HR+ HER2- advanced breast cancer (Baselga J 2012) but eventually patients progress. Studies demonstrate that resistance to hormonal therapy, mTOR inhibition, and cytotoxic chemotherapy are at least in part mediated by upregulation of CDK4/6-cyclin D activity in breast cancer, suggesting that there might be a role for CDK4/6 inhibition + mTOR inhibition in patients who have progressed on these therapies. The effect of combining ribociclib with the mTORC1-inhibitor everolimus (RAD001; Afinitor®) in the ER+, PIK3CA mutant MCF-7 xenograft model was examined (RD-2013-50141). While single agent treatments with ribociclib and everolimus resulted in modest tumor regressions of -9% and -21%, respectively, combination of ribociclib with everolimus increased tumor regressions to -49%. Data from in vivo studies showed that ribociclib, when combined with the mTOR inhibitor, everolimus (RAD001; Afinitor®), induced synergistic growth inhibitions in multiple tumor models, including cell lines derived from MCL, ER+ breast cancer, and MRT.

	There is a role for continuing targeted therapies in patients with breast cancer, even beyond the point of disease progression. Everolimus appears to restore sensitivity to anti-estrogens by inhibiting resistance mediated by the PI3K/Akt/mTOR pathway. Currently, there is no clinical data available that reports the efficacy of further treatments after prior CDK4/6 inhibitor failure, which represents an unmet medical need and requires further exploration. Potential reasons for progression on CDK4/6 inhibitor include loss of the retinoblastoma protein (pRb) (the direct target of CDK4/6 inhibitors), alterations in the estrogen receptor pathway as a consequence of endocrine therapy resistance, or activation of other signaling pathways including the PI3K/AKT/mTOR pathway. The heterogeneity of the anticipated mechanism of resistance requires further exploration since some patients may still benefit from a sustained inhibition of the CDK4/6 pathway. Anecdotal observations of a small subset of patients treated on 1st line therapy trials with CDK 4/6 inhibitors + aromatase inhibitors have suggested that some patients who discontinue therapy with the CDK 4/6 inhibitors develop an impressively rapid disease progression at initial imaging assessment to second line therapy. This lends the question of maintaining CDK 4/6 inhibition as a backbone therapy to keep the cell cycle arrested in G1 while adding mTOR inhibition to overcome resistance. The CLEE011X2106 Phase-1b clinical trial tested a combination of exemestane + everolimus + ribociclib. The recommended dose for expansion was declared as exemestane 25 mg daily, everolimus 2.5 mg daily and ribociclib 300 mg 3 weeks on/1 week off. This combination appeared to be safe and demonstrated clinical activity. Clinical activity was seen in a heavily pre-treated population (median number of 4 prior therapies) with 25.7% pts receiving prior PI3K/AKT/mTOR or CDK4/6 inhibitors for metastatic disease. The clinical benefit rate in these patients was 26% in 74 evaluable patients and disease control rate was noted to be 73%. Furthermore, there was a trend towards longer duration of treatment in the CCND1 amplified group (n=10; median 166 days) than in the non-amplified group (n=22; median 60 days), something which was not appreciated with the treatment of everolimus + exemestane in BOLERO-2 (Bardia A 2015). PK analysis suggested that ribociclib increased dose-dependent exposure of everolimus during the time that both everolimus + ribociclib were dosed concurrently (Bardia A 2014), however, dose exposure of everolimus decreased during the week off of ribociclib therapy. By dosing ribociclib at a lower and continuous dose when combined with everolimus, both safety and efficacy could potentially be improved by lowering the Cmax concentration and continuously inhibiting both CDK 4 and 6, while maximizing everolimus' dose exposure. Thus, triplet combination of endocrine therapy with mTOR and CDK4/6 inhibition is tolerable, and shows preliminary signs of clinical activity, including in patients with prior exposure to PI3K/AKT/mTOR

[redacted]

	or CDK4/6 inhibitors, suggesting that triplet therapy could potentially overcome resistance to doublet therapy in a subset of patients. Therefore, this study proposes to examine continuous dosing of ribociclib when administered concurrently with everolimus (Phase I) and to test whether the addition of everolimus + exemestane to ribociclib can reverse resistance to a CDK 4/6 inhibitor and ultimately improve the efficacy of the approved combination regimen (everolimus + exemestane) in patients that progressed on CDK 4/6 inhibitors (Phase II).
Phase I	
Primary Objective(s)	To determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase II dose (RP2D) for the triplet combination of ribociclib + everolimus + exemestane when administered continuously in subjects with HR+ HER2-negative advanced/metastatic breast cancer
Secondary Objectives	Characterize the safety and tolerability of the triplet combination of ribociclib + everolimus + exemestane when all drugs are administered continuously Determine the PK profile of the combination of ribociclib + everolimus + exemestane when administered continuously; evaluate the DDI potential (effect of ribociclib on the PK profile of everolimus) Determine the overall response rate (ORR) by RECIST 1.1 on treatment with combination of ribociclib + everolimus +exemestane when administered continuously
Phase II	
Primary Objective(s)	Determine the Clinical Benefit Rate (CBR) at 24 weeks among subjects receiving triple therapy with ribociclib + everolimus + exemestane for HR+, HER2-negative, advanced/metastatic breast cancer following progression on CDK 4/6 inhibitor.
Secondary Objectives	**Secondary:** • Progression Free Survival (PFS) • Overall Response Rate (ORR) • Duration of overall response (DOR) • Overall Survival (OS) • Time to deterioration of ECOG performance status • Safety and tolerability • Determine the PK profile of ribociclib and everolimus when administered continuously. [redacted]

[redacted]

	[redacted]
Study design	**Phase I:** A Phase I dose escalation (cohort A and B) and dose de-escalation (cohort C) will be initiated to ensure the safety and tolerability of daily dosing of ribociclib + everolimus + exemestane in patients with HR+, HER2-negative advanced/metastatic breast cancer. Once the recommended Phase II dose is confirmed and safety and tolerability are established, the trial will commence into a Phase II study. **Phase II:** This portion of the trial will be an open label, Phase II study to evaluate the antitumor activity of the ribociclib + everolimus + exemestane combination in patients that have progressed on CDK4/6 inhibitor based therapy. Patients with advanced/metastatic HR+, HER2-negative, breast cancer will receive one of two RP2D determined by Phase 1, both Group 1 and Group 2.. All subjects that participate in Phase 2 must have progressed on a CDK 4/6 inhibitor. Prior CDK 4/6 inhibitor will be defined as disease progression while on, or within 30 days of discontinuing any CDK 4/6 inhibitor therapy (i.e. palbociclib, ribociclib, or abemaciclib). Dose adjustment (reduction, interruption or dose re-escalation) according to safety findings will be allowed. Safety reviews by an Independent Data Monitoring Committee (IDMC) will be performed. Tumor assessments will be performed every 8 weeks starting from the date of first dose of study treatment, and as clinically indicated, until the first 12 months of treatment are completed or disease progression. If no progression, tumor assessments will occur every 12 weeks, and as clinically indicated until disease progression. Every 28 days will be considered one cycle. Clinical visits will be twice per cycle for the 1st two cycles, then once per cycle from there on. The therapy on clinical trial will continue until disease progression (radiological), or intolerable adverse effects, or subject's wish to withdraw consent. **Follow up:** Subjects will be followed for safety until 30 days after study treatment discontinuation. After treatment discontinuation for any reason other than progression, tumor assessments will continue every 8 weeks for up to 12 months after the first dose of study treatment.

[redacted]

Population	**For both Phase I and Phase II**: Men and postmenopausal women with HR+, HER2-negative, locally advanced or metastatic breast cancer whose disease is refractory to at least one endocrine therapy. Refractory disease to endocrine therapy is defined as: • Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, tamoxifen, exemestane or fulvestrant • Progression while on, or within one month of end of letrozole, anastrozole, tamoxifen or fulvestrant treatment for locally advanced or metastatic breast cancer. **For Phase II only:** Patients must have a documented recurrence or progression while on a CDK 4/6 inhibitor. Documented radiological recurrence or progression on a CDK 4/6 inhibitor is defined as: • Remained on a CDK 4/6 inhibitor ≥4 months prior to disease progression, AND • Progressed while on or within 30 days of discontinuing treatment with a CDK 4/6 inhibitor, AND • CDK 4/6 inhibitor must have been the last treatment regimen prior to starting study treatment. ***Note: Phase I does not require prior CDK 4/6 inhibitor exposure.***
Key Inclusion criteria (see protocol for detailed list)	Patients eligible for inclusion in this study have to meet all of the following criteria: 1. Adult men and women (≥18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy. 2. Histological or cytological confirmation of hormone-receptor positive (ER+ and/or PR+) breast cancer per local laboratory testing 3. Patient has HER2-negative breast cancer (based on most recently analyzed biopsy) defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing. 5. A representative tumor specimen must be available for molecular testing. Newly obtained tumor biopsy specimen is required if accessible prior to entry on trial. If tissue is not accessible based on surgical evaluation, an archival tumor sample from metastatic site may be submitted. 6. Women must be postmenopausal. Postmenopausal status is defined either by: • Amenorrhea for at least 12 months and both follicle-stimulating hormone (FSH) and estradiol levels are in postmenopausal range (according to the local laboratory) OR • History of bilateral oophorectomy (with or without hysterectomy) OR

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	• History of partial hysterectomy with FSH and/or estradiol within post-menopausal range OR • Ovarian function suppressed with a GnRH agonists (negative HCG required) with estradiol levels in the postmenopausal range (according to the local laboratory) 7. Disease refractory to either, AI, tamoxifen or fulvestrant defined as: • Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, exemestane, tamoxifen or fulvestrant OR • Progression while on, or within one month of discontinuing letrozole, anastrozole, tamoxifen or fulvestrant for the treatment of locally advanced or metastatic breast cancer. ***Note: There are no restrictions as to which endocrine therapy the patients received as their last line of therapy just prior to study treatment.*** 8. Patients who received up to 3 lines of therapy for advanced breast cancer are allowed. This includes a maximum of 1 line of chemotherapy and a maximum of 3 lines of endocrine therapy in the advanced setting so long as the patient has not received more than a total of 3 lines of therapy. Patients must have recovered to grade 1 or better from any adverse events (except alopecia and or neuropathy) related to previous therapy prior to starting study treatment. **** Note: If patient relapsed with documented evidence of progression on/or within 12 months from completion of adjuvant endocrine therapy, then this is considered one line of therapy*** 9. Patients previously treated on any CDK 4/6 inhibitor (i.e. ribociclib, abemaciclib OR palbociclib) must have: • Remained on treatment for ≥4 months for advanced breast cancer or metastatic disease prior to progression, AND • Progressed on, or within 30 days following the discontinuation of a CDK 4/6 inhibitor. **Phase II Only:** • Patients must have progressed on only one CDK 4/6 inhibitor. A CDK 4/6 inhibitor must have been the last treatment prior to starting study treatment. ***Note: Phase I does not mandate prior CDK 4/6 inhibitor exposure.*** ****Note: For patients who received prior CDK4/6 inhibition as part of a clinical trial, patients must be unblinded in order to verify that the patient did receive a CDK4/6 inhibitor.***

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	10. ECOG Performance Status 0 – 1. 11. Radiological evidence of recurrence or progression on or after the last endocrine therapy prior to starting study treatment. 12. Patients must have: • Measurable disease: defined as at least one lesion that can be accurately measured in at least one dimension ≥20 mm with conventional imaging techniques or ≥10 mm with spiral CT or MRI OR • Evaluable disease: bone lesions- lytic or mixed (lytic + sclerotic) in the absence of measurable disease 13. Patient has adequate bone marrow and organ function as defined by the following LOCAL laboratory values at screening: • Absolute neutrophil count ≥1.5 × 10^9/L • Platelets ≥100 × 10^9/L • Hemoglobin ≥9.0 g/dL • Potassium within normal limits, total calcium (corrected for serum albumin), magnesium and sodium within normal limits as per local lab's normal range or corrected to normal limits with supplements before first dose of study medication • INR ≤1.5 or ≤2.5 while on anti-coagulant • Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min • Total bilirubin <ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN. • Alanine aminotransferase (ALT) and aspartate transaminase (AST) <2.5 × ULN, except for patients with liver metastasis, who are only included if the AST and ALT are <5 × ULN 14. Must be able to swallow ribociclib, everolimus and exemestane capsules/tablets 15. Patients with metastatic disease are allowed to receive ≤28 days of endocrine therapy prior to starting study treatment
Key Exclusion criteria (see protocol for detailed list)	Patients eligible for this study must <u>not</u> meet any of the following criteria: 1. Patients with visceral crisis or any disease burden that makes the patient ineligible for this study per the investigator's best judgment. 2. Patients who received more than one line of chemotherapy for advanced breast cancer. 3. HER2 overexpression by local laboratory testing (IHC 3+ staining or in situ hybridization positive).

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	4. Patient has received prior treatment with anthracyclines at cumulative doses of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin. 5. Patient with a known hypersensitivity to any of the excipients of ribociclib, mTOR inhibitors, e.g. sirolimus (rapamycin), or exemestane. 6. Previous treatment with mTOR inhibitors 7. Previous treatment with exemestane for advanced disease (except patients who received ≤28 days of exemestane for advanced breast cancer) 8. Disease progression on more than one CDK 4/6 inhibitor, or have progressed more than once on the same CDK 4/6 inhibitor. 9. Patient is concurrently using other anti-cancer therapy. All anti-cancer therapy must be discontinued at least 7 days prior to study treatment (C1D1). Drugs with overlapping toxicities with either everolimus or ribociclib must also be discontinued at least 7 days prior to C1D1. All AEs related to prior treatment should have resolved to CTCAE version 4.03 Grade ≤1 prior to study treatment (including any CDK 4/6 inhibitor)." 10. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects due to surgery. 11. Patients with Child Pugh score B or C. 12. Active, bleeding diathesis, or on oral anti-vitamin K medication (except low dose warfarin, LMWH and acetylsalicylic acid or equivalent, as long as the INR is ≤2.5 while on anti-coagulant). Fondaparinux is allowed. 13. Radiotherapy < 2 weeks prior to starting study treatment. Patients must have recovered from radiotherapy toxicities prior to starting study treatment, and recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia). Radiotherapy is not allowed at target site following screening. 14. Another malignancy within 3 years prior to starting study treatment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell skin carcinoma. 15. Patients with central nervous system (CNS) involvement unless they are at least 4 weeks out from prior therapy completion (including radiation and/or surgery) to starting the study treatment. 16. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). 17. Patient has a known history of HIV infection (testing not mandatory)

[redacted]

	18. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient's participation in the clinical study or compromise compliance with the protocol such as: • chronic pancreatitis • active untreated or uncontrolled fungal, bacterial or viral infections, sepsis etc. • Uncontrolled diabetes as defined by fasting serum glucose >1.5 × ULN • Acute and chronic, active infectious disorders including viral and nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy 19. Fasting serum cholesterol >300 mg/dl or 7.75 mmol/L and fasting triglycerides >2.5 × ULN. In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy and when the above mentioned values have been achieved. 20. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates. • Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following: • History of angina pectoris, symptomatic pericarditis, coronary artery bypass graft (CABG) or myocardial infarction within 6 months prior to study entry • Documented cardiomyopathy • Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) detected during screening • History of cardiac failure or significant/symptomatic bradycardia Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome or any of the following: • Known risk to prolong the QT interval or induce Torsade's de Pointes. • Uncorrected hypomagnesemia or hypokalemia • Systolic Blood Pressure (SBP) >160 mmHg or <90 mmHg • Bradycardia (heart rate <50 at rest), by ECG or pulse. • On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or

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	QTcF >450 msec for men and >470 msec for women (using Frederica's correction). All as determined by screening ECG (based on a mean of 3 ECGs). 21. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1: • That have a known risk to prolong the QT interval or induce Torsade's de Pointes. • Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges. • Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5. • Herbal preparations/medications, (except for vitamins). . 22. Not able to understand and to comply with study instructions and requirements. 23. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 24. Sexually active males unless they use a condom during intercourse while taking drug and for 21 days after stopping medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
Safety Assessments	• Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 (Phase I only) • Adverse Events (AEs), serious AE (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity
Efficacy Assessments	CT/ MRI every 8 weeks for the first 12 months, then every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. • Brain CT or MRI as clinically indicated. • Whole body bone scan at screening and as clinical indicated • Bone x-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 12 months and then every 12 weeks thereafter until disease progression • Skin color photography (if skin lesions at screening) every 8 weeks during the first 12 months and then every 12 weeks thereafter.

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	• CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at baseline) every 8 weeks for the first 12 months and then every 12 weeks thereafter. • Survival status
Other Assessments	**Pharmacokinetic:** Ribociclib, everolimus and exemestane pharmacokinetic (PK) evaluations. PK parameters, including but not limited to AUC $_{0\text{-}6hrs}$, C_{max}, C_{trough}. [redacted]
Investigational and reference therapy	The investigational or study drug refers to ribociclib. Investigational treatment/arm refers to the triple combination of ribociclib + everolimus + exemestane (R-E-E).
IDMC and SSC	An Independent Data Monitoring Committee (IDMC) will be constituted. A Study Steering Committee (SSC) will also be constituted for overseeing the clinical trial
Dose, regimen	Every 28 days will be considered one cycle. Everolimus, exemestane and ribociclib will be administered daily.
Statistical methods	**Phase I:** The primary purpose of the Phase I is to estimate the MTD(s) and/or identify the RP2D of the combination treatment of ribociclib+ everolimus + exemestane when dosed continuously in adult men and postmenopausal women with HR+ HER2-negative advanced breast cancer resistant to the non-steroidal aromatase inhibitors (letrozole or anastrozole), fulvestrant or tamoxifen. The corresponding primary endpoint is the incidence of DLTs in the first cycle. A patient is considered to have met the minimum exposure requirement if having received at least 75% of the planned combination doses for all compounds administered together (in the same day) for one cycle. The length of a cycle is 28 days. **Phase II:** Open label, Phase II trial will evaluate the anti-tumor activity of exemestane, everolimus and ribociclib triplet. This part of the study will be continued after the MTD/RP2D is determined in the Phase I.

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	A minimum of approximately 60 evaluable patients (30 per group (group 1, and group 2) are required for Phase II of this study to evaluate clinical benefit rate at 24 weeks. The sample size is based on an exact test for single proportion to test the null hypothesis H0: $p \leq 0.10$, where p is the clinical benefit rate in 24 weeks. If the true rate is $p \geq 30\%$, then with one-sided alpha level of 0.05% and a power of 80%, a minimum of approximately 30 evaluable patients for each group are required for the study. Including dropout rate of 10%, to get at least 30 evaluable patients, a total of approximately 33 patients for each group (group 1 and group 2) will be enrolled. If 8 or more patients show clinical benefit at 24 weeks then the null hypothesis will be rejected and significant clinical benefit will be demonstrated. (See Section 10) Details of the statistical analysis and data reporting will be provided in the RAP.

1 Background

1.1 Overview of current treatment

1.1.1 Epidemiology of breast cancer

There was an estimated 231,840 o f new cases of invasive breast cancer diagnosed amongst women in the US in 2015; excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. An estimated 40,730 breast cancer deaths (40,290 women) were expected in 2015. Breast cancer ranks second as a cause of cancer death in women after lung cancer (Cancer facts & figures 2015). Subtypes of BC are classified by the presence of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2) antigens as well as by distinct gene expression profiles (Perou et al 2000; Sotiriou and Pusztai 2009; Sotiriou and Pusztai 2009) and other features for prognostic and treatment purposes. Seventy percent of invasive breast cancers in women >45 years of age, express ER and/or PgR, but not HER2, and are termed hormone receptor positive (HR+, HER2-negative) (Huang 2005).

1.1.2 Treatment options for hormone receptor positive advanced breast cancer

Expression of the estrogen receptor (ER) and/or progesterone receptor (PgR) is one of the most important prognostic factors in invasive breast cancer and is detected in approximately 70% of cases. Estrogen deprivation therapy is the core treatment modality in patients with hormone receptor positive (HR+) advanced breast cancer. Endocrine therapy options for postmenopausal women with HR+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer) include selective estrogen receptor modulators (SERM; tamoxifen), estrogen receptor antagonists (fulvestrant), selective nonsteroidal aromatase inhibitors (NSAI; anastrozole and letrozole) and steroidal aromatase inhibitors (exemestane). Tamoxifen is

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indicated for the treatment across the whole continuum of HR+ breast cancer in premenopausal women, ranging from risk reduction in women at high risk of developing breast cancer to treatment of metastatic disease. In postmenopausal women, aromatase inhibitors (AI) reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens in non-ovarian tissues; synthesis in these tissues is the primary source of estrogens in postmenopausal women. Aromatase inhibitors are generally used as the first line of therapy for women with ER+ breast cancer (Beslija 2009, Cardoso 2011, NCCN Guidelines 2016).

Despite the broad spectrum of available options for patients with HR+ advanced breast cancer, most eventually develop resistance to hormonal deprivation. One mechanism of endocrine resistance is aberrant signaling via phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (Burstein 2011, Johnston 2006, Schiff 2004). Hyperactivation of PI3K/mTOR is observed in endocrine-resistant breast cancer cells, and treatment with mTOR inhibitors, including rapamycin analogs, reverses this resistance (Miller 2010). Growing evidence also supports a close interaction of the mTOR pathway with ER signaling. S6 kinase-1 (S6K1), a substrate of mTOR Complex 1 (mTORC1), phosphorylates the activation domain AF-1 of the ER, and stimulates ligand-independent activation of the receptor (Yamnik 2009; Yamnik 2010; Yamnik 2010).

Everolimus is a rapamycin derivative that inhibits mTORC1 through allosteric binding; it does not inhibit mTORC2 (Efeyan 2010). In the clinic, everolimus active in combination with exemestane in patients with ER+ advanced breast cancer resistant to previous hormonal deprivation therapy (BOLERO-2 study; Baselga 2012; Baselga 2012).

Recently, the United States Food and Drug Administration (FDA) approved palbociclib (Ibrance®) in combination with letrozole for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease and fulvestrant in premenopausal, perimenopausal and postmenopausal women with AI refractory HR+ HER2- negative advanced breast cancer. For additional information, please refer to the Ibrance® Prescribing Information.

In premenopausal women who received a prior endocrine therapy within 12 months, the preferred therapy involves ovarian ablation or suppression + endocrine therapy - such as aromatase inhibitors (AIs) - as for post-menopausal patients. (NCCN Breast Cancer Guidelines, version 2.2016).

Based on the clinical benefit shown in postmenopausal patients, AIs in combination with ovarian function suppression (OFS) have been investigated in premenopausal patients with breast cancer in neoadjuvant, adjuvant and advanced settings. Results from the randomized phase III trials SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and EXemestane Trial) showed that adjuvant treatment with exemestane+OFS as compared with tamoxifen+OFS, significantly reduced recurrence in premenopausal women with HR+ early breast cancer. Results from both trials (N=5,738) showed statistically significant differences in disease free survival (DFS) at 5 years (91.1% in exemestane + OFS vs 87.3% in tamoxifen + OFS) and rate of freedom from breast cancer at 5 years (92.8% in exemestane+OFS vs 88.8% in tamoxifen+OFS) (Pagani 2014). Studies exploring the combination of third generation AIs

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and goserelin in metastatic premenopausal BC patients are shown below in Table 1-1. (Montagna 2013)

Table 1-1 Goserelin and third generation AIs in metastatic premenopausal BC patients

Study	N	AI+goserelin (G)	ORR (CR+PR) (%)	CB (CR+PR+SD) (%)	TTP (months)	First line endocrine therapy
Forward (2014)	16	Anastrozole+G	6.2	75	N/R	No
Cheung (2010)	36 13	Anastrozole+G Exemestane+G*	36 N/R	67 38	12 N/R	Yes No
Carlson (2010)	35	Anastrozole+G	37	72	8.3	Yes
Park (2011)	35	Letrozole+G	46	77	9.5	Yes
Roche (2009)	52	Letrozole+G	21	71	10	Yes/No
Nishimura (2012)	33	Anastrozole+G	55	64	13	Yes
Forward (2014)	37	Anastrozole+G	19	62	7.2	Yes/No

ORR=Objective response rate, CR=Complete response, PR=Partial response, CB=Clinical benefit, SD=Stable disease, PD=Progressive disease, TTP=Time to progression, N/R=Not reported

*In study by Cheung et al, patients received treatment with exemestane after they received treatment with anastrozole.

Although data are limited (Montagna 2013), clinical benefit of the combination of AIs and OFS in premenopausal women with advanced ER+ breast cancer has been shown in small phase II studies with letrozole and anastrozole. In one study (Cheung 2010), patients received exemestane, but only after they had received anastrozole, so the effect of single–agent exemestane has not been well characterized. Lastly, novel therapeutic approaches targeting promising pathways should be explored to further improve efficacy in premenopausal women with advanced HR+ breast cancer.

Male breast cancer is rare, with less than 1% of all breast carcinomas occurring in men (Giordano 2005). The pathology is similar to that of female breast cancer, and infiltrating ductal cancer is the most common tumor type. Male breast cancers have high rates of hormone-receptor expression, with approximately 90% of male breast cancers expressing estrogen receptor, and 81% expressing progesterone receptor.

In general, the approach to the treatment of metastatic breast cancer is similar in male and female patients with breast cancer, with hormonal therapy being the often the first approach. Although, historically, surgical ablative therapies such as orchiectomy, adrenalectomy, and hypophysectomy have been used effectively to control metastatic breast cancer in male patients, these surgical procedures are rarely used today and have been supplanted by additive hormonal therapies. Tamoxifen has established efficacy in metastatic male breast cancer, with an approximate 50% response rate, and is considered an acceptable treatment option. Luteinizing hormone–releasing hormone agonists, with or without antiandrogens, have also been reported to be effective in male breast cancer. There have been case reports of responses to a wide variety

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of hormonal therapies including progestins, androgens, steroids, aminoglutethamide, estrogens, and letrozole.

Since the hormonal environment in male patients differs from that observed in female patients, the role of AIs in male patients may be different (Doyen, J 2010). In men, 80% of circulating estrogens are derived from peripheral aromatization of testicular and adrenal androgens, with direct production from the testes accounting for the remaining 20%. Studies in men patients had demonstrated that non-steroidal AIs lead to a decrease in plasma E2 levels, but these levels can still be detectable in some patients, potentially because of the baseline levels of peripheral androgens (with are subtracts for aromatization) and the testicular production of estrogens, which is not inhibited by NSAIs. Additionally, the use of NSAIs can be associated with feedback loop leading to increase of LH and FSH, which can lead of additional production of androgens, with increased availability of subtracts for aromatization. All these elements converge to a suboptimal suppression of estrogen production in male patients submitted to treatment with monotherapy AI, and create a rational for the combined use of these agents together with targeted therapy.

The use of aromatase inhibitors together with LHRH was studied as first- or second-line therapy for male patients with HR+ metastatic breast cancer (Giordano SH 2005); 19 patients were evaluated with promising results: 2 patients (10.5 %) had complete response, 7 patients (36.8 %) experienced a partial response, 7 patients (36.8 %) had stable disease lasting ≥6 months, and 3 patients (15.8 %) had progressive disease. Overall, the disease control rate was 84.2 %. Median progression-free survival was 12.5 months (95 % CI 8.2–16.9), median overall survival was 35.8 months (95 % CI 24.4–49.2), 1- and 2-year survival rates were 89.5 and 67 %, respectively. Safety profile was expected and manageable, with no grade 3/4 adverse events.Cyclin-dependent kinases in breast cancer

Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases. The cyclin D proteins are important in cancer, as their abundance and functions are regulated by extracellular growth factor and adhesion signaling. The cyclin D proteins act through the cyclin-dependent kinases 4 (CDK4) and cyclin-dependent kinases 6 (CDK6) protein kinases to promote G1 progression (Musgrove 2011). CDK4 and CDK6, in turn, hyperphosphorylate and activate the retinoblastoma protein Rb to promote cell cycle entry and cell proliferation. Consistent with their having an important role in human cancer, focal copy number abnormalities that result in increased CDK activity are among the most commonly described mutations observed in diverse tumor types; these mutations include amplifications of the genes that encode cyclin D1 or CDK4, and deletions affecting the *CDKN2* locus, which encodes the $p16^{INK4a}$ inhibitor of CDK activity (Beroukhim 2010). In a mouse model of HER2+ breast cancer, deletion of either the CCND1 or CDK4 gene prevented breast cancer formation (Yu 2006).

Data from The Cancer Genome Atlas highlight the importance of the Cyclin/CDK/Rb pathway in luminal breast cancer (Beroukhim 2010). Abnormalities that result in CDK activation are highly enriched in the luminal A and B molecularly defined subgroups, ~85% of which were ER+/HER2−. Cyclin D1 amplifications were observed in 29% and 58% of the luminal A and B subtypes, respectively, and CDK4 amplifications were observed in 14% and 25% of luminal

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A and B subtypes, respectively. Luminal A subtype tumors also have loss of CDKN2. The luminal subtypes also maintain expression of Rb (Beroukhim 2010), which would be essential for benefit from treatment with a CDK4/6 inhibitor.

Recent clinical data showed that inhibitors of CDK4/6 are active in advanced HR+ breast cancer. Palbociclib is an oral, potent, selective inhibitor of CDK4/6 that when used in combination with the non-steroidal aromatase inhibitor letrozole significantly prolonged progression-free survival in postmenopausal women with locally recurrent or advanced ER+, HER2− breast cancer (Finn et al 2012, Finn et al 2015). Among patients with HR+, HER2- negative metastatic breast cancer who had progression of disease during prior endocrine therapy, palbociclib combined with fulvestrant resulted in significant longer progression-free survival than fulvestrant alone (Turner et al 2015). These encouraging data warrant further clinical investigation of CDK inhibitors in breast and other cancers. In anticipation of the imminent shift of treatment paradigms for HR+ HER2-negative advanced breast cancer, additional study in the post-CDK4/6 inhibitor settings would be valuable.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

1.2.1 Overview of ribociclib (LEE011)

In the mammalian cell cycle, entry into S phase is achieved by CDK4/6.Ribociclib is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that induces G1 arrest at sub-micro molar concentrations in a variety of pRb-positive cancer cells *in vitro*. Ribociclib has proven efficacious when combined with other targeted therapies *in vitro* and *in vivo* in cancers driven by a variety of oncogenic signaling pathways. Ribociclib may therefore be an effective anti-cancer agent in a variety of pRb-positive human neoplasms, especially in those that contain activated CDK4/6-pRb pathway. Ribociclib is currently being developed in phase III for the treatment of hormone receptor positive breast cancer patients; several other phase I or II clinical studies are being conducted and presented below.

1.2.1.1 Pharmacology of ribociclib (LEE011)

Ribociclib inhibits the CDK4/CCND1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC_{50}) values of 0.01 and 0.039 μM in biochemical assays, respectively. In Jeko-1 cells, the compound inhibits CDK4/6-dependent pRb phosphorylation with an average IC_{50} of 0.06 μM. Consistent with the observed inhibition of pRb phosphorylation, ribociclib also inhibited G1 to S phase cell cycle progression in Jeko-1 cells as judged by both the inhibition of bromodeoxyuridine (BrdU) uptake (IC_{50} of 0.1 μM) and fluorescence activated cell sorting (FACS) analysis (half-maximal increase in cells in G1 at 0.11 μM).

The effect of ribociclib on pRb phosphorylation, BrdU uptake and cell cycle progression has been assessed in more than 40 cell lines derived from hematological, esophageal, liposarcoma and breast cancers. In pRb+ cell lines, ribociclib inhibits pRb phosphorylation with a median IC_{50} value of 0.275 μM (range: 0.06 to 8.8 μM). Similarly, ribociclib interferes with G1 to

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S phase cell cycle progression in these cells as determined by either BrdU uptake or FACS analysis with a median IC_{50} value of 0.46 μM. In contrast, in lineage-matched pRb- cell lines no effect of ribociclib on either pRb phosphorylation or cell cycle progression is observed.

Thus, ribociclib is able to impact cell cycle progression in cell lines derived from a variety of tumor types that harbor a diversity of genetic alterations in a manner dependent on intact pRb.

1.2.1.1.1 *In vivo* pharmacology

Ribociclib was well-tolerated in mice and rats with body weight loss not exceeding 12.5% at doses up to 250 mg mg/kg qd po or 150 mg/kg qd po, respectively, for up to 28 days. However, myelosuppression was observed and correlated with pRb phosphorylation inhibition. Treatment with ribociclib resulted in tumor regression in the Jeko-1 MCL xenograft model at doses greater than or equal to 75 mg/kg, qd po. *In vivo* pharmacokinetics (PK)/pharmacodynamics (PD) studies demonstrated dose-related inhibition of pRb phosphorylation in tumors, with continuous dosing over at least 3-5 days being required to achieve optimal target inhibition.

Ribociclib has demonstrated *in vivo* anti-tumor activity in subsets of tumor xenograft models. Consistent with the compound mechanism of action, efficacy was only observed in tumor expressing pRb. Tumor types where ribociclib has demonstrated robust anti-tumor activities include but are not limited to breast, melanoma, neuroblastoma, malignant rhabdoid, lung, pancreas and hematological malignancies.

In addition, ribociclib has shown anti-tumor activity when combined with targeted agents which inhibit signaling pathways known to regulate D-cyclin levels, including inhibitors of the RAF/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PIK3) and mTOR pathways.

1.2.1.2 Nonclinical pharmacokinetics (PK) and metabolism of LEE011 (ribociclib)

The PK of ribociclib was investigated in mouse, rat, dog and monkey. Ribociclib showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life ($T_{1/2}$) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h). Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%); moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (T_{max}) occurred between 2 to 4 h across species. Gender dependent toxicokinetics were observed in rats with higher exposure to ribociclib in males as compared to females and higher exposure to the metabolite, LEQ803. Plasma protein binding was moderate in all species (unbound fraction (fu) in human: 30%).

In a rat ADME (absorption, distribution, metabolism and excretion) study, extensive distribution of [3H]LEE011 and its metabolites was observed. In pigmented rats, radioactivity was specifically found in melanin-containing structures; the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This

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metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels *in vitro*.

Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.9% of dose after p.o.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

In vitro, ribociclib was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. Ribociclib may inhibit CYP3A4 under therapeutic conditions. No induction of CYP1A2, CYP2B6 or CYP3A4 was observed. The in vitro inhibitory potency of ribociclib observed for the transporters organic anion transporting polypeptide 1B1 (OATP1B1), breast cancer resistance protein (BCRP), organic cation transporter 1 (OCT1), OCT2, multidrug and toxin extrusion protein 1 (MATE1), MATE2K and bile salt export pump (BSEP) may translate into clinically relevant inhibition at therapeutic doses. Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4. Although ribociclib is a substrate of the P-glycoprotein (P-gp) efflux transporter, this process is likely not clinically relevant due to the high passive permeability of ribociclib.

1.2.1.3 Safety pharmacology and toxicology of ribociclib (LEE011)

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels.

The effects of ribociclib on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition.

An increased number of ovarian corpora luteal was observed in a single female dog in the 4-week toxicity study at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of ribociclib (arrest of estrous cycle).

The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) and the kidney (concurrent degeneration and regeneration of tubular epithelial cells) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of ribociclib.

Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver.

Generally all changes demonstrated either reversibility or a clear tendency towards reversibility. Data from a rabbit embryofetal development study, shows that ribociclib is teratogenic in the rabbit in the absence of maternal toxicity

[redacted]

Based on its mechanism of action and preclinical toxicology studies, the major potential toxicities for ribociclib include myelosuppression, hepatic toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4 or other combination treatments.

Please refer to (LEE011 Investigator's Brochure) for additional details.

1.2.1.4 Clinical experience with ribociclib (LEE011)

As of 5-July-2016, ribociclib is being investigated in patients as a single agent in 3 phase I studies, in 1 phase II study and in combination in 15 studies: 12 phase Ib/II studies and 3 randomized phase III studies. Five studies were closed to enrollment: (CLEE011A2201), a randomized phase II study; (CLEE011A2112C), a phase I dose finding study; (CLEE011X2102), a phase I study in malignant rhabdoid tumors and neuroblastomas; and (CLEE011X2105), a phase Ib/II study in BRAF mutant melanoma; and (CLEE011X2201), a phase II study of relapsed refractory unresectable teratoma. Ribociclib is also being investigated in 2 clinical pharmacology studies. Five clinical pharmacology studies in healthy patients have been completed.

Refer to latest edition of (LEE011 Investigator's Brochure) for more details.

1.2.1.4.1 Clinical safety of ribociclib (LEE011) as single agent

As of 18-Sep-2015, 153 patients have been treated with single agent ribociclib in the first-in-human (FIH) phase I study (CLEE011X2101); 134 patients have been treated in the initial dose escalation part for the 3 week on/1 week off regimen and 47 patients in the dose expansion part of the study; 19 patients were enrolled for the continuous dosing regimen with ribociclib and, 8 patients were enrolled in the liquid formulation cohort.

Patients with advanced solid tumors or lymphomas were treated with increasing doses of ribociclib orally, once daily (qd) for 21 days followed by a 1-week rest (28-day cycle). Doses ranging from 50 mg to 1200 mg were evaluated on this schedule. Treatment has been discontinued in 127 (95%) patients; the primary reasons for treatment discontinuation were: disease progression (111 [83%] patients); adverse events (AEs) (9 [7%] patients); death (1.5%] patients); withdrawal of consent (4 [3%] patient); and loss to follow up (1 [1%] patient).

The most frequently reported AEs (≥10%), regardless of grade, causality and ribociclib dose

Were (50mg-1200mg): nausea (51.5%); fatigue (42.5%); diarrhea (36.6%); vomiting (35.8 %); neutropenia (35.1%); anemia (33.6%); decreased appetite (23.1%); constipation (22.4%); leukopenia (21.6 %); dyspnea (20.1%); asthenia (19.4%); cough (17.9%); headache (17.9%);

hyperglycemia and hypoalbuminemia (17.2% for each); AST increase, electrocardiogram

QT prolongation (15.7% for each); abdominal pain (14.9%); lymphopenia (14.9%); blood creatinine increased, dizziness, pyrexia (14.2% for each); neutrophil count decreased, peripheral edema (13.4 %); ALT increase (12.7%); Pain in extremity (11.9%); hypocalcemia (11.2%) and blood alkaline phosphatase increase (10.4%).

[redacted]

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday for the three weeks on/one week off schedule. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

There have been no deaths related to study drug reported on study (CLEE011X2101).The following serious adverse events shown in Table 1-2 have been reported with a suspected causal relationship in study (CLEE011X2101) as of 18-Sep-2015. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to ribociclib refer to the (LEE011 Investigator's Brochure).

Table 1-2 Serious adverse events with a suspected causal relationship with ribociclib single agent

Serious suspected adverse events which have occurred with ribociclib (single agent)	
System Organ Class Preferred Term	**Preferred Term**
Blood and lymphatic system disorders	Anemia, Febrile neutropenia, Neutropenia,Thrombocytopenia
Gastrointestinal disorders	Diarrhea, Nausea, *Pancreatitis*
General disorders and administration site conditions	Generalized edema
Infections and infestations	Herpes simplex
Investigations	***Blood creatinine increased,*** *Electrocardiogram QT prolonged*

Events in *italic font* indicate those events which are newly included since the previous edition of the reference safety information.

1.2.1.4.2 Clinical efficacy with ribociclib as single agent

Preliminary anti-tumor activity of ribociclib from trial (CLEE011X2101) was assessed across all dose levels (50 mg – 1200 mg). Out of 134 evaluable patients as of 18-Sep-2015, 4 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2-, PIK3CA mutant, CCND1 amplified breast cancer (on the continuous daily dosing regimen). Stable disease (SD) was the best overall response in 47 (35%) patients. Enrollment in this study is completed. Stable disease ≥4 cycles and ≥6 cycles was observed in 30 (22%) and 21 (16%) patients, respectively. Six patients with SD ≥4 cycles received treatment for >1 year, of these 2 patients were on study for >2 years (Infante, JR ASCO 2014 abstract 2528).

Refer to (LEE011 Investigator's Brochure) for more details.

1.2.1.4.3 Clinical Experience with Continuous Dosing of Ribociclib In Combination

CLEE011X2108 study is an ongoing Phase Ib/II study of ribociclib in combination with fulvestrant and alpelisib or buparlisib in postmenopausal women with hormone receptor

[redacted]

positive, HER2 negative, locally recurrent or advanced metastatic breast cancer. Patients were enrolled to one of the following dose combinations: (1) ribociclib (600 mg) + fulvestrant (500 mg), n=13, (2) ribociclib (400 mg) [continuous] + fulvestrant (500 mg), n=9, (3) ribociclib (200 mg) + alpelisib (200 mg) + fulvestrant (500 mg), n=3, (4) ribociclib (400 mg) + alpelisib (150 mg) + fulvestrant (500 mg), n=6, (5) ribociclib (400 mg) + alpelisib (200 mg mg) + fulvestrant (500 mg), n=9, (6) ribociclib (400 mg) + buparlisib (30 mg) + fulvestrant (500 mg), n=9, (7) ribociclib (400 mg) + buparlisib (40 mg) + fulvestrant (500 mg), n=6, (8) ribociclib (600 mg) + buparlisib (30 mg) + fulvestrant (500 mg), n=8. In the cohort with continuous ribociclib dosing at 400mg (n = 9), one DLT was reported, a Grade 3 AST elevation. The most frequently reported (≥10%) adverse events suspected to be related to study drug in the continuous ribociclib dosing cohort were: nausea (55.6%), neutropenia (44.4%), fatigue (33.3%), diarrhea, ALT increase, stomatitis, headache (22.2%), AST increase, decreased appetite, rash, vomiting, and pruritus (11.1%), Grade 3/4 adverse events in this group were neutropenia (22.2%) and AST increase (11.1%).

1.2.1.4.4 Clinical pharmacokinetics of ribociclib (LEE011)

As of 18-Sep-2015 preliminary PK data were available from approximately 153 patients from the FIH study CLEE011X2101 across the dose range of 50 to 1200 mg. Following oral dosing, ribociclib was rapidly absorbed with median T_{max} ranging from 1 to 4 h. Ribociclib plasma exposure exhibited slightly over-proportional increases in exposure.

Steady-state was generally reached by Day 8 and the mean effective $T_{1/2}$ based on accumulation ratio (i.e., $T_{1/2}$, acc) ranged from 12.0 to 33.1 h. The accumulation ratio based on area under the curve (AUC) obtained in a dosing interval (Racc) ranged from 1.34 to 2.5.

In a food effect study CLEE011A2111 in 24 healthy subjects, a single dose of ribociclib (600 mg) was administered as drug-in-capsule (DiC) with a high-fat, high-calorie meal and under fasted conditions. Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib DiC with a high-fat, high-calorie meal decreased the rate of absorption of ribociclib resulting in a 23% decrease in Cmax (geometric mean ratio: 0.775; 90% confidence interval [CI]: 0.700, 0.858) and a median difference in Tmax of 2 hours. However, there was no effect on the extent of absorption of ribociclib as the overall exposure (AUCinf) was unaffected under fed conditions (geometric mean ratio: 0.994; 90% CI: 0.925, 1.070). A similar trend was observed for LEQ803, an active metabolite of ribociclib, with a decrease in Cmax (32%), a delay in median Tmax, and no substantial effect on overall exposure. Based on these data, ribociclib DiC can be taken without regard to meals.

In the human ADME study CLEE011A2102, a single oral dose of 600 mg [^{14}C] LEE011 was administered to 6 healthy male subjects. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Absorption was estimated to be approximately 58.8%. Ribociclib accounted for approximately 23% of the total radioactivity in plasma, based on AUCinf. Metabolites M1 (glucuronidation of M15), M4 (LEQ803, N-demethylation) and M13 (CCI284, N-hydroxylation) were the most abundant metabolites in plasma, representing an estimated 7.78%, 8.60% and 9.39% of total [^{14}C]AUC0-48h, and 17.9%, 19.8% and 21.6% of ribociclib AUC0-48h, based on metabolite profiles.

[redacted]

A drug-drug interaction (DDI) study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) was conducted in 48 healthy subjects (CLEE011A2101). Compared to ribociclib alone, ritonavir (100 mg bid for 14 days) increased ribociclib Cmax and AUCinf by 1.7-fold and 3.2-fold, respectively, following a single oral dose of 400 mg ribociclib. Cmax and AUClast for LEQ803 decreased by 96% and 98%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inhibitors may markedly increase ribociclib exposure and are prohibited.

Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib Cmax and AUCinf by 81% and 89%, respectively, following a single oral dose of 600 mg ribociclib. LEQ803 Cmax increased 1.7-fold and AUCinf decreased by 27%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inducers may markedly decrease ribociclib exposure and are prohibited.

A DDI cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) conducted in 25 healthy subjects (CLEE011A2106) indicated that ribociclib (400 mg) is a moderate inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans. PK data indicated that compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg qd for 8 days) increased midazolam Cmax and AUCinf by 2.1-fold and 3.8-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with Cmax decreased by approximately 10% and AUCinf increased slightly by 20%. Based on these data, ribociclib (400 mg) is a moderate CYP3A4 inhibitor (≥ 2- fold but < 5-fold increase in AUC). Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index is prohibited.

Ribociclib (400 mg) did not have a substantial effect on CYP1A2 in humans; therefore concurrent use of CYP1A2 substrates is not expected to lead to clinically significant DDIs.

Refer to the (LEE011 Investigator's Brochure) for more details.

1.2.2 Summary of results from patients treated with the combination of ribociclib 600 mg and letrozole 2.5 mg daily from study CLEE011A2301 (MONALEESA-2)

MONALEESA-2 – (CLEE011A2301); a randomized, double blind, placebo controlled, multicenter global Phase III trial evaluated the safety and efficacy of ribociclib in combination with letrozole compared to letrozole alone in postmenopausal women with HR+/HER2- aBC who received no prior therapy for their advanced disease. See Table 1-3.

The study met its primary objective at the pre-planned interim analysis; ribociclib in combination with letrozole demonstrated statistically significant benefit over placebo in combination with letrozole in prolonging PFS based on Investigator assessment. Clinical benefit was evident relative to placebo plus letrozole with a 44.4% estimated risk reduction in the primary PFS endpoint as per Investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; $p=3.29\times10^{-6}$).

Six hundred, sixty eight patients were randomized; 334 patients each to the ribociclib plus letrozole arm and the placebo plus letrozole arm. The median study follow-up was 15.3 months,

[redacted]

as of the 29-Jan-2016 data cut-off date, and the proportion of patients continuing to receive treatment in the ribociclib plus letrozole arm was higher than in placebo plus letrozole arm (58.4% vs 46.1%, respectively). Disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo plus letrozole arm compared to the ribociclib plus letrozole arm (43.7% vs. 26%). Adverse events led to the discontinuation of study treatment in 32 patients (4.8%): 25 patients (7.5%) in ribociclib plus letrozole arm and 7 patients (2.1%) in placebo plus letrozole arm.

The median age of patients was 62 years (range: 23-91) and 44.2% were ≥ 65 years old. The majority of the patients were Caucasian (82.2%). All patients had ECOG performance status of either 0 or 1. Approximately one-third (34.0%) of the patients in this study were de novo metastatic breast cancer patients. Nearly two-thirds (58.8%) of patients had visceral disease (19.8% with liver and 45.4% with lung involvement) and 22.0% had bone only metastases at study entry. All except four patients had stage IV disease at the time of study entry (other four had stage III disease). One-third (34.0%) of the patients had ≥ 3 metastatic sites.

Table 1-3 Patient Demographic and baseline characteristics in study (CLEE011A2301)

Characteristic	Ribociclib + Letrozole n=334	Placebo + Letrozole n=334
Median age, years (range)	62 (23–91)	63 (29–88)
Race, n (%)		
Caucasian	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Other/unknown	27 (8.1)	24 (7.2)
ECOG performance status, n (%)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Metastatic sites, n (%)		
Visceral disease (lung and/or liver metastases)	197 (59.0)	196 (58.7)
Bone-only disease	69 (20.7)	78 (23.4)
De novo metastatic disease, n (%)	114 (34.1)	113 (33.8)
Disease-free interval, n (%)		
≤12 months	4 (1.2)	10 (3.0)
>12 months	216 (64.7)	210 (62.9)
Prior (neo)adjuvant therapy, n (%)		
Chemotherapy and endocrine therapy	123 (36.8)	120 (36.0)
Endocrine therapy only	52 (15.6)	51 (15.3)

As of 29-Jan-2016 (cutoff date), the median duration of exposure to study treatment was 13.0 months in the ribociclib arm and 12.4 months in the placebo arm. The median duration of exposure to ribociclib/ placebo was 12.2 months in the ribociclib arm and 12.4 months in the placebo arm; 240 patients (71.9%) were exposed to ribociclib plus letrozole therapy for ≥ 9

[redacted]

months. Median relative dose intensity was 87.5% for ribociclib and 100% for placebo. Ribociclib dose interruptions occurred in 257 (76.9%) patients, and letrozole was interrupted in 132 (39.5%) patients in the ribociclib arm. Placebo was interrupted in 134 (40.6%) patients and letrozole was interrupted in 107 (32.4%) patients in the placebo arm. Dose reductions occurred in 53.9% and 7.0% of patients in the ribociclib and placebo arms, respectively, most commonly for adverse events (169 [50.6%] vs. 14 [4.2%] patients; ribociclib vs. placebo arm). Dose reduction due to neutropenia occurred in 65% of patients who had a dose reduction due to AEs in the ribociclib arm.

The majority of the patients experienced at least one AE in both treatment groups (98.5% vs. 97%); the most commonly (≥ 30%) reported AEs in ribociclib plus letrozole group irrespective of causality were: neutropenia (60.8%), nausea (51.5%), fatigue (36.5%), diarrhea (35%), and alopecia (33.2%) AEs where a higher proportion of ribociclib plus letrozole-treated patients reported events (and where there was a ≥ 10% difference to the placebo plus letrozole group) included neutropenia (+56.6%), nausea (+23%), decreased neutrophil count (+18%), alopecia (+17.7%), decreased white blood cell count (+17.4%), vomiting (+13.8%), anemia (+13.8%), diarrhea (+12.9%), leukopenia (+12.9%), increased ALT (+11.7%), and increased AST (+11.4%). The incidence of SAEs was 21.3% and 11.8% in the ribociclib plus letrozole and placebo plus letrozole arms, respectively. Twenty-five patients (7.5%) from the ribociclib plus letrozole group experienced SAEs that were considered by the Investigator to be related to study treatment. Febrile neutropenia was the only suspected SAE reported in >1% of patients (1.2%). Permanent discontinuations due to adverse events were reported in 7.5% of patients receiving ribociclib plus letrozole and in 2.1% of patients receiving placebo plus letrozole. The most common AEs leading to treatment discontinuation of both ribociclib and letrozole were ALT increased (2.7%), AST increased (2.4%) and vomiting (1.5%) (Table 1-4).

Table 1-4 Adverse events with suspected relationship to study treatment in study (CLEE011A2301)

Adverse events with suspected relationship to study treatment by preferred term and maximum grade (greater than 5% in either arm) (Safety set)	**Ribociclib + Letrozole n=334**			**Placebo + Letrozole n=330**		
Preferred Term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Total	**319 (95.5)**	**199 (59.6)**	**43 (12.9)**	**249 (75.5)**	**27 (8.2)**	**1 (0.3)**
Neutropenia	199 (59.6)	130 (38.9)	29 (8.7)	13 (3.9)	2 (0.6)	0
Nausea	144 (43.1)	6 (1.8)	0	54 (16.4)	0	0
Alopecia	95 (28.4)	0	0	44 (13.3)	0	0
Fatigue	92 (27.5)	5 (1.5)	1 (0.3)	64 (19.4)	2 (0.6)	0
Diarrhoea	72 (21.6)	3 (0.9)	0	39 (11.8)	0	0
Neutrophil count decreased	63 (18.9)	44 (13.2)	3 (0.9)	3 (0.9)	1 (0.3)	0
Vomiting	62 (18.6)	6 (1.8)	0	22 (6.7)	1 (0.3)	0

[redacted]

Adverse events with suspected relationship to study treatment by preferred term and maximum grade (greater than 5% in either arm) (Safety set)	Ribociclib + Letrozole n=334			Placebo + Letrozole n=330		
Preferred Term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Total	**319 (95.5)**	**199 (59.6)**	**43 (12.9)**	**249 (75.5)**	**27 (8.2)**	**1 (0.3)**
White blood cell count Decreased	57 (17.1)	37 (11.1)	2 (0.6)	5 (1.5)	1 (0.3)	0
Hot flush	51 (15.3)	1 (0.3)	0	63 (19.1)	0	0
Arthralgia	48 (14.4)	1 (0.3)	0	52 (15.8)	1 (0.3)	0
Leukopenia	48 (14.4)	25 (7.5)	1 (0.3)	9 (2.7)	1 (0.3)	0
Anaemia	46 (13.8)	2 (0.6)	0	9 (2.7)	3 (0.9)	0
Rash	45 (13.5)	2 (0.6)	0	10 (3.0)	0	0
Alanine aminotransferase Increased	42 (12.6)	22 (6.6)	5 (1.5)	8 (2.4)	1 (0.3)	0
Constipation	40 (12.0)	0	0	20 (6.1)	0	0
Decreased appetite	39 (11.7)	3 (0.9)	0	18 (5.5)	0	0
Aspartate aminotransferase increased	36 (10.8)	12 (3.6)	2 (0.6)	8 (2.4)	3 (0.9)	0
Stomatitis	33 (9.9)	1 (0.3)	0	15 (4.5)	0	0
Pruritus	30 (9.0)	1 (0.3)	0	3 (0.9)	0	0
Asthenia	27 (8.1)	1 (0.3)	0	23 (7.0)	1 (0.3)	0
Headache	27 (8.1)	1 (0.3)	0	24 (7.3)	0	0
Dyspepsia	23 (6.9)	0	0	12 (3.6)	0	0
Dry mouth	21 (6.3)	1 (0.3)	0	14 (4.2)	0	0
Dizziness	19 (5.7)	0	0	21 (6.4)	0	0
Thrombocytopenia	19 (5.7)	1 (0.3)	0	0	0	0
Lymphocyte count decreased	18 (5.4)	12 (3.6)	0	3 (0.9)	2 (0.6)	0

For additional information about the safety profile of ribociclib (as monotherapy or in combination with letrozole), please refer to [ribociclib Investigator's Brochure] (Section 6 Reference Safety Information).

Key efficacy results

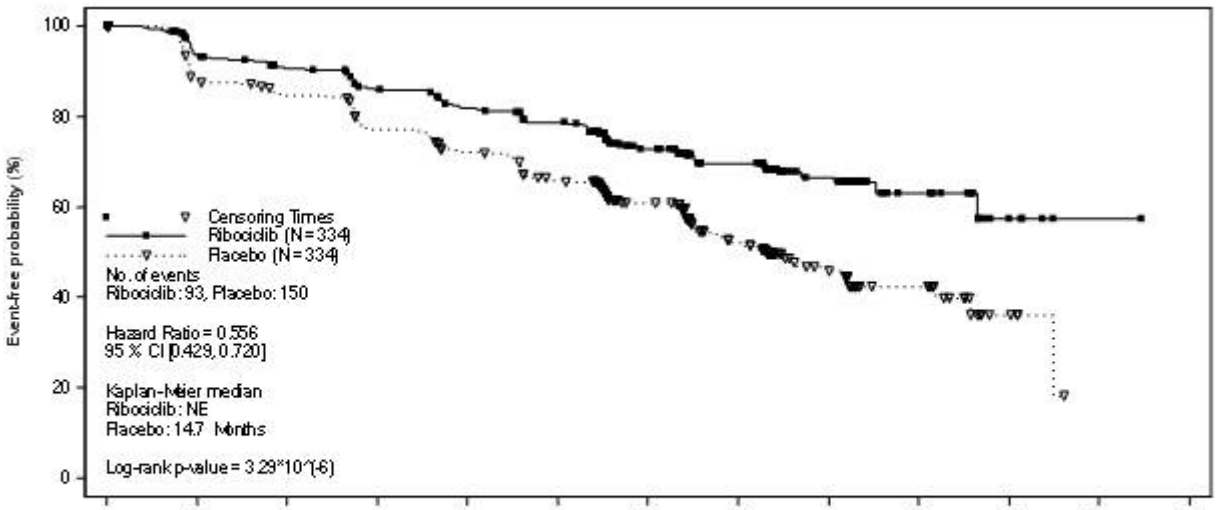
Study CLEE011A2301 met its primary objective at the primary analysis, with statistically significant clinical benefit in the treatment arm versus control arm. A 44.4% estimated risk reduction in ribociclib plus letrozole treated patients was evident in the primary PFS endpoint as per investigator assessment (HR=0.556, 95% CI: 0.429, 0.720; one sided p value=3.29×10^{-6}). Updated analysis resulted in a PFS of 25.3 months in the treatment arm and 16 months in the control arm. Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease (See Figure 1-3).

[redacted]

Overall survival data were immature at the time of this interim analysis with 43 deaths being reported (23 patients [6.9%] and 20 patients [6.0%], respectively), from the ribociclib plus letrozole and placebo plus letrozole treatment arms.

There was an ORR of 52.7% vs. 37.1% and CBR of 80.1% vs. 71.8% in patients with measurable disease. See Figure 1-1.

Figure 1-1 Kaplan-Meier plot of PFS based on Investigator assessment (Full Analysis Set)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24
Ribociclib	334	294	277	257	240	226	164	119	68	20	6	1	0
Placebo	334	279	264	237	217	192	143	88	44	23	5	0	0

1.2.3 Overview of everolimus (RAD001/ Afinitor®)

Everolimus (RAD001; Afinitor®) is a derivative of rapamycin and has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets for cardiac and renal transplantation, and in the United States for the prevention of organ rejection of kidney transplantation. In July 2012, everolimus in combination with exemestane was approved for advanced breast cancer in the US, EU and other countries.

The following is a brief summary of the main characteristics of everolimus. More detailed information can be obtained from the (everolimus Investigator's Brochure).

Everolimus is a selective mTOR inhibitor, specifically targeting the mTOR-raptor (regulatory-associated protein of mTOR, Raptor) signal transduction complex 1 (mTORC1). Everolimus potently inhibits proliferation of endothelial cells (Yu 1999, Lane 2009) and has antiangiogenic activity *in vivo* (Guba 2002, Tsutsumi 2004, Mabuchi 2007, Lane 2009).

[redacted]

1.2.3.1 Nonclinical experience

Everolimus inhibits the proliferation of a wide range of human tumor cell lines *in vitro* at IC50s ranging from sub/low nM to µM.

The antitumor efficacy of everolimus was compared to other compounds in a panel of six breast cancer xenograft models established after direct transplantation of patients' tumors onto nude mice (Report RD-2011-50492). This panel included an ER + model, HBCx-3 (XTS-181), (Marangoni et al 2007). Everolimus given daily by oral gavage for 21 to 35 days at 20 mg/kg was well tolerated with no significant mean body weight loss. In all breast cancer models tested, tumor growth was significantly inhibited, and was particularly evident in the HBCx-3 (XTS-181) model with nine partial regressions in ten mice tested (-13.5% mean tumor volume regression, $p<0.001$).

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an antiproliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

Based on data generated using human liver microsomes and microsomes from cells expressing single human cytochrome P450s enzymes, CYP3A4 was identified as the major enzyme involved in the microsomal biotransformation of everolimus. Everolimus inhibited competitively the metabolism of the CYP3A4 substrate cyclosporine with a Ki value of 2.3 µMol/L (2204 ng/mL) under *in vitro* conditions.

Further details can be found in the (everolimus Investigator's Brochure).

1.2.3.2 Clinical experience

1.2.3.2.1 Everolimus pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of one to two hours. The steady-state $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg when given weekly and 5 and 10 mg when given daily. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens.

In healthy subjects, high fat meals reduced systemic exposure of a 10 mg dose of everolimus (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food had no apparent effect on the post absorption phase concentration-time profile (Study RAD001C2120).

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus

[redacted]

10 mg/day [DMPK R303044]. Plasma protein binding is similar in healthy patients and in subjects with moderate hepatic impairment (approximately 74%, (Study RAD001A2303)).

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man was CYP3A4 (DMPK(US)1998/005; DMPK(CH) R99-2448), (Kuhn 2001). Other CYP isoenzymes either do not metabolize everolimus or do so at very low rates. Everolimus is a moderate inhibitor of P-glycoprotein-like mediated efflux systems, although the compound has a high intrinsic permeability when P-glycoprotein is inhibited (Crowe 1998, Laplante 2002, DMPK(CH) 1997/417). Following oral administration, everolimus is the main circulating component in human blood and contributes the majority of the overall pharmacologic activity (Study W107). Everolimus was also shown to increase exposure of exemestane: In (Study RAD001Y2301), average exemestane C_{min} and C_{2h} were 45% and 71% higher, respectively, when co-administered with everolimus.

No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces.

1.2.3.2.2 Everolimus in combination with endocrine therapy in HR+ breast cancer

The combination of everolimus with hormonal therapy has been assessed in different disease settings in HR+ breast cancer and showed evidence of efficacy of everolimus in this patient population (Bachelot et al 2012; Baselga et al 2012; Piccart et al 2012).

In newly diagnosed patients with ER+ breast cancer, a neoadjuvant randomized 270-patient Phase II study compared the combination of everolimus 10 mg QD and letrozole 2.5 mg QD to letrozole alone for 16 weeks of therapy prior to surgery. The overall response rate in the investigational everolimus + letrozole arm was higher than that with letrozole alone: 68% vs.59% based on palpation ($p = 0.062$) and 58% vs. 47% based on ultrasound ($p = 0.021$) respectively, meeting the predetermined endpoint for efficacy. Additionally, there was a greater antiproliferative response in the investigational arm, with a decrease of the Ki67 proliferation index to <1 in 57% of patients in the everolimus arm compared to 30% of patients in the placebo arm ($p<0.01$) (Baselga 2009). A randomized Phase III, double-blind, placebo-controlled study (BOLERO-2 Study) demonstrated very significant improvements in treatment of HR+ breast cancer that had recurred or progressed on letrozole or anastrozole. Response rate, progression-free survival (PFS), and clinical benefit rate were all significantly improved relative to exemestane monotherapy. The median PFS by local assessment was 7.8 months for everolimus + exemestane versus 3.2 months for exemestane (HR = 0.45; 95% CI: 0.38-0.54; p<.0001). Overall response rate (12.6% vs 1.7%; p<.0001) and clinical benefit rate (51.3% vs 26.4%; p<.0001) were superior in the everolimus + exemestane arm versus exemestane + placebo. Analyses by central assessment showed a median progression-free survival of 11 months with everolimus versus 4.1 months with placebo (HR = 0.38; 95% CI: 0.31 – 0.48; p<.0001) confirming the results of the primary PFS analysis (Piccart 2012, Baselga 2012).

[redacted]

1.2.3.3 Safety profile of everolimus

The following AEs are considered to be class-effects of mTOR inhibitors: stomatitis/oral mucositis/ulcers, infections and infestations, rash and similar events, cytopenia, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, and thromboembolism. The more common metabolic side effects reported with mTOR inhibitors result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents. Virtually all of the side effects associated with mTOR inhibitors can be managed effectively with dose modification and/or supportive intervention.

The safety profile of everolimus observed in the Phase III BOLERO-2 study is consistent with prior experience in the oncology setting; events are predominantly low grade (grade 1 or 2). An increased risk of non-infectious pneumonitis, infection, and stomatitis in the everolimus plus exemestane arm relative to the control arm [exemestane + placebo] was observed, although each of these events can be effectively managed in this setting.

The most common adverse events (AEs) suspected to be related to treatment, with an incidence ≥10%, reported in association with everolimus plus exemestane therapy were consistent with what was previously reported: stomatitis, rash, fatigue, decreased appetite, diarrhea, dysgeusia, nausea, pneumonitis, weight loss, anemia, epistaxis, hyperglycemia, thrombocytopenia, and pruritus. The most common grade 3-4 AEs suspected to be related to treatment with an incidence of ≥2% were: stomatitis, hyperglycemia, anemia, pneumonitis, fatigue, elevated alanine and aspartate transaminase concentrations, elevated γ- glutamyltransferase concentrations, dyspnea, neutropenia, and thrombocytopenia (Piccart et al 2012; Baselga et al 2012). No new safety concerns have emerged compared to previous experience with everolimus monotherapy or combination therapy.

Further details related to everolimus safety can be found in the (everolimus Investigator's Brochure) and package insert of the local supply of everolimus (if available) for more details.

1.2.4 Overview of exemestane

Exemestane is an irreversible steroidal aromatase inhibitor that has demonstrated efficacy in the treatment of postmenopausal patients with advanced breast cancer. It is indicated for adjuvant treatment of postmenopausal women with ER+ early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. It is also indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or following anti-estrogen therapy (in Europe).

Exemestane is initially recognized by the aromatase enzyme as a false substrate and is then transformed through an NADPH-dependent mechanism to an intermediate that binds irreversibly to the enzyme, causing inactivation. Exemestane significantly lowers circulating estrogen concentrations (estradiol, estrone and estrone sulfate) but has no detectable effect on

[redacted]

adrenal biosynthesis of corticosteroids or aldosterone (Aromasin prescribing information Pfizer-Pharmacia 2005).

The recommended daily dose of exemestane is 25 mg via oral administration. Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. The terminal half-life for exemestane is 18-24 hours. The time needed to reach maximal E_2 suppression is 7 days (Demers 1993, Plourde 1995, Buzdar 2003). Exemestane is metabolized by CYP3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1 and 3A4. Although no formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP isoenzyme inhibitors appear unlikely (Aromasin prescribing information Pfizer-Pharmacia 2011, Hutson 2005, Buzdar 2003). As noted in Section 1.2.3.2.1, everolimus increases exposure of exemestane.

The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg edema. Thrombocytopenia and leukopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane. A total of 1058 patients were treated with exemestane 25 mg once daily in the clinical trials program. Exemestane was generally well tolerated, and adverse events were usually mild to moderate. Adverse events occurring in greater than 10% of patients include hot flushes (14%), nausea (11.9%), insomnia, headache, increased sweating, joint and musculoskeletal pain, and fatigue (USPI Aromasin SmPC August 2008 (UK as RMS for EU MRP)). Androgenic effects were reported in a limited number of patients (4.3%) (Buzdar 2003).

Refer to the prescribing information of the local supply of exemestane for more details.

1.2.5 Ribociclib in combination with everolimus

1.2.5.1 Synergy with everolimus and ribociclib (LEE011)

The effect of combining ribociclib with the mTORC1-inhibitor RAD001 (everolimus; Afinitor®) in the ER+, PIK3CA-mutant MCF-7 xenograft model was examined. As demonstrated in Figure 1-2 single agent treatments with ribociclib and RAD001 resulted in modest tumor regressions of -9% and -21%, respectively. When ribociclib was combined with RAD001 tumor regression increased to -49%. Moreover, single agent and combination treatments were well tolerated as judged by body weight loss (not shown). In addition, the triplet combination of ribociclib plus everolimus plus the endocrine therapy, fulvestrant, was evaluated in the ER+, PIK3CA-mutant KPL-1 and PTEN-null XR751 xenograft models. The triplet combination demonstrated superior tumor regression compared to single agent LEE011 or LEE011 plus fulvestrant (see Figure 1-3) or compared to single agent everolimus or everolimus combined with fulvestrant. These data suggest that combining inhibitors that target the mTOR pathway with LEE011 may be an effective therapeutic strategy in ER+/PIK3CA-mutant tumors.

[redacted]

Figure 1-2 LEE011 and everolimus in MCF 7 xenograft

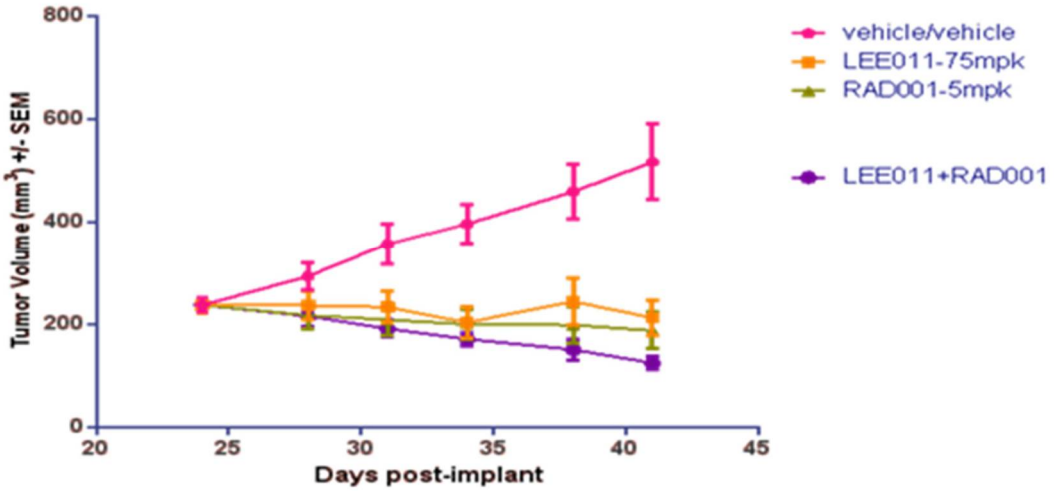
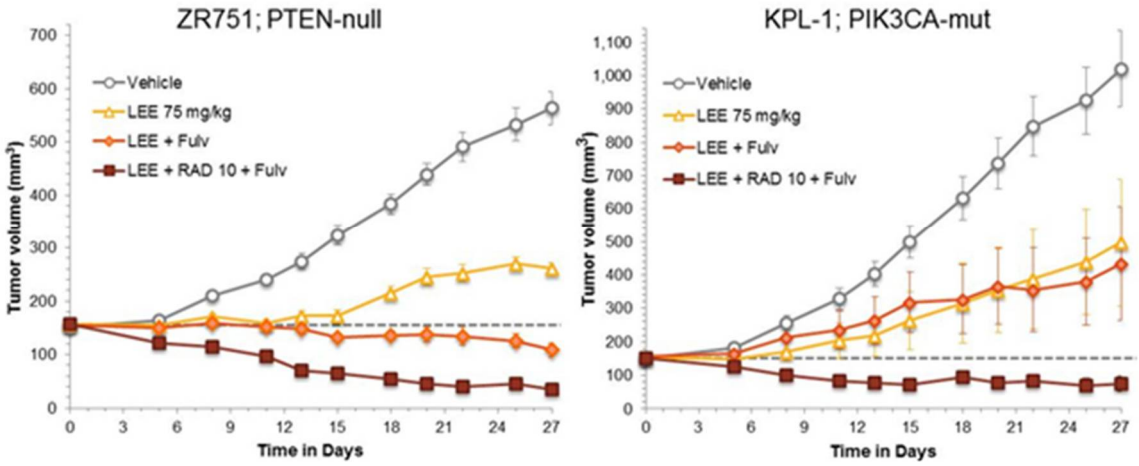


Figure 1-3 Triplet combination of LEE011, everolimus and fulvestrant in ZR and KPL-1 xenograft models



Mice treated with vehicle, LEE011 (LEE011;75 mg/kg qd x 28), fulvestrant (Fulv; 5 mg qwk x 4) and/or everolimus (RAD; 10 mg/kd qd x 28).

1.2.5.1.1 Drug interaction (ribociclib and everolimus)

In vitro experiments observed time-dependent inhibition of CYP3A4 by ribociclib with a KI value of 5 µM and a kinact value of 0.0245 min^{-1}; a clinical DDI confirmed these in vitro results. Everolimus is a sensitive CYP3A4 substrate. Therefore, a PK DDI was possible with the combination of everolimus and ribociclib (LEE011 Investigator Brochure).

As of March 2, 2015, 84 patients have been treated with the combination of ribociclib + everolimus + exemestane in a Phase Ib study (CLEE011X2106). Everolimus (RAD001) was

[redacted]

administered at 2.5 mg (qd) concurrently with 200 mg, 250 mg and 300 mg of ribociclib (qd, 3 weeks on/1 week off) with or without food. Additionally 350 mg of ribociclib was administered with 1 mg of everolimus without food or 2.5 mg everolimus with food and 200 mg of ribociclib was administered with 5 mg of everolimus with food. A fixed dose of 25 mg of exemestane (qd) was administered in each combination (Bardia A et al 2015).

Preliminary PK data for C_{max} and AUC_{0-24h} for ribociclib and everolimus were available on Day 1 and after multiple doses on Day 15. Everolimus (2.5 mg qd) exposure (AUC_{0-24h}) was increased in the presence of ribociclib (200-350 mg) to levels of 5 to 10 mg when compared to historical single agent data (Kovarik et al 2002; Kovarik et al 2005a; Urva et al 2013; Everolimus Investigator's Brochure). In general, mean steady state exposure for ribociclib and everolimus appeared to be lower in the presence of food at the same dose level; however, individual C_{max} and AUC_{0-24h} values with food were within the range of values observed without food. Further evaluation of 2.5 mg of everolimus (RAD001) (qd) with 300 mg ribociclib (qd, 3 weeks on/1 week off) with food is ongoing in CLEE011X2106 dose expansion (Bardia A et al 2015). See Table 1-5 for full PK parameters.

Table 1-5 Pharmacokinetic Parameters of Ribociclib and Everolimus at Steady State (Cycle 1, Day 15)

Analyte	Dose (ribociclib + EVE + EXE, mg	Fasted/Fed	N	C_{max} (ng/mL), Mean (SD) [n]	AUC_{0-24h} (h*ng/mL), mean (SD) [n]
Ribociclib	200 + 2.5 + 25	Fasted	6	473 (305) [6]	5200 (3540) [5]
	200 + 2.5 + 25	Fed	3	315 (163) [3]	4330 (3920) [3]
	250 + 2.5 + 25	Fasted	16	818 (549) [14]	9460 (6280) [11]
	250 + 2.5 + 25	Fed	5	720 (301) [2]	10 000 (4960) [2]
	300 + 2.5 + 25	Fasted	11	1250 (690) [8]	14 800 (9390) [8]
	300 + 2.5 + 25	Fed	12	924 (505) [11]	13 500 (7680) [8]
	350 + 1 + 25	Fasted	6	989 (362) [5]	11 900 (3390) [4]
	350 + 2.5 + 25	Fed	5	896 (376) [5]	12 700 (5640) [5]
	200 + 5 + 25	Fed	6	580 (216) [5]	6860 (2470) [5]
EVE	200 + 2.5 + 25	Fasted	6	20 (5) [5]	170 (47) [5]
	200 + 2.5 + 25	Fed	3	8 (2) [3]	1120 (32) [3]
	250 + 2.5 + 25	Fasted	16	33 (14) [13]	327 (161) [10]
	250 + 2.5 + 25	Fed	5	24 (17) [2]	257 (182) [2]
	300 + 2.5 + 25	Fasted	11	35 (18) [7]	365 (197) [7]
	300 + 2.5 + 25	Fed	12	26 (9) [11]	305 (135) [9]
	350 + 1 + 25	Fasted	6	13 (3) [4]	106 (30) [3]
	350 + 2.5 + 25	Fed	5	26 (8) [5]	287 (103) [5]
	200 + 5 + 25	Fed	6	40 (12) [5]	403 (124) [5]
Historical single-agent data (steady state)					
EVE	5 mg[13]		4	32 (9) [4]	223 (74) [4]
	10 mg[13]		7	60 (17) [7]	560 (283) [7]

[redacted]

Analyte	Dose (ribociclib + EVE + EXE, mg	Fasted/Fed	N	C_{max} (ng/mL), Mean (SD) [n]	AUC_{0-24h} (h*ng/mL), mean (SD) [n]
	5 mg[14]		23	54 (12) [23]	418 (87) [23]
AUC_{0-24h}, area under the curve from time zero to 24 h; C_{max} maximum plasma concentration; EVE, everolimus; EXE, exemestane; SD, standard deviation					

1.2.5.1.2 Clinical safety of ribociclib when combined with everolimus and exemestane

In the ongoing Phase Ib/II clinical trial (CLEE011X2106), out of 70 patients treated with the triplet combination, ribociclib (200–350 mg 3 weeks on, 1 week off), everolimus (most at 2.5 mg), and exemestane (25 mg), the median number of prior regimens was 4, and 18 (25.7%) pts had received prior PI3K/AKT/mTOR or CDK4/6 inhibitors for metastatic disease. Grade 3/4 treatment-related AEs (≥5% patients) were neutropenia (45.7%), leukopenia (8.6%), and thrombocytopenia (5.7%). Two (2.9%) patients discontinued due to AEs. Grade 3 AST/ALT AEs were appreciated in 2 patients, febrile neutropenia and hypophosphatemia (1 patient), oral mucositis (1 patient), rash and thrombocytopenia (1 patient), and thrombocytopenia with bleeding (1 patient). MTD and RDE were declared at ribociclib 300 mg 3 weeks on, 1 week off, everolimus 2.5 mg daily and exemestane 25 mg daily. This combination dose appeared to be tolerable and safe. (Bardia A et al 2015). See Table 1-6 for full AE listing

Table 1-6 LEE011X2106: Adverse Events (All-grade greater than or equal to 15% in All Patients Receiving Triplet Therapy) Suspected to Be Related to Treatments

Adverse Event	Grade	R 200 mg + E 2.5 mg		R 250 mg + E 2.5 mg		R 300 mg + E 2.5 mg		R 350 mg + E 1 mg	R 350 mg + E 2.5 mg	R 200 mg + E 5 mg	All Patients With Triplet Therapy
Fasted / Fed N		Fasted n=6	Fed n=3	Fasted n=18	Fed n=6	Fasted n=11	Fed n=12	Fasted n=6	Fed n=9	Fed n=6	N/A N=77
Total	All	6 (100)	3 (100)	17 (94)	5 (83)	11 (100)	12 (100)	6 (100)	9 (100)	6 (100)	75 (97)
	G3/4	2 (33)	0	11 (61)	1 (17)	10 (91)	10 (83)	2 (33)	8 (89)	4 (67)	48 (62)
Stomatitis	All	4(67)	3 (100)	8 (44)	5 (83)	7 (64)	6 (50)	2 (33)	5 (56)	2 (33)	42 (55)
	G3/4	0	0	0	0	0	1 (8)	0	0	0	1 (1)
Anemia	All	3 (50)	1 (33)	9 (50)	2 (33)	7 (64)	6 (50)	2 (33)	3 (33)	3 (50)	36 (47)
	G3/4	0	0	2 (11)	1 (17)	1 (9)	0	0	0	1 (17)	5 (7)
Neutropenia	All	4 (67)	0	5 (28)	1 (17)	6 (55)	6 (50)	3 (50)	8 (89)	3 (50)	36 (47)
	G3/4	2 (33)	0	2 (11)	1 (17)	6 (55)	4 (33)	0	7 (78)	2 (33)	24 (31)

[redacted]

Adverse Event	Grade	R 200 mg + E 2.5 mg		R 250 mg + E 2.5 mg		R 300 mg + E 2.5 mg		R 350 mg + E 1 mg	R 350 mg + E 2.5 mg	R 200 mg + E 5 mg	All Patients With Triplet Therapy
Neutrophil count decreased	All	0	1 (33)	10 (56)	1 (17)	5 (46)	5 (42)	1 (17)	2 (22)	2 (33)	27 (35)
	G3/4	0	0	6 (33)	0	3 (27)	4 (33)	0	0	1 (17)	14 (18)
White blood cell count decreased	All	1 (17)	2 (67)	5 (28)	1 (17)	7 (64)	3 (25)	4 (67)	1 (11)	1 (17)	25 (33)
	G3/4	0	0	2 (11)	0	3 (27)	2 (17)	1 (17)	1 (11)	0	9 (12)
Thrombocytopenia	All	1 (17)	0	6 (33)	1 (17)	5 (46)	6 (50)	1 (17)	4 (44)	1 (17)	25 (33)
	G3/4	0	0	0	1 (17)	2 (18)	1 (8)	0	1 (11)	0	5 (7)
AST increase	All	2 (33)	1 (33)	5 (28)	0	4 (36)	4 (33)	1 (17)	2 (22)	2 (33)	21 (27)
	G3/4	0	0	0	0	2 (18)	0	0	1 (11)	0	3 (4)
ALT increase	All	3 (50)	0	2 (11)	1 (17)	6 (55)	5 (42)	0	1 (11)	3 (50)	21 (27)
	G3/4	0	0	0	0	2 (18)	1 (8)	0	0	1 (17)	4 (5)
Nausea	All	1 (17)	1 (33)	6 (33)	1 (17)	3 (27)	3 (25)	1 (17)	2 (22)	1 (17)	19 (25)
	G3/4	0	0	0	0	0	0	0	0	0	0
Rash	All	1 (17)	1 (33)	2 (11)	1 (17)	5 (46)	2 (17)	0	2 (22)	2 (33)	16 (21)
	G3/4	0	0	0	0	1 (9)	0	0	0	0	1 (1)
Platelet count decrease	All	2 (33)	0	3 (17)	1 (17)	3 (27)	2 (17)	0	2 (22)	2 (33)	15 (20)
	G3/4	1 (17)	0	0	0	0	0	0	0	0	1 (1)
Diarrhea	All	1 (17)	1 (33)	4 (22)	0	2 (18)	2 (17)	0	1 (11)	3 (50)	14 (18)
	G3/4	0	0	0	0	0	0	0	0	0	0
Lymphopenia	All	3 (50)	1 (33)	4 (22)	0	1 (9)	2 (17)	2 (33)	0	1 (17)	14 (18)
	G3/4	1 (17)	0	3 (17)	0	0	1 (8)	0	0	0	5 (7)
Fatigue	All	0	1 (33)	3 (17)	1 (17)	2 (18)	2 (17)	2 (33)	1 (11)	1 (17)	13 (17)
	G3/4	0	0	0	0	0	0	0	0	0	0
Lymphocyte count decreased	All	0	0	5 (28)	1 (17)	4 (36)	1 (8)	1 (17)	0	1 (17)	13 (17)
	G3/4	0	0	3 (17)	0	0	0	0	0	0	3 (4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; E, everolimus; G, Grade; R, ribociclib.

[redacted]

At the time of the completion of cohort A, and cohort B in the phase I portion of TRINTI-1 (LEE011XUS29) an interim analysis was done on 16 evaluable patients (8 patients in cohort A [250mg qd Ribociclib + 2.5mg qd Everolimus + 25mg qd Exemestane], and 8 patient in cohort B [300mg qd Ribociclib + 2.5mg qd Everolimus + 25mg qd Exemestane]). The most common all-grade AEs (>20% in either cohort) were neutropenia (Cohort A, 4 patients [50.0%]; Cohort B, 4 patients [50.0%]), fatigue (Cohort A, 3 patients [37.5%]; Cohort B, 0 patients), thrombocytopenia (Cohort A, 2 patients [25.0%]; Cohort B, 2 patients [25.0%]), and mucositis (Cohort A, 0 patients; Cohort B, 2 patients [25.0%]). The most common Grade 3/4 AE (>20% in either cohort) was neutropenia (Cohort A, 3 patients [37.5%]; Cohort B, 3 patients [37.5%]). 2 patients (12.5%) experienced Grade 3/4 febrile neutropenia, 1 in each cohort. There were no cases of QT interval prolongation, abnormal liver function tests, or pneumonitis in either cohort. (Hurvitz S et al 2017). See Table 1-7 for full AE listing.

Table 1-7 LEE011XUS29: Adverse Events (cohort A and B) Suspected to Be Related to Treatments

	Patients, n (%)					
	Ribociclib 250 mg + EVE 2.5 mg + EXE 25 mg (n=8)		Ribociclib 300 mg + EVE 2.5 mg + EXE 25 mg (n=8)		All patients (n=16)	
Adverse event, n (%)	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Total	7 (87.5)	6 (75.0)	7 (87.5)	6 (75.0)	14 (87.5)	12 (75.0)
Neutropenia[a]	4 (50.0)	3 (37.5)	4 (50.0)	3 (37.5)	8 (50.0)	6 (37.5)
Thrombocytopenia[b]	2 (25.0)	0	2 (25.0)	1 (12.5)	4 (25.0)	1 (6.3)
Fatigue	3 (37.5)	0	0	0	3 (18.8)	0
Anemia	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	2 (12.5)	2 (12.5)
Febrile neutropenia	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	2 (12.5)	2 (12.5)
Mucositis	0	0	2 (25.0)	0	2 (12.5)	0
Urticaria	1 (12.5)	1 (12.5)	1 (12.5)	0	2 (12.5)	1 (6.3)
AKI	1 (12.5)	1 (12.5)	0	0	1 (6.3)	1 (6.3)
Diarrhea	0	0	1 (12.5)	0	1 (6.3)	0
Dry mouth	0	0	1 (12.5)	0	1 (6.3)	0
Dyspepsia	0	0	1 (12.5)	0	1 (6.3)	0
GGT increased	0	0	1 (12.5)	0	1 (6.3)	0
Hyperglycemia	0	0	1 (12.5)	1 (12.5)	1 (6.3)	1 (6.3)
Leukopenia	0	0	1 (12.5)	1 (12.5)	1 (6.3)	1 (6.3)
Lymphopenia	0	0	1 (12.5)	0	1 (6.3)	0
Muscle spasm	0	0	1 (12.5)	0	1 (6.3)	0
Nausea	0	0	1 (12.5)	0	1 (6.3)	0
Pruritus	1 (12.5)	0	0	0	1 (6.3)	0
Vomiting	0	0	1 (12.5)	0	1 (6.3)	0
Weight decreased	1 (12.5)	0	0	0	1 (6.3)	0

AKI, acute kidney injury; EVE, everolimus; EXE, exemestane; GGT, gamma-glutamyltransferase. [a] Includes neutropenia, neutrophil count decreased, and white blood cell count decreased. [b]Includes thrombocytopenia and platelet count decreased.

[redacted]

2 Rationale

2.1 Study rationale and purpose

Hormone receptor-positive breast cancer is the most common form of breast cancer. Resistance to hormonal-deprivation therapy is the leading cause of death for women with this diagnosis. Disruption of the PI3K/mTOR pathway and cyclin D-CDK4/6–INK4–Rb pathway has been implicated in resistance to endocrine therapy and disease progression. Activating mutations in the mTOR, AKT, PIK3CA genes are oncogenic drivers in a variety of cancer types, including ER+ breast cancer. The addition of everolimus to exemestane significantly improves progression-free survival of women with disease resistant to hormonal deprivation (Baselga J 2012); however, this too ultimately results in disease progression. Studies demonstrate that resistance to hormonal therapy, mTOR inhibition, and cytotoxic chemotherapy are at least in part mediated by upregulation of CDK4/6-cyclin D activity in breast cancer, suggesting that there might be a role for CDK4/6 inhibition + mTOR inhibition in patients who have progressed on these therapies. Cyclin-dependent kinase (CDK) 4/6 inhibitors are believed to be critical mediators of this pathway as they act downstream of the PIK3CA/Protein Kinase B (AKT)/mTOR axis. The effect of combining ribociclib with the mTORC1-inhibitor everolimus (RAD001; Afinitor®) in the ER+, PIK3CA mutant MCF-7 xenograft model was examined (RD-2013-50141). While single agent treatments with ribociclib, and everolimus resulted in modest tumor regressions of -9% and -21%, respectively, combination of ribociclib with everolimus increased tumor regressions to -49%. Data from in vivo studies showed that ribociclib, when combined with the mTOR inhibitor, everolimus (RAD001; Afinitor®), induced synergistic growth inhibitions in multiple tumor models, including cell lines derived from MCL, ER+ breast cancer, and MRT (LEE011 Investigator's Brochure).

There is a role for continuing targeted therapies in patients with breast cancer, even beyond the point of disease progression. Inhibition of CDK 4/6 has been associated with autophagy-senescence transition (AST) in stromal fibroblasts, which leads to mitochondrial dysfunction and catabolism, a process that releases high-energy mitochondrial fuels into the stroma where they drive anabolic tumor growth and cancer metastasis (Capparelli C, 2012). When fibroblasts with induced senescence were co-cultured with the MDA-MB-231 breast cancer cell line, a near 2-fold increase in tumor growth was noted compared to control (Capparelli C, 2012). Release of CDK inhibition in a primed microenvironment could have the potential to cause rapid tumor progression, although this is still not well understood. Additional preclinical experiments have also suggested that inhibition of cyclin D1 or CDK 4/6 enhances mobility in both breast and pancreatic cancer cell lines, predominately through activation of TGF-β, which induces Akt-TOR signaling (Tobin NP, 2011) As such, treatment with the mTOR inhibitor everolimus may overcome a potential pathway of drug resistance to CDK 4/6/Cyclin D inhibition.

Everolimus appears to restore sensitivity to anti-estrogens by inhibiting resistance mediated by the PI3K/AKT/mTOR pathway. Currently, there is no clinical data available reporting the efficacy of further treatments after prior CDK4/6 inhibitor failure, which represents an unmet medical need and requires further exploration. Potential reasons for progression on CDK4/6

[redacted]

inhibitor include loss of the retinoblastoma protein (pRb) (the direct target of CDK4/6 inhibitors), alterations in the estrogen receptor pathway as a consequence of endocrine therapy resistance, or activation of other signaling pathways including the PI3K/AKT/mTOR pathway. Anecdotal observations of a small subset of patients treated on 1st line therapy trials with CDK 4/6 inhibitors + aromatase inhibitors have suggested that some patients who discontinue therapy with the CDK 4/6 inhibitors develop rapid disease progression at initial imaging assessment to second line therapy. This lends the question of maintaining CDK 4/6 inhibition as a backbone therapy to keep the cell cycle arrested in G1 while adding mTOR inhibition to overcome secondary resistance.

The heterogeneity of the anticipated mechanism of resistance requires further exploration in identifying the subset of patients that may still benefit from a sustained inhibition of the CDK4/6 pathway. Therefore, the analysis of newly acquired tumor biopsy at progression after CDK4/6 inhibitor based therapy will be a preferred way to identify potential mechanisms of resistance in such patients.

The LEE011X2106 Phase-1b clinical trial tested a combination of exemestane + everolimus + ribociclib. This combination appeared to be safe and demonstrated clinical activity at the RDE of ribociclib 300 mg (3weeks on/1 week off), everolimus 2.5 mg daily, and exemestane 25 mg daily. PK analysis indicated that ribociclib (200 mg-350 mg) increased exposure of everolimus (2.5 mg) due to CYP3A4 inhibition by ribociclib. At steady-state, everolimus exposure was largely within the exposures achieved with multiple doses of 5 and 10 mg of single agent everolimus. (Bardia A 2015). Clinical activity was seen in a heavily pre-treated population with median number of prior regimens being 4, and 25.7% pts had received prior PI3K/AKT/mTOR or CDK4/6 inhibitors for metastatic disease. The clinical benefit rate (confirmed CR + PR + SD ≥24 weeks + NCRNPD ≥24 weeks) was 26% in 74 evaluable patients (n=19; 95% CI: 16–37%) and a disease control rate (CR + PR + SD + NCRNPD) of 73% (n=56; 95% CI: 61–82%). Furthermore, there was a trend towards longer duration of treatment in the CCND1 amplified group (n=10; median 166 days) than in the non-amplified group (n=22; median 60 days), something which was not seen in BOLERO-2 (Bardia A 2015). Thus, triplet combination of endocrine therapy with mTOR and CDK4/6 inhibition is feasible, permits lower dosing of everolimus with acceptable dose exposure levels, and shows encouraging signs of clinical activity, including in patients with prior exposure to PI3K/AKT/mTOR or CDK4/6 inhibitors, suggesting that triplet therapy might overcome resistance to doublet therapy in a subset of patients.

Therefore, this study proposes to test whether the addition of everolimus + exemestane to ribociclib can reverse resistance to a CDK 4/6 inhibitor and ultimately improve the efficacy of the approved combination regimen (everolimus + exemestane) in patients that progressed on CDK 4/6 inhibitors.

2.1.1 Rationale for Continuous Dosing- Phase I-Dose Escalation

The RDE for the Phase I CLEE011X2106 dose escalation study, was declared at ribociclib (300 mg 3 weeks on/ 1 week off), everolimus 2.5 mg daily, and exemestane 25 mg daily. Based on the PK data from CLEE011X2106 study, when ribociclib (300 mg) and everolimus (2.5 mg)

[redacted]

were dosed concurrently, steady state exposure of ribociclib was generally within the range of exposures observed for single agent ribociclib at similar doses (Bardia A 2015). However, ribociclib increased the exposure of everolimus by approximately 2 and 4 fold (5 and 10 mg respectively) when ribociclib was dosed 21/28 days at 200 mg and 300 mg respectively (see Section 1.2.5.1.1). During the week of rest for ribociclib (days 22-28), levels of everolimus decreased below the single agent recommended dose levels of everolimus.

Continuous dosing of ribociclib has been evaluated in both X2108 (400 mg ribociclib daily + fulvestrant) and X2101 300 mg and 400 mg single agent ribociclib. Both studies demonstrate acceptable tolerability. In X2108, when compared to 600 mg 3 weeks on/1 week, daily dosing of ribociclib at 400 mg resulted in a decrease in neutropenia, ALT elevation, QTc prolongation and fatigue (Section 1.2.1).

The design of the Phase I, open label, dose finding part of the study was chosen in order to establish the MTD(s)/RP2D of continuous dosing of ribociclib at 250 mg starting dose in combination with a fixed, dose of everolimus (2.5 mg) based on the CLEE011X2106 Phase I study and standard dose of exemestane (25 mg) in men and postmenopausal women with HR+ HER2 negative advanced breast cancer. Based on the decreased levels of everolimus during the rest week of ribociclib and the improved safety data demonstrated with the continuous dosing of ribociclib in both the CLEE011X2101 study and CLEEX2108 study, it is believed that dosing ribociclib continuously with daily everolimus and exemestane may lead to improved safety and efficacy. Because the exposure of ribociclib does not change when administered concurrently with everolimus, we believe that 250 mg of ribociclib will be safe to administer with 2.5 mg of everolimus daily.

The decisions on new dose combinations are made by the Investigators and Novartis study personnel and will be based upon a synthesis of the recommendations made by the independent data monitoring committee (IDMC), patient tolerability and safety, PK and efficacy information available at the time of the decision. The discussion and decisions will be documented in the dose escalation meeting minutes.

The dose escalation part of this study will also assess the PK of everolimus and ribociclib in HR+ HER2-negative advanced breast cancer patients receiving the triplet combination (ribociclib + everolimus + exemestane) with continuous dosing and will compare the findings with historical data for the approved combination of everolimus + exemestane as well as the data from the ongoing CLEE011X2106 study. This comparison will be done in order to determine the optimal dosing of the triplet combination when all drugs are dosed continuously. Each cycle was determined to be 28 days. In the initial cohort(s) of subjects, if therapy is well tolerated after two cycles and have no evidence of grade 3 or 4 clinically significant AEs, subjects may undergo intra-patient dose escalation(s) to ensure that they receive a therapeutic dose of everolimus and ribociclib. See Section 6.2 for details on starting dose and escalation guidelines.

[redacted]

2.1.2 Rational for stomatitis prevention mouthwash

2.1.2.1 Overview of stomatitis and current treatment

Stomatitis, the inflammation of mucous membranes lining the mouth and throat, has been observed in approximately 44-86% of everolimus-treated patients (Afinitor® prescribing information Novartis 2013). In the BOLERO-2 trial, patients who received everolimus +exemestane had a 67% overall reported incidence of stomatitis (Afinitor® prescribing information Novartis 2013) including 33% incidence grade ≥2 (Data on file). The median time to first onset of stomatitis (Gr≥2) in the BOLERO-2 trial was 15.5 days (Perez et al 2013) and the incidence of new stomatitis (Gr≥2) plateaued at 6 weeks (Rugo et al 2013). Reports from clinicians indicate that in routine practice, everolimus treated advanced breast cancer patients who develop stomatitis tend to develop it within the first month of therapy. Clinicians also report that once resolved the stomatitis typically either doesn't recur or recurs at lower grade, even in patients who have been maintained or re-escalated to full-dose everolimus.

Specific strategies to prevent and/or ameliorate the severity of everolimus-associated stomatitis are still ongoing. One recent study evaluated the clinical presentation and management of stomatitis in 17 patients treated with an mTOR inhibitor. The majority of patients were treated with topical corticosteroids including an oral dexamethasone solution which was rinsed and expectorated. Clinical improvement was noted in over 85% of topical corticosteroid-treated patients (de Oliveira et al 2011). Another recent study prospectively evaluated the presentation and management of oral stomatitis in advanced breast cancer patients being treated with everolimus combined with exemestane. Seven out of 15 women (46.6%) developed stomatitis grade ≥2. All (100%) ulcers were treated with topical dexamethasone solution and healed after a median of 2 weeks.

Four patients (57.1%) required a temporary interruption of their everolimus, and two patients (28.6%) required an everolimus dose reduction (Nicolatou-Galitis et al 2013).

Anecdotal reports from clinicians indicate that prophylactic use of a steroid-based oral mouthwash may help to prevent stomatitis in patients treated with everolimus. Texas Oncology–Baylor Charles A. Sammons Cancer Center in Dallas, Texas reported overwhelming success in preventing Gr≥2 stomatitis since they began prescribing a prophylactic mouthwash (hydrocortisone, tetracycline, nystatin, and diphenhydramine) to their advanced breast cancer patients on everolimus (Divers et al 2013). A Phase II single arm stomatitis prevention trial (SWISH) with Dexamethasone mouthwash administered QID for 56 days is currently ongoing and interim results will be reported at American Society of Clinical Oncology (ASCO) in June 2016.

2.2 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria, study procedures and close clinical monitoring.

[redacted]

2.2.1 Potential benefits to clinical trial participation

All subjects enrolled in this trial will receive an active and valid endocrine therapy for second or later line treatment of men and post-menopausal women (see Section 1.1.2). They will receive triplet (ribociclib + everolimus + exemestane) combination to evaluate their effect on delaying the emergence of resistance to endocrine therapy and CDK 4/6 inhibitors. Based on preclinical and clinical data (Section 1.2.5), treatment with ribociclib in combination everolimus + exemestane is expected to be well tolerated and it is hypothesized that it will result in delayed disease progression by inhibiting proliferation of endocrine-resistant and CDK 4 and 6 resistant breast cancer cells.

2.2.2 Potential risks to clinical trial participants

Subjects in this study will be carefully monitored for key toxicities that have been observed with ribociclib (Section 1.2.1), everolimus (Section1.2.3), and exemestane (Section1.2.4) with the following assessments (Section 7): periodic laboratory, renal and liver function, urinalysis and ECG. Risk will be further minimized by adherence to inclusion/exclusion selection criteria (Section 5), avoidance of prohibited medication (Section 6.5.2), close safety monitoring (Section 8) and dose adjustment guidelines (Section 6.4 and current everolimus and exemestane prescribing information). PK sampling will be conducted in patients to assess plasma concentration of the study drug to further evaluate the drug-drug interaction when ribociclib is dosed continuously. An independent data monitoring committee (IDMC) will be constituted and will monitor safety, efficacy and available PK data as comprising of investigators and Novartis personnel participating in the trial to ensure transparent management of the trial according to the protocol. A Novartis Safety Management Team (SMT) periodically reviews and evaluates all emerging data across the ribociclib program for potential safety signal assessment in a timely manner.

3 Study objectives and endpoints

3.1 Objectives and related endpoints-Phase I

Table 3-1 Objectives and related endpoints-Phase I

	Objective	Endpoint
PHASE I		
Primary	To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) for the combination of ribociclib + everolimus +exemestane when dosed continuously	Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 (28 day cycle)
Secondary	To determine the safety and tolerability based on NCI	Incidence and severity of adverse events(AE) and serious

[redacted]

	Objective	Endpoint
	Common Terminology for Adverse Events Version 4 when treated with ribociclib + everolimus + exemestane continuously in subjects with HR+ HER2- negative advanced breast cancer.	adverse events (SAE), clinical laboratory values, vital signs and electrocardiogram (ECGs), dose interruptions, reductions and dose intensity.
	To determine the pharmacokinetic (PK) profile of everolimus and ribociclib when dosed continuously in the triplet combination.	PK parameters including, but not limited to, AUC $_{0\text{-}4h}$, C_{trough}, C_{max}, accumulation ratio (Racc).
	To assess the preliminary anti-tumor activity of the triplet combination of ribociclib + everolimus + exemestane when combination is given continuously.	Overall response rate (ORR), Disease Control Rate (DCR), Clinical benefit rate (CBR) based on central assessment per RECIST v1.1, CBR is defined as CR, PR,SD or Non-CR, Non-PD (NCRNPD) lasting 24 weeks or longer.

3.2 Objectives and related endpoints-phase II

Table 3-2 Objectives and related endpoints-phase II

	Objective	Endpoint
PHASE II		
Primary	Determine the Clinical Benefit Rate (CBR) at 24 weeks amongst patients receiving triple therapy with ribociclib + everolimus + exemestane, for advanced/metastatic HR+, HER2-negative breast cancer following progression on CDK 4/6 inhibitor.	Clinical Benefit Rate (CBR) defined as the proportion of patients with a complete (CR) or partial response (PR), or with stable disease (SD) at 24 weeks as per RECIST 1.1 or Non-CR Non-PD (NCRNPD) at week 24.
Secondary	To determine centrally assessed progression Free Survival (PFS) in HR+ HER2-negative advanced breast cancer.	Progression-free survival (PFS), defined as the time from date of treatment to the date of first documented progression or death due to any cause. If a

[redacted]

	Objective	Endpoint
		subject has not had an event, PFS will be censored at the date of last adequate tumor assessment. Disease progression for primary efficacy endpoint derivation will be based on the central radiologist's tumor assessment.
	To determine overall response rate (ORR)	Overall response rate (ORR) defined as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST 1.1.
	To determine Overall Survival (OS)	This is defined as the time from treatment initiation with study treatment until death as a result of any cause.
	To determine Duration of Overall Response (DOR)	Duration of Overall Response defined as the time between the initial response to the treatment with the combination of ribociclib+everolimus+ exemestane, and subsequent disease progression or recurrence.
	To evaluate time to deterioration or ECOG performance status	Time to definitive deterioration of ECOG performance status from baseline.
	To determine safety and tolerability	Adverse Events (AEs), serious AE (SAEs), changes in hematology and chemistry values, vital signs, dose interruptions, reductions and dose intensity.
	To determine the PK profile of ribociclib and everolimus in the triplet combination	PK parameters including, but not limited to, AUC $_{0\text{-}4h}$, C_{trough}, C_{max}, accumulation ratio (Racc)

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a multi-center, open-label, Phase I/II study consisting of two phases: Phase I and Phase II. The Phase I will be conducted in men and postmenopausal women with HR+, HER2-negative advanced breast cancer that is endocrine resistant, and a Phase II part in men and postmenopausal women with HR+, HER2 negative advanced breast cancer that is resistant to at least one endocrine therapy and who have progressed on a CDK 4/6 inhibitor.

Phase I: The dose escalation part of the study is designed to estimate the MTD and/or RP2D for the combination of ribociclib when dosed continuously with everolimus and exemestane. It will consist of 3 cohorts (A and B, and C). Each cohort will enroll 3-6 evaluable patients, including at least 6 patients at the RP2D level. Between 9-24 patients are expected to be treated in the phase I part of this study. Once an optimal safety dose is determined based on tolerability, AEs, serious AE (SAEs), changes in hematology and chemistry values, vital signs, dose interruptions, reductions and dose intensity, this study will commence to a phase II design.

The study will initiate with a 2 cohort dose escalation design. Cohort A: ribociclib (250 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily). If no DLTs are appreciated after 1 cycle, patients will then be enrolled in Cohort B: ribociclib (300 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily). The optimal dose will then be selected and expanded in Group 1 of the Phase II part of the study.

An additional cohort, Cohort C, will be explored as a dose de-escalation cohort. A starting dose of: Ribociclib (200 mg daily), everolimus (5 mg daily) and exemestane (25 mg daily) will we explored. If DLT's are appreciated, a lower dose of: Ribociclib (200 mg daily), everolimus (2.5 mg daily) and exemestane (25 mg daily) will be explored. For further details about DLT criteria reference section 6.2.1.

[redacted]

Phase II: This is a multi-center open label study to evaluate the antitumor activity of the ribociclib (LEE011) + everolimus + exemestane combination in patients with advanced/metastatic HR+, HER 2 negative breast cancer that have progressed on CDK4/6 inhibitor based therapy. This part of the study will be continued after the MTD/RP2D is determined in the Phase I.

A minimum of approximately 60 evaluable patients (30 per group(Group 1 and Group 2)) are required for Phase II of this study to evaluate clinical benefit rate at 24 weeks.

In each phase II group (1 and 2), if 8 or more patients show clinical benefit at 24 weeks then the null hypothesis will be rejected and the study will demonstrate significant clinical benefit.

RP2D:

Following completion of the phase I, dose escalation portion of this trial, it was determined that the RP2D to be explored in group 1 of phase II is as follows:

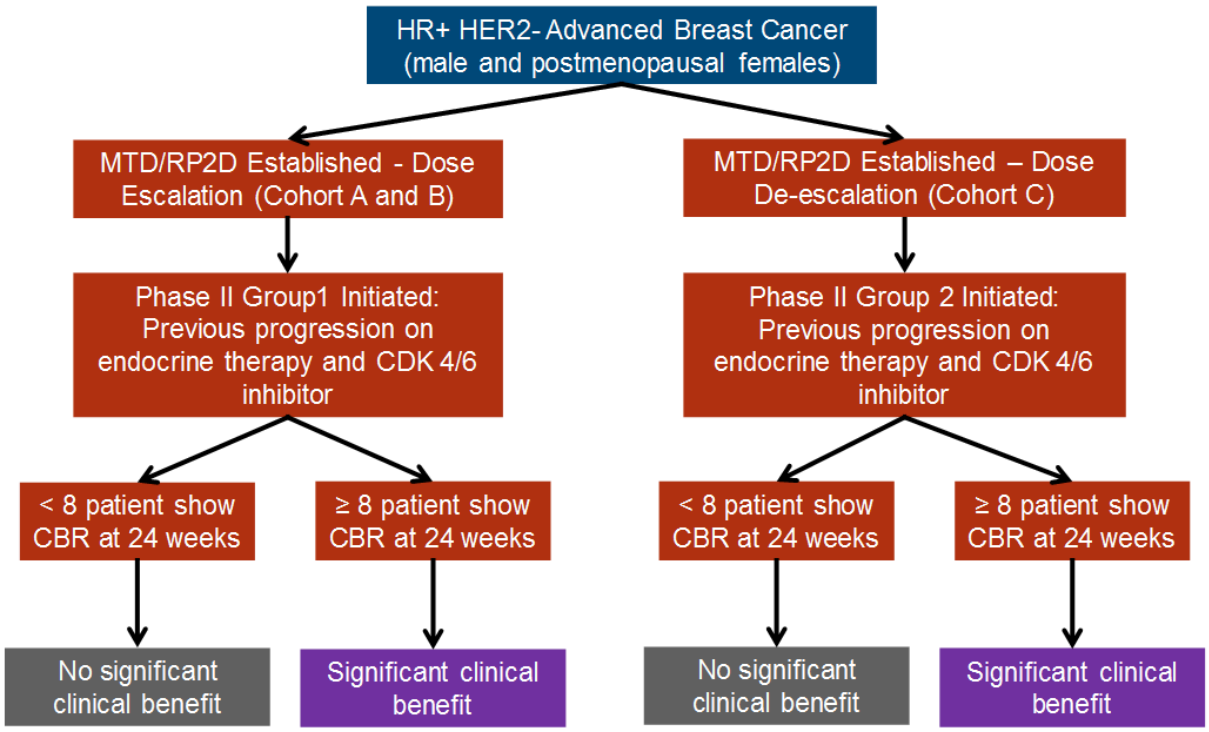
300mg ribociclib (daily) + 2.5mg everolimus (daily) + 25mg exemestane (daily)

RP2D for group 2 of phase II was determined after completion of cohort C, of phase I, as follows:

200mg ribociclib (daily) + 5mg everolimus (daily) + 25mg exemestane (daily) During Phase II, all patients must have progressed on any CDK 4/6 inhibitor. Prior CDK 4/6 inhibitor will be defined as disease progression while on, or within one month of discontinuing any CDK 4/6 inhibitor (i.e. palbociclib, ribociclib, or abemaciclib).

[redacted]

Figure 4-1 Study design



4.1.1 Screening phase (Phase I and II)

Men and postmenopausal women with HR+, HER2-negative advanced breast cancer will be screened for eligibility within a 21 day screening window prior to starting study treatment of ribociclib + everolimus + exemestane . During this time, the inclusion and exclusion criteria will be assessed and all screening assessments, laboratory tests, and procedures will be performed. [redacted]. Results of all screening/baseline eligibility criteria must be reviewed by the investigator or his/her designee prior to patient enrollment into the study in order to assure that all inclusion and exclusion criteria have been satisfied.

All study patients must be thoroughly informed about all aspects of the study, including the study agents, visit schedule, required evaluations, and all regulatory requirements for informed consent. The signed informed consent must be obtained to participate in this study prior to the performance of any study-related activities. If the patient is unable to read, an impartial witness must be present during the entire informed consent discussion. Eligibility will be determined according to the inclusion/exclusion criteria as described in Section 5.2. A list of procedures to be performed at the time of screening is summarized in Table 7-1. Patients must meet all eligibility criteria to be considered for enrollment in the study.

[redacted]

4.1.2 Treatment phase

Patient eligibility will be checked once all screening procedures are completed. An eligibility review and confirmation will be embedded in the Interactive Response Technology (IRT) system. Please refer to and comply with detailed guidelines in the IRT manual.

Subjects may continue study treatment until disease progression, occurrence of unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, or the sponsor terminates the study.

Dose adjustment (reduction, interruption or dose re-escalation) according to safety findings will be allowed. Regular safety reviews by an IDMC will be performed.

Tumor assessments will be performed every 8 weeks (+/- 1 week) starting from the first date of study treatment, and as clinically indicated, until the first 12 months of treatment are complete, or disease progression. Following 12 months if no disease progression, tumor assessments will occur every 12 weeks (+/- 2 weeks), and as clinically indicated until disease progression. Scans could be obtained earlier if there is concern of disease progression. If additional tumor assessments are performed prior to starting further anticancer therapy, the corresponding tumor assessments should also be sent for central review. Additional evaluation should be performed to confirm response at least 4 weeks after it was first observed.

Every 28 days will be considered one cycle. All the medications will be given with food. Clinical visits will be twice a cycle for the 1st two cycles, then once a cycle from there on.

The therapy on clinical trial will continue until disease progression (radiological), or intolerable adverse effects, or patient wishes to withdraw consent.

4.1.3 Treatment discontinuation

Subjects will continue to be followed for response until progression, or for up to 15 months after last patient enrolled in the study, whichever occurs first. If treatment discontinuation for any reason, other than progression, tumor assessments will continue every 8 weeks +/-1 week for at least 12 months after their first dose of study treatment.

The study evaluation completion (SEC) eCRF page records the end of study for every individual subject.

4.1.4 Safety follow-up

After the permanent discontinuation of study drug, all patients must complete End of Treatment assessments within 15 days and the safety follow-up assessments for 30 days after the last dose of the study treatment.

4.2 Timing of interim analyses

Not applicable.

[redacted]

4.3 Definition of end of study

The end of the study for a given patient is defined as when the patient permanently discontinues study treatment with ribociclib + everolimus + exemestane (Phase 1 and 2) and all the end of trial procedures are completed.

End of study (Last Patient Last Visit [LPLV]) will be upon completion of the follow up period for the last patient treated in the study. This will be after all patients have been on study for at least 15 months after last patient enrolled.

4.4 Early study termination

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

5 Population

5.1 Patient population

Men and postmenopausal women with hormonal receptor positive (HR+), HER2-negative, locally advanced or metastatic breast cancer whose disease is refractory to at least one endocrine therapy and have a documented recurrence or progression on their last therapy for breast cancer.

Refractory disease to endocrine therapy is defined as (Phase I and Phase II):

- Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, tamoxifen, exemestane or Fulvestrant
- Progression while on, or within one month of end of letrozole, anastrozole, tamoxifen or fulvestrant treatment for locally advanced or metastatic breast cancer.

Phase II will require that patients with HR+, HER2-negative advanced/metastatic breast cancer have documented progression on a CDK 4/6 inhibitor.

Documented progression on a CDK 4/6 inhibitor is defined as:

- Treatment duration while on a CDK 4/6 inhibitor must have been for $\geq$4 months prior to progression, AND
- Progressed while on or within 30 days of discontinuing CDK 4/6 inhibitor for locally advanced or metastatic disease, AND
- CDK 4/6 inhibitor must have been the last treatment prior to starting study treatment.

[redacted]

Of note, Phase I does not require prior CDK 4/6 inhibitor exposure.

Patients must have documented radiological evidence of recurrence or progression on last therapy prior to starting study treatment. No more than 1 line of chemotherapy with a maximum of 3 lines of therapy (including endocrine therapy and chemotherapy) is allowed in the advanced setting.

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality (Loomba et al. 2008).

5.1.1 Screening for Hepatitis B

Prior to enrollment, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

1. All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and/or Greece.
2. Patients with any of the following risk factors:
   - known or suspected past hepatitis B infection
   - blood transfusion(s) prior to 1990
   - current or prior IV drug users
   - current or prior dialysis
   - household contact with hepatitis B infected patient(s)
   - current or prior high-risk sexual activity
   - body piercing or tattoos
   - mother known to have hepatitis B
   - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
3. Additional patients at the discretion of the investigator.

The management guidelines for patients in dose escalation, in Section 6.4 are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

5.1.2 Screening for Hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon ‘curative’ treatment)
- blood transfusions prior to 1990
- current or prior IV drug users
- current or prior dialysis

[redacted]

- household contact of hepatitis C infected patient(s)
- current or prior high-risk sexual activity
- body piercing or tattoos

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

5.2 Inclusion criteria

Written informed consent must be obtained prior to study entry. Patients eligible for inclusion in this study have to meet all of the following criteria:

1. Adult men and women (≥18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.

Note: sexually active males should use a condom during intercourse while taking study treatment and for 21 days after stopping medication and should not father a child in this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

2. Histological or cytological confirmation of hormone-receptor positive (ER+ and/or PR+) breast cancer by local laboratory testing per local laboratory testing.
3. Patient has HER2-negative breast cancer (based on most recently analyzed biopsy) defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.
5. A representative tumor specimen must be available for molecular testing. Newly obtained tumor biopsy specimen is required if accessible prior to entry on trial. If tissue is not accessible based on surgical evaluation, an archival tumor sample from metastatic site may be submitted.
6. Women must be postmenopausal. Postmenopausal status is defined either by:
    - Amenorrhea for at least 12 months and both follicle-stimulating hormone (FSH) and/or estradiol levels are in postmenopausal range (according to the local laboratory) OR
    - History of bilateral oophorectomy (with or without hysterectomy) OR
    - History of partial hysterectomy with FSH and/or estradiol within post-menopausal range OR
    - Ovarian function suppressed with a GnRH agonists (negative HCG required) with estradiol levels in the postmenopausal range (according to the local laboratory)
7. Disease refractory to either, AI, tamoxifen or fulvestrant defined as:

[redacted]

- Recurrence while on, or within 12 months of end of adjuvant treatment with letrozole, anastrozole, exemestane, tamoxifen or fulvestrant OR
- Progression while on, or within one month of discontinuing letrozole, anastrozole, tamoxifen or fulvestrant for the treatment of locally advanced or metastatic breast cancer.

Note: There are no restrictions as to which endocrine therapy patients received as their last line of therapy just prior to randomization.

8. Patients who received up 3 lines of therapy for advanced breast cancer are allowed. This includes a maximum of 1 line of chemotherapy and a maximum of 3 lines of endocrine therapy in the advanced setting so long as the patient has not received more than a total of 3 lines of therapy. Patients must have recovered to grade 1 or better from any adverse events (except alopecia and/or neuropathy) related to previous therapy prior to starting study treatment.

Note: If patient relapsed with documented evidence of progression on/or within 12 months from completion of adjuvant endocrine therapy, then this is considered one line of therapy.

9. Patients previously treated on any CDK 4/6 inhibitor (i.e. ribociclib, abemaciclib OR palbociclib) must have:
   - Remained on treatment for ≥4 months for advanced breast cancer or metastatic disease prior to progression, AND
   - Progressed on, or within 30 days following the discontinuation of a CDK 4/6 inhibitor.

Phase II Only:

- Patients must have progressed on only one CDK 4/6 inhibitor. A CDK 4/6 inhibitor must have been the last treatment regimen prior to starting study treatment.

Note: Phase I does not require prior CDK 4/6 inhibitor exposure

Note: For patients who received prior CDK4/6 inhibition as part of a clinical trial, patients must be unblinded in order to verify that the patient did receive a CDK4/6 inhibitor.

10. ECOG Performance Status 0 – 1.
11. Radiological evidence of recurrence or progression on or after the last therapy prior to starting study treatment.
12. Patients must have:
    - Measurable disease (based on RECIST 1.1): defined as at least one lesion that can be accurately measured in at least one dimension ≥20 mm with conventional imaging techniques or ≥10 mm with spiral CT or MRI,
      OR
    - Evaluable disease: bone lesions- lytic or mixed (lytic + sclerotic) in the absence of measurable disease
13. Patient has adequate bone marrow and organ function as defined by the following LOCAL laboratory values at screening:

[redacted]

- Absolute neutrophil count $\geq 1.5 \times 10^9$/L.
- Platelets $\geq 100 \times 10^9$/L.
- Hemoglobin ≥9.0 g/dL.
- Potassium, total calcium (corrected for serum albumin), magnesium and sodium within normal limits for the institution or corrected to within normal limits with supplements before first dose of study medication.
- INR ≤1.5 or ≤2.5 while on anti-coagulant.
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m2 according to the Modification of Diet in Renal Disease (MDRD) formula
- Serum creatinine <1.5 mg/dL or creatinine clearance ≥50 mL/min.
- Total bilirubin <ULN except for patients with Gilbert's syndrome who may only be included if the total bilirubin is ≤3.0 × ULN or direct bilirubin ≤1.5 × ULN.
- Alanine aminotransferase (ALT) and aspartate transaminase (AST) <2.5 × ULN, except for patients with liver metastasis, who are only included if the AST is <5 × ULN.

14. Must be able to swallow ribociclib, everolimus and exemestane capsules/tablets.
15. Patients with metastatic disease are allowed to receive ≤28 days of endocrine therapy prior to starting study treatment.

5.3 Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patient with visceral crisis or any disease burden that makes the patient ineligible for this study per the investigator's best judgment.
2. Patients who received more than one line of chemotherapy for advanced breast cancer.

Note: A chemotherapy line in advanced disease is an anticancer regimen(s) that contains at least 1 cytotoxic chemotherapy agent and given for greater 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted 21 days or less, then this regimen does not count as a "prior line of chemotherapy"

3. HER2 overexpression by local laboratory testing (IHC 3+ staining or *in situ* hybridization positive).
4. Patient has received prior treatment with anthracyclines at cumulative doses of 450mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin.
5. Patient with a known hypersensitivity to any of the excipients of ribociclib, mTOR inhibitors, e.g. sirolimus (rapamycin), exemestane.
6. Previous treatment with mTOR inhibitors.
7. Previous treatment with exemestane for metastatic disease (except patients who received ≤ 28 days of exemestane for advanced breast cancer and did not progress).

[redacted]

8. Disease progression on more than one CDK 4/6 inhibitor, or have progressed more than once on the same CDK 4/6 inhibitor.
9. Patient is concurrently using other anti-cancer therapy. All anti-cancer therapy must be discontinued atleast 7 days to study treatment (C1D1). Drugs with overlapping toxicities with either everolimus or ribociclib must also be discontinued at least 7 days prior to C1D1. All AEs related to prior treatment should have resolved to CTCAE version 4.03 Grade ≤1 prior to study treatment (including any CDK 4/6 inhibitor).".
10. Patient has not recovered from all toxicities related to prior anticancer therapies to Grade ≤1 (based on NCI CTCAE version 4.03). Exception to this criterion: patients with any grade of alopecia and or neuropathy are allowed to enter the study.
11. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
12. Patients with Child Pugh score B or C.
13. Active, bleeding diathesis, or on oral anti-vitamin K medication (except low dose warfarin, Low molecular weight heparin (LMWH) and acetylsalicylic acid or equivalent, as long as the INR is ≤2.5 while on anti-coagulant). Fondaparinux is allowed.
14. Radiotherapy <2 weeks prior to starting study treatment. Patients must have recovered from radiotherapy toxicities prior to starting study treatment, and recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia). Radiotherapy is not allowed at target site following screening.
15. Another malignancy within 3 years prior to starting study treatment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell skin carcinoma.
16. Patients with central nervous system (CNS) involvement unless they are at least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.

17. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
18. Patient has a known history of HIV infection (testing not mandatory).
19. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient's participation in the clinical study or compromise compliance with the protocol such as:
    - chronic pancreatitis.
    - active untreated or uncontrolled fungal, bacterial or viral infections, sepsis etc.
    - Uncontrolled diabetes as defined by fasting serum glucose >1.5 × ULN.
    - Acute and chronic, active infectious disorders including viral and nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy.

[redacted]

20. Fasting serum cholesterol >300 mg/dl or 7.75 mmol/L and fasting triglycerides >2.5 × ULN. In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy and when the above mentioned values have been achieved.
21. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates.
22. Active skin, mucosa, ocular or GI disorders of Grade >1.
23. Bilateral diffuse lymphangitic carcinomatosis.
24. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:
    - History of angina pectoris, symptomatic pericarditis, coronary artery bypass graft (CABG) or myocardial infarction within 6 months prior to study entry.
    - Documented cardiomyopathy.
    - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) detected during screening.
    - History of cardiac failure, significant/symptomatic bradycardia, Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome or any of the following:
        - Known risk to prolong the QT interval or induce Torsade's de Pointes.
        - Uncorrected hypomagnesemia or hypokalemia.
        - Systolic Blood Pressure (SBP) >160 mmHg or <90 mmHg.
        - Bradycardia (heart rate <50 at rest), by ECG or pulse.
        - On screening, inability to determine the QTcF interval on the ECG (i.e.: unreadable or not interpretable) or QTcF >450 msec for men and >470 msec for women (using Frederica's correction). All as determined by screening ECG (based on a mean of 3 ECGs).
25. Patient is currently receiving any of the following substances and cannot be discontinued 5 half-lives prior to Cycle 1 Day 1:
    - That have a known risk to prolong the QT interval or induce Torsade's de Pointes.
    - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
26. Not able to understand and to comply with study instructions and requirements.
27. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

28. Sexually active males unless they use a condom during intercourse while taking drug and for 21 days after stopping medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

For this study, the terms "investigational drug" or "study drug" refer to ribociclib (LEE011). "Investigational treatment", or "study treatment/group" refers to the triplet combination of ribociclib, everolimus and exemestane. "Study treatment" refers to all drug combinations given during the course of the trial. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drugs for subsequent dosing.

In phase I dose escalation (cohort A and B) the subjects will receive everolimus 2.5 mg orally, once daily, and exemestane 25 mg orally, once daily and an increasing/decreasing doses of ribociclib to establish MTD and/or RP2D for Phase II Group 1.

In phase I dose de-escalation (cohort C) the subjects will receive ribociclib 200mg orally, once daily, and exemestane 25 mg orally, once daily and an increasing/decreasing doses of everolimus to establish MTD and/or RP2D for Phase II Group 2.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule for the following combination: ribociclib + everolimus +exemestane (Phase II)

Study treatments	Form and route of administration	Dose	Frequency/regimen
Ribociclib	Capsules/tablets - 50 mg, 200 mg For oral use	RP2D Group 1 or RP2D Group 2	Days 1–28 of each cycle Continuous – no rest days
Everolimus	Tablet - 2.5 mg For oral use	RP2D Group 1 or PR2D Group 2	Days 1–28 of each cycle Continuous – no rest days
Exemestane	Tablet - 25 mg	25 mg	Days 1–28 of each cycle

[redacted]

	For oral use		Continuous – no rest days
Dexamethasone mouthwash (500mL bottle): TID swish and spit (NPO X1 h) for 2 cycles (56 days)			

The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. Everolimus and exemestane will be taken orally, once a day every day. Ribociclib will be administered based on RP2D.

6.2 Dose escalation and de-escalation guidelines: Phase I Safety Run-in

The starting doses for the ribociclib + everolimus + exemestane (R-E-E) combination in the dose escalation (cohort A and B) is 250 mg QD for ribociclib, 2.5 mg QD for everolimus, and exemestane at the approved dose of 25 mg QD. The doses of everolimus and exemestane for all patients in this portion will be fixed at 2.5 mg and 25 mg respectively.

The starting doses for the ribociclib + everolimus + exemestane (R-E-E) combination in the dose de-escalation (Cohort C) is 200 mg QD for ribociclib, 5 mg QD for everolimus, and exemestane at the approved dose of 25 mg QD. The doses of ribociclib and exemestane for all patients in this portion will be fixed at 200 mg and 25 mg respectively.

The starting doses of ribociclib and everolimus are based upon a review of the safety, tolerability, and PK observed in the clinical studies outlined in Section 1.2. Because of the potential drug interaction between ribociclib and everolimus that may inhibit the metabolism of everolimus and increase drug exposure by approximately 3-5-fold, the dose of everolimus will be reduced to 2.5mg or 5mg (based on CLEE011X2106 RDE) from the standard dose recommended in the treatment of breast cancer of 10 mg QD (Section 1.2.2). The starting dose of ribociclib is supported by a recommendation from the CLEE011X2106 study (Section 1.2.4), CLEE011X2101 study and CLEEX2108 study (Section 1.2.1.4).

Table 6-2 Dose levels for ribociclib, everolimus and exemestane in Phase I dose escalation (cohort A and B)

Dose Level	Ribociclib	Everolimus	Exemestane
+1 Cohort B	300 mg PO daily	2.5 mg PO daily	25 mg PO daily
1 Cohort A (Start)	250 mg PO daily	2.5 mg PO daily	25 mg PO daily

Table 6-3 Dose levels for ribociclib, everolimus and exemestane in Phase I dose de-escalation (cohort C)

Dose Level	Ribociclib	Everolimus	Exemestane
0 (start)	200 mg PO daily	5 mg PO daily	25 mg PO daily
-1	200 mg PO daily	2.5 mg PO daily	25 mg PO daily

[redacted]

6.2.1 Criteria for dose escalation and determination of MTD(s)/RP2D

6.2.1.1 MTD definition

The MTD is defined as the highest combination drug dosage not causing medically unacceptable DLTs in more than 33% of the treated patients in the first cycle of treatment. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-4. Only one RP2D will be tested in the Phase II.

In the dose escalation a total of 6 patients will be treated at dose-level 1 (cohort A). Patients must complete a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.

- If ≤33% of patients experience a DLT in cohort A (dose level 1), the dose will be escalated to the next level cohort B (dose level +1) where 3 patients will be enrolled.
- If ≤33% patients experience DLTs in cohort B, an additional 3 patients will be treated at the same dose level.
- If ≤33% patients experience a DLT in both cohorts, then the optimal treatment dose based on tolerability and safety profile after two cycles will move into Phase II.
- If >33% patients experience DLTs in both cohorts, the dose will be de-escalated to the next level down .

Dose escalation and R2PD decisions will be/were made jointly by the independent Data Monitoring Committee, Steering Committee, and Novartis study personnel.

In the dose de-escalation (cohort C), the starting dose of ribociclib and everolimus are based upon a review of the safety, tolerability, and PK observed in the clinical studies outlined in Section 1.2. Because of the potential drug interaction between ribociclib and everolimus that may inhibit the metabolism of everolimus and increase drug exposure by approximately 2-fold, if ribociclib is dosed at 200mg (based on CLEE011X2106) from the standard dose recommended in the treatment of breast cancer of 10 mg QD (Section 1.2.2). The starting dose of ribociclib is supported by a recommendation from the CLEE011X2106 study (Section 1.2.4)

The MTD is defined as the highest combination drug dosage not causing medically unacceptable DLTs in more than 33% of the treated patients in the first cycle of treatment. AEs and laboratory abnormalities considered to be DLTs are defined in Table 6-4. Only one RP2D will be tested in the Phase II.

Three patients will be treated at dose-level 0 (cohort C). Patients must complete a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure or have had

[redacted]

a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions.

- If ≤33% of patients experience a DLT in cohort C (dose level 0), then an additional 3 patients will be added.
- If ≤33% of patients experience a DLT then an expansion phase will be initiated pending approval from DMC.
- If >33% patients experience a DLT in Dose level 0, the dose will be de-escalated to the next level down (-1). A total of 6 patients with ≤33% of patients experience a DLT will be needed in order for dose to be considered for expansion

6.2.2 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as having a reasonably possible relationship to the study medication(s) and is unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment (cycle 1) with ribociclib + everolimus + exemestane and meets any of the criteria included in Table 6-4. National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading.

Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug combination will be interrupted and the toxicity will be followed up as described in Section 6.2.3. For the purposes of dose escalation and determination of the MTD(s), DLTs that occur during cycle 1 will be necessarily considered, including those in which the event started in Cycle 1 and the confirmation of the DLT occurs in a subsequent cycle. The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥2 adverse events will be reviewed for all patients at the current dose level.

Patients must have completed ≥75% of ribociclib + everolimus + exemestane in cycle 1 (≥21 days out of 28 days) to be considered for DLT evaluation. Patients not evaluable for DLT could be replaced after discussing with the steering committee.

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study drug induced adverse events are provided in Table 6-5 and Table 6-6.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. These changes must be recorded on the Dosage Administration Record eCRF.

Table 6-4 Criteria for defining Dose Limiting Toxicities

TOXICITY	DLT CRITERIA
	CTCAE grade 3 thrombocytopenia with bleeding

[redacted]

Hematology	Febrile neutropenia (decrease in neutrophils associated with fever ≥38.5°C, ANC <1.0 x 10^9/L)
	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
Gastro-intestinal	CTCAE grade ≥3 vomiting ≥48 hrs. despite optimal anti-emetic therapy
	CTCAE grade ≥3 diarrhea ≥48 hrs. despite optimal anti-diarrhea treatment
Hepato-biliary	CTCAE grade ≥3 total bilirubin
	CTCAE grade ≥2 ALT or AST with total bilirubin >2.0 x ULN without evidence of cholestasis*** OR For subjects with abnormal baseline AST or ALT or total bilirubin value: [AST or ALT>2x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]
	≥ CTCAE grade 3 ALT for more than 4 consecutive days
Cardiac	Cardiac toxicity ≥CTCAE grade 3
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or Troponin ≥CTCAE grade 3
ECG QT Interval	QTcF interval ≥501 ms on at least two separate ECGs
Renal	CTCAE grade ≥3 serum creatinine
Stomatitis	CTCAE grade ≥4 stomatitis
Hyperglycemia	CTCAE grade ≥4 hyperglycemia
Events not	CTCAE grade ≥3, except for the exclusions noted below
Exceptions to DLT criteria	<7 days of CTCAE grade 3 fatigue
	<48 hours of CTCAE grade 3 edema
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
*** *"Cholestasis" defined as ALP elevation [>2.0 xULN and R value < 2] in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis)* *Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury)* CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

6.2.3 Follow up for dose limiting toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value must be followed up at least once every 7 days (or more frequently if required by institutional practices, or if clinically indicated) for 30 days, and subsequently

[redacted]

at approximately 30 day intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts should be consulted as deemed necessary.

6.2.4 Doses for Phase II

The dose used in Phase II, group 1 recommended by the dose escalation part of this study (Phase I), was determined to be 300mg ribociclib (daily) + 2.5mg everolimus (daily) + 25mg exemestane (daily).

The dose used for phase II, group 2 recommended by the dose escalation part of this study (Phase I), was determined to be 200mg ribociclib (daily) + 5mg everolimus (daily) + 25mg exemestane (daily).

6.2.4.1 Ribociclib, everolimus and exemestane administration

Detailed instructions regarding administration of ribociclib capsules/tablets will be supplied to Investigator sites in a separate document from this protocol.

Complete guidelines for management and administration of exemestane can be found in (Section 6.4) and the package insert.

Ribociclib, everolimus and exemestane should be taken as follows:

- Patients should be instructed to take the study drug combination of one or more capsules/tablets of ribociclib with one tablet of everolimus and one tablet of exemestane with a large glass of water (~250 mL) daily approximately the same time every day.
- Patients should be instructed to swallow the ribociclib capsules/tablets and everolimus and exemestane tablets whole and not to chew, crush or open them.
- Patients should take all three drugs after eating a light low fat meal
- On days when PK collection/ECG is scheduled at the clinic, patients will take ribociclib, everolimus and exemestane in the clinic under the supervision of the investigator or designee. On all other days patients will take the ribociclib, everolimus and exemestane combination at home.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting and/or diarrhea (or increase stool frequency) during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, Seville oranges, grapefruit hybrids, pomelos, star fruit or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

[redacted]

- Herbal or dietary supplements known as strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation are not permitted. Multivitamins are permitted. If the potential for interactions are unknown, then the herbal / dietary supplements should be avoided.

6.2.4.2 Additional dosing guidelines for scheduled visit days

On days with PK, ECG sampling, chemistry and/or lipid profile sampling as outlined in Table 7-1, the following additional guidelines should be followed:

- On a day when PK blood collection is scheduled at the clinic, patients must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days patients may take the study treatment at home.
- The patient must be fasting for at least 8 hours prior to cycle visits that include fasting glucose and lipid profile samples. Coffee, tea and water without milk and sugar (or artificial sweeteners) are allowed.
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of the study treatment.
- When both PK and ECG are required, please complete the ECG prior to PK draw.
- Post-dose ECGs and PKs should be collected after dosing of the study treatment. ECG will be performed according to Section 7.2.2.6 and Table 7-5.
- Pre-dose samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be precisely recorded in the eCRF.
- Post-dose PK samples should be collected after dosing of the study treatment. PK sample collection will be performed according to Table 7-6.

6.3 Overview of Dexamethasone oral solution

Dexamethasone steroid-based oral solution comprised of 0.5 milligrams per 5mL of alcohol free dexamethasone. The oral solution contains citric acid, disodium edentate, flavoring, glycerin, methylparaben, propylene glycol, propylparaben, sorbitol and water.

6.3.1.1 Dexamethasone administration

All patients will be given 0.5 mg/5 mL dexamethasone steroid mouthwash. The patient will initiate the dexamethasone steroid mouthwash on the same day that they initiate the study treatment (C1D1). The alcohol-free, 0.5 mg/5 mL dexamethasone steroid mouthwash should be administered based on the following instructions:

- 10 mL of mouthwash swish and spit 3 times daily (TID). The mouthwash is to be held in mouth and swished around mouth to come in contact with entire buccal mucosa surface for a minimum of two minutes, and then spit out.
- Patient should remain NPO (no food, no drinks, nothing in mouth) for at least an hour after administering mouthwash, with the exception of Nystatin (or another topical antifungal).

[redacted]

6.3.1.2 Dexamethasone treatment regimen

Cycle 1 Day 1 (C1D1) is the day the patient initiates the mouthwash regimen and study drugs. A treatment cycle consists of 28 days. Patients should use mouthwash regimen for two consecutive treatment cycles (56 days).

All patients will be instructed to perform routine "good oral care" each day during the trial. Good oral care will consist of: brushing teeth at least twice daily with soft bristled toothbrush continue current daily flossing routine (if patients were not already flossing daily, they should not be instructed to start flossing as this could cause oral trauma), and continue routine dental care/maintenance with their dentist, if they have one.

Salt water mouth rinse and the steroid mouthwash should be administered based on the following instructions:

- The Salt water mouth rinse will only be administered once the onset of Grade 1 stomatitis has been noted.

If the salt water (0.9%) mouth rinse is needed, it will be administered as 10mL swish and spit TID and must be done prior to the dexamethasone mouthwash. The patient should administer the salt water (0.9%) mouth rinse (swish and spit) and wait for 10-15 minutes before administering the dexamethasone mouthwash.

The alcohol-free, 0.5mg/5mL dexamethasone steroid mouthwash should be administered based on the following instructions:

- 10 mL of mouthwash swish and spit TID. The mouthwash is to be held in mouth and swished around mouth to come in contact with entire buccal mucosa surface for a minimum of two minutes, and then spit out.
- Patient should remain NPO (no food, no drinks, nothing in mouth) for at least an hour after administering mouthwash, with the exception of Nystatin (or another topical antifungal).

6.4 Dose modification

6.4.1 Dose cohort modification

For patients who do not tolerate the protocol-specified dosing schedule, ribociclib adjustments are **recommended** in order to allow the patient to continue the study treatment.

Dose reductions are not permitted for everolimus, exemestane or GnRH agonists (if patient is currently taking). Any changes to the dose or interruption of dosing must be recorded on the Dosage Administration Record eCRF. Patients who require a study treatment hold of more than 28 days will be discontinued from the study unless discussed and approved by the sponsor (Section 7.1.2). Once dose-reduced the dose may be re-escalated once discussed and approved by the sponsor. All patients will be followed for AEs and for SAEs for 30 days following the last dose of study drug.

[redacted]

6.4.1.1 Ribociclib (LEE011)

Management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy. Each patient is allowed a maximum of two dose reductions for ribociclib. After this, the patient will be discontinued from the study treatment. For each patient, once a dose level reduction for ribociclib has occurred, the dose level may be re-escalated during subsequent treatment cycles once discussed and approved by the sponsor. If a dose reduction is required, ribociclib should be reduced one dose level. Dose levels for ribociclib are provided in Table 6-5.

A dose-dependent DDI was observed between ribociclib and everolimus based on clinical PK analyses in a separate dose escalation trial, where everolimus exposure increased 2- to 4-fold in the presence of ribociclib. If a dose adjustment of both ribociclib and everolimus are required, a dose reduction in ribociclib is considered as a method to reduce exposure to both drugs since everolimus exposure is increased with increased ribociclib doses through a DDI. After permanent discontinuation of either ribociclib, everolimus or exemestane, patients should be discontinued from study treatment The dose modification guidelines for study treatment are found in Table 6-5 and Table 6-6.

Table 6-5 Phase I dose escalation (cohort A and B) and Phase II group 1: Dose modification guidelines for Ribociclib + everolimus + exemestane

	Ribociclib	**Everolimus**	**Exemestane**
	Dose	**Dose**	**Dose**
Starting dose	Phase I: refer to cohort A, or B. Phase II cohort 1: 300mg (daily)	2.5 mg daily	25 mg
First dose reduction	Reduced by 50mg	2.5 mg daily	
Second dose reduction	Change current dose to 21days out of 28	2.5 mg daily	

Table 6-6 Phase I dose de-escalation (cohort C) and Phase II cohort 2: Dose modification guidelines for Ribociclib + everolimus + exemestane

	Ribociclib	**Everolimus**	**Exemestane**
	Dose	**Dose**	**Dose**
Starting dose	200mg daily	If starting at dose level 0: 5mg daily	25 mg

[redacted]

		If starting at dose level -1: 2.5mg daily	
First dose reduction	200mg daily	If starting at dose level 0: 2.5mg daily If starting at dose level -1: 2.5mg every other day	
Second dose reduction	200mg daily	If starting at dose level 0: 2.5mg every other day If starting at dose level -1: discontinue from trial	

Management of everolimus specific adverse reactions may require temporary dose reduction and/or interruption of everolimus therapy longer than 3 weeks. Recommendations for dose interruption of everolimus longer than 3 weeks in the management of everolimus specific adverse reactions are summarized in Table 6-7. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (USA Afinitor® PI 2012).

Table 6-7 Dose modification guidelines for ribociclib (if everolimus is held longer than 3 weeks for pneumonitis)

	Ribociclib	**Exemestane**
	Dose	**Dose**
Starting dose	400 mg daily	25 mg
First dose reduction	200mg daily	
Second dose reduction	200mg 3 weeks on, 1 week off	

6.4.1.2 Exemestane

No specific dose modifications are recommended for exemestane. Toxicities attributed to exemestane should be managed in a manner consistent with the investigator's usual clinical practice. Per (exemestane package insert).

[redacted]

6.4.2 Anticipated Risks and safety considerations of the study drug combination

Preclinical and Phase I clinical data available from ongoing studies with ribociclib and everolimus with exemestane separately suggest few overlapping toxicities for the proposed combinations. Special attention will be paid to blood counts (cytopenias), mucositis, liver function test abnormalities and QTc prolongation. Clinical data from the [CLEE011X2101] study do not show marked accumulation in ribociclib with time, suggesting that it does not substantially inhibit its own metabolism or clearance. Based on the known properties of exemestane and ribociclib, a clinically significant drug-drug interaction that would increase the toxicities of either drug is not anticipated.

Everolimus and ribociclib are *in vitro* inhibitors and substrates of CYP3A4, and the latter is also a time-dependent CYP3A4 inactivator. The available preclinical and clinical data therefore suggest the possibility of a drug interaction, specifically one that may increase exposure to everolimus. Based on simulation using Simcyp software (Simcyp Version 12, release 1), the projected increase in the AUCleac 0-6h of everolimus was 3.5-fold following the starting daily dose of 200 mg ribociclib co-administered with 2.5 mg of everolimus for 14 days. No significant effect on ribociclib metabolism was predicted when co-administered with everolimus. Appropriate eligibility criteria, dose modification guidelines and stopping rules are included in this protocol.

6.4.3 Dose modifications for ribociclib+everolimus+exemestane combination

6.4.3.1 Dose modifications and management recommendations for hematologic adverse reactions

Table 6-8 Dose modifications and management recommendations for hematologic adverse reactions

(see Table 6-5 and Table 6-6 for dose reduction guide)

Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	Thrombocytopenia	
	Grade 1(≥75 x 10^9/L)	No dose adjustment required.
	Grade 2 (≥50 x 10^9/L – <75 x 10^9/L)	Dose interruption of ribociclib and everolimus until recovery to grade ≤1. Re-initiate study treatment at the same dose.
	Grade 3 (≥25 x 10^9/L - <50 x 10^9/L)	Dose interruption of ribociclib and everolimus until recovery to grade ≤1.

[redacted]

Toxicity	Grade	Dose Adjustment and Management Recommendations
		Re-initiate study treatment at the same dose level. If toxicity recurs at grade 3: temporary dose interruption of ribociclib and everolimus until recovery to grade ≤1 and reduce to the next lower dose level. Maintain everolimus at same dose
	Grade 4(<25 x 10^9/L)	Dose interruption of ribociclib and everolimus until recovery to grade ≤1. Re-initiate study treatment at the next lower dose level. If toxicity recurs at grade 4: discontinue study treatment
Neutropenia	Absolute neutrophil count (ANC)	
	Grade 1 (≥1.5 x 10^9/L)	No dose adjustment required.
	Grade 2 (≥1.0 - <1.5 x 10^9/L)	No dose adjustment required.
	Grade 3 (≥0.5 - <1.0 x 10^9/L)	Dose interruption of ribociclib and everolimus until recovery to ≥1.0 x 10^9/L. Re-initiate study treatment at the same dose level. If toxicity recurs at grade 3: temporary dose interruption of ribociclib and everolimus until recovery to grade ≤1 and reduce to the next lower dose level, or continue at same dose with growth-factor support at the discretion of the treating investigator.
	Grade 4 (<0.5 x 10^9/L)	Dose interruption of ribociclib and everolimus until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level (first dose reduction level). Maintain everolimus at same dose If toxicity recurs at grade 4: temporary dose interruption of ribociclib and everolimus until recovery to ≥1.0 x 10^9/L and reduce at the next lower dose

[redacted]

Toxicity	Grade	Dose Adjustment and Management Recommendations
		level. Maintain everolimus at same dose
Febrile Neutropenia	Grade 3: ANC<1.0 x 10^9/L with [a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour] .	Dose interruption of both ribociclib and everolimus until improvement of ANC ≥1.0 x 10^9/L and no fever. Restart at the next lower dose level. If febrile neutropenia recurs, discontinue study treatment. Colony Stimulating Factors should be considered in patients with fever and profound neutropenia (<1.0 x 10^9/L)
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue study treatment
Anemia (Hemoglobin)	Grade 1: ≥10.0 – LLN g/dL	No dose adjustment required
	Grade 2: ≥8.0 – <10.0 g/dL	No dose adjustment required.
	Grade 3: <8.0 g/dL	Dose interruption of ribociclib and everolimus recovery to grade 1. Re-initiate study treatment at the same dose.
	Grade 4: Life-threatening consequences; urgent intervention indicated	Discontinue study treatment PRBC transfusion to be considered per NCCN guidelines

6.4.3.2 Ribociclib/everolimus dose modification and management for QTcF prolongation

Table 6-9 Ribociclib/everolimus dose modification and management for QTcF prolongation

(see Table 6-5 and Table 6-6 for dose reduction guide)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
QTcF prolongation	For All Grades	Check the quality of the ECG and the QT value and repeat if needed.

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
		Perform analysis of serum electrolytes (K+, Ca++, Phosphorus, Mg++). If outside of normal range, hold ribociclib and everolimus, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. Check compliance with correct dose and administration of study treatment Consider collecting a time matched PK sample; record date and time of last study drug intake.
	Grade 1 QTc 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustment required.
	Grade 2 QTc 481-500 ms	Hold ribociclib and everolimus. Perform steps 1-4 as directed in "For All Grades." Repeat ECG as clinically indicated until the QTcF returns to <481 ms. Restart ribociclib withdose reduced by 1 dose level. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Repeat ECGs 7 days and 14 days after doseresumption of study treatment (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥481 ms.
	Grade 3 QTc ≥501 ms on at least two separate ECGs	Hold ribociclib and everolimus. Perform steps 1-4 as directed in "For All Grades." Transmit ECG immediately and confirm prolongation/

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
		abnormalities with central assessment. Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. If QTcF remains ≥501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms. If QTcF returns to <481 ms, study treatment will be reduced by 1 dose level; If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥501ms If QTcF of ≥501 ms recurs, discontinue study treatment. Perform frequent ECGs until the QTcF is <500 msec. Address electrolyte, calcium and magnesium abnormalities.
	Grade 4 QT/QTc ≥501 or >60 ms change from baseline and Torsade's de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia	Discontinue study treatment. Perform steps 1-4 as directed in "For All Grades." Transmit ECG immediately and confirm prolongation/ abnormalities with central assessment. Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

[redacted]

6.4.3.3 Ribociclib/everolimus dose modification and management for cardiac dysfunction

Table 6-10 Ribociclib/everolimus dose modification and management for cardiac dysfunction

(see Table 6-5 and Table 6-6 for dose reduction guide)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Cardiac - Left Ventricular Systolic Dysfunction	Asymptomatic, resting ejection fraction 40-50%; or 10-20% drop from baseline	Maintain dose level, and continue ribociclib and everolimus with caution. Repeat LVEF within 4 weeks or as clinically appropriate.
	Symptomatic, responsive to intervention, ejection fraction 20-39% or >20% drop from baseline	Hold ribociclib and everolimus until resolved, then reduce study treatment by one dose level; LVEF measurement to be repeated, if not resolved within 28 days permanently discontinue ribociclib and everolimus if applicable.

6.4.3.4 Ribociclib/everolimus dose modification and management for hepatotoxicity's

Table 6-11 Ribociclib/everolimus dose modification and management for hepatotoxicity

(see Table 6-5 and Table 6-6 for dose reduction guide)

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48 to 72hrs later)	If confirmed, maintain dose level with LFTs monitored bi-weekly until normalizes.
Grade 2 (>1.5 – 3.0 x ULN)	Dose interruption of ribociclib and everolimus If resolved to ≤grade 1 in ≤21 days, then maintain dose level If resolved to ≤grade 1 in >21 days or toxicity recurs, lower 1 dose level,.Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions, discontinue study treatment

[redacted]

Grade 3 (>3.0 – 10.0 x ULN)	Dose interruption of ribociclib and everolimus If resolved to ≤ Grade 1 in ≤21 days, lower 1 dose level. Repeat liver enzymes and bilirubin tests twice weekly for 2 weeks after dose resumption If resolved to ≤grade 1 in >21 days or toxicity recurs, discontinue study treatment
Grade 4 (>10.0 x ULN)	Discontinue ribociclib
Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤1 x ULN) due to hemolysis or Gilbert's Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs. For patients with Gilbert's Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.	

HEPATOTOXICITY (AST or ALT)	
AST or ALT without bilirubin elevation >2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (>3.0 – 5.0 x ULN)	Dose interruption of ribociclib and everolimus until recovery to ≤baseline If resolved to ≤baseline in ≤21 days, then maintain dose level If resolved to ≤baseline in >21 days or toxicity recurs, then reduce 1 dose level. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤baseline grade is >28 days, discontinue study treatment
Increase from baseline grade 0 or 1 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of ribociclib and everolimus until resolved to ≤baseline grade, then lower 1 dose level of study treatment. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If recovery to ≤baseline grade is >28 days, discontinue study treatment If toxicity recurs after two dose reductions or recovery to baseline is > 28 days, discontinue study treatment
Increase from baseline grade 2 to grade 3 (>5.0 – 20.0 x ULN)	Dose interruption of ribociclib and everolimus until resolved to baseline, then lower 1 dose level of study treatment Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption If toxicity recurs after two dose reductions or recovery to ≤baseline grade is >28 days, discontinue study treatment
Grade 4 (>10.0 x ULN)	Discontinue study treatment

[redacted]

AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3 x ULN combined with total bilirubin > 2 x ULN without evidence of cholestasis or For patient with elevated AST or ALT or total bilirubin at baseline: baseline : [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower- **combined with** [total bilirubin 2 x baseline AND >2.0 x ULN]	Discontinue study treatment
Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.	

6.4.3.4.1 Additional follow-up for hepatic toxicities

Hepatic toxicity monitoring includes assessment of the following liver function tests (LFTs): albumin, ALT, AST, total bilirubin, direct and indirect bilirubin alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatinine kinase, prothrombin time (PT)/(PTT), international normalized ratio (INR) and Gamma-glutamyl transpeptidase (GGT). For patients with Gilbert's Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only. Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves: Repeating liver enzyme and serum bilirubin tests **approx. two times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.

- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections cytomegalovirus (CMV), Epstein-Barr virus (EBV), or herpes simplex virus (HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

[redacted]

- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Obtaining a PK sample, as close as possible to last dose of study drug.
- Liver biopsy as clinically indicated to assess pathological change and degree of potential liver injury.

Increase in transaminases combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI), and should be considered as clinically important events. The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT AND AST AND TBIL value at baseline: AST or ALT >3.0 x ULN combined with TBIL >2.0 x ULN.
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2 x baseline AND >3.0 x ULN] OR [AST or ALT >8.0 x ULN], whichever is lower, combined with [TBIL >2 x baseline AND >2.0 x ULN].

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as: Alkaline phosphatase (ALP) elevation >2.0 x ULN with R value <2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values [R value = ALT/ULN)/(ALP/ULN)]. It denotes the relative pattern of ALT and/or ALP elevation is due to cholesteric or hepatocellular liver injury or mixed type injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus met the definition of SAE (Section 8.2), and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4.4 Dose modification and management for everolimus specific toxicities

Table 6-12 Everolimus specific toxicities management and recommendations

(Refer to dose modification Table 6-5 and Table 6-6)

Adverse drug reaction	Severity	Dose adjustment and management recommendations
Stomatitis	**Grade 1**	No dose adjustment required.

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
	Minimal symptoms, normal diet	Manage with non-alcoholic steroid mouthwash and salt water (0.9%) mouth wash four times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Interrupt everolimus and ribociclib until recovery to grade 1. Re-initiate study treatment at the same dose. If stomatitis recurs, interrupt ribociclib and everolimus until recovery to grade 1. Re-initiate study treatment at a one dose lower. Manage with topical analgesic mouth treatments (e.g. benzocaine,butyl minobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).
	Grade 3 Symptomatic and unable to adequately aliment or hydrate orally	Interrupt everolimus and ribociclib until recovery to grade ≤1.Re-initiate study treatment at a reduced dose; If reoccurs, interrupt ribociclib and everolimus until recovery to grade ≤1.Re-initiate study treatment at second dose level. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).
	Grade 4 Symptoms associated with life-threatening consequences	Hold ribociclib and everolimus and provide appropriate medical therapy. If recovered to ≤grade 1 within 3 weeks, Re-initiate study treatment at a reduced dose. If >3 weeks, then discontinue study treatment.
Serum creatinine	Grade 1	No dose adjustment required. Initiate appropriate monitoring.

[redacted]

Adverse drug reaction	Severity	Dose adjustment and management recommendations
	Grade 2	Hold ribociclib and everolimus until resolved to grade ≤1, then re-initiate study treatment at the same dose level. If toxicity recurs at Grade 2, interrupt ribociclib and everolimus until recovery to grade ≤1, re-initiate and study treatment by one dose level.
	Grade 3	Hold ribociclib and everolimus until resolved to grade ≤1, then reduce study treatment by 1 dose level. If toxicity recurs after two dose reductions, discontinue study treatment
	Grade 4	Discontinue study treatment and manage appropriately.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and closely monitor. Consider metformin for hyperglycemia
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor. For hyperglycemia, consider metformin and follow up with endocrinologist
	Grade 3	Hold ribociclib and everolimus until resolved to grade ≤1, then reduce study treatment by 1 dose level;. Manage with appropriate medical therapy and monitor.
	Grade 4	Hold ribociclib and everolimus until resolved to grade ≤1 then discontinue study treatment

6.4.4.1 Pneumonitis

Table 6-13 Management of Pneumonitis

(refer to Table 6-5 and Table 6-6 for dose reduction guide)

[redacted]

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Dose Adjustment
Grade 1 Asymptomatic radiographic findings only	CT scans with lung windows Repeat at least every 8-12 weeks until return to within normal limits.	No specific therapy is required Consider flovent until resolution	Administer 100% of study treatment dose.
Grade 2 Symptomatic, not interfering with ADL	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 Saturation at rest Repeat at least every 8-12 weeks until return to within normal limits. Consider a bronchoscopy with biopsy and / or BAL	Symptomatic only. Consider flovent and corticosteroids if symptoms are troublesome.	Reduce study treatment by one level until recovery to ≤Grade 1. Ribociclib and everolimus may also be interrupted if symptoms are troublesome. If failure to recover to ≤Grade 1 within 3 weeks, subjects can resume ribociclib at full treatment dose (Table 6-5 and Table 6-6) until recovery to Grade ≤1. Once recovered, to Grade ≤1, reinitiate study treatment and reduce study treatment (ribociclib+everolimus+ exemestane)by one dose level.
Grade 3 Symptomatic, interfering with ADL; O2 indicated	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold study treatment until recovery to Grade ≤1. May restart study treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4 Life threatening; ventilatory support	CT scan with lung windows and required pulmonary	Consider corticosteroids if infective origin is ruled out. Taper as	Discontinue study treatment

[redacted]

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Dose Adjustment
indicated	function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat at least every 6 weeks until return to within normal limits. Bronchoscopy with biopsy and / or BAL is recommended if possible.	medically indicated.	

6.4.5 Recommended actions to be taken for positive baseline hepatitis B test

Table 6-14 Recommendations for positive baseline hepatitis B test

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 6 weeks		No prophylaxis Monitor HBV-DNA approximately every 4 weeks at the end of treatment and until EOT + 30 days		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For hepatitis B reactivation, definition and management guidelines see Table 6-15 Guidelines for management of hepatitis B.

Table 6-15 Guidelines for management of hepatitis B

Reactivation is Defined as:	Treatment
Increase of 1 log in HBV-DNA relative to baseline HBV- DNA value OR new	Start appropriate antiviral therapy **AND** Interrupt ribociclib and everolimus administration until resolution:

[redacted]

appearance of measurable HBV-DNA **AND** ALT elevation x 5 ULN	≤grade 1 ALT (or baseline ALT, if >grade 1) and ≤baseline HBV-DNA levels If resolution occurs within ≤21 days study treatment should be re-started at one dose lower, if applicable. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs >21 days Patients should discontinue study treatment but continue both antiviral therapies at least 4 weeks after last dose of study treatment

6.4.6 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt ribociclib/everolimus administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Table 6-16 Ribociclib/everolimus dose adjustment and management recommendation for all other adverse reactions

(see Table 6-5 and Table 6-6for dose reduction guide)

Grade/Severity	Dose adjustment and management recommendations
Grade 1	No dose adjustment- maximize AE management
Grade 2	Dose interruption of ribociclib/everolimus until recovery to Grade ≤1 Initiate appropriate medical therapy and monitor Re-initiate study treatment at the same dose If the same toxicity recurs at Grade 2, interrupt ribociclib/everolimus until recovery to Grade ≤1. Re-initiate study treatment at the next lower dose level.
Grade 3	Hold both everolimus and ribociclib until it resolves to ≤Grade 1. Initiate appropriate medical management and monitor Re-initiate study treatment at the next lower dose level If toxicity recurs at grade 3, discontinue study treatment
Grade 4	Discontinue study treatment
Additional recommendations (see supplementary management brochure for further recommendations): **Nausea**: Ensure adequate hydration or fluid repletion. Consider performing an analysis of serum potassium, calcium, phosphorus and magnesium, if indicated. If electrolyte values are below LLN, interrupt ribociclib, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization.	

[redacted]

Diarrhea: At the first sign of loose stools (Grade 1), initiate loperamide. Patient should remain well hydrated. Fluids and electrolytes should be replaced as needed. Consider performing an analysis of serum potassium, calcium, phosphorus and magnesium, if indicated. If electrolyte values are below LLN, interrupt ribociclib, correct electrolytes with supplements as soon as possible, and repeat electrolyte testing until documented normalization.

6.5 Concomitant medications

6.5.1 Permitted concomitant therapy for all treatment groups

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as packed red blood cells (PRBCs), pain medications, anti-emetics, short courses of steroids, chronic use of a low dose steroid for physiologic replacement, topical treatments for stomatitis and anti-diarrheal are allowed. The use of any other potential new concomitant medications may be discussed between the investigator and the sponsor on a case by case basis.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug combination. All medications (other than study drugs) and significant non-drug therapies (including vitamins, herbal medicines, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

Patients taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible.

Refer to the (LEE011 Investigator's Brochure), (everolimus Investigator's Brochure), (aromasin package insert) and (Appendix 1 for concomitant medications).

6.5.1.1 Hematopoietic growth factors

The use of Transfusions or Hematopoietic growth factor support (e.g. erythropoietins, G-CSF and GM-CSF) should be according to ASCO guidelines.

6.5.1.2 Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with existing bone metastases is permitted.
- If bisphosphonate therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

[redacted]

6.5.1.3 Palliative radiotherapy

Palliative radiation is permitted while on study after discussion with sponsor. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow.

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study treatment is needed during palliative radiotherapy.

6.5.1.4 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential according to a the definition of antineoplastic agent emetogenicity (Grunberg et al 2010). Antiemetic therapy can be used according to clinical guidelines for antineoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting as a result of study treatment (NCCN Clinical Practice Guidelines in Oncology. Antiemesis, 2017; Roila F et al 2016).

Potential drug interaction between ribociclib and antiemetic medications should always be taken into consideration. Example of a prohibited antiemetic medication is ondansetron that in combination with ribociclib may precipitate TdP. Refer to Appendix 1 for list of medications that are prohibited or allowed to be used with ribociclib.

6.5.2 Prohibited concomitant therapy during combined ribociclib + everolimus + exemestane

The following medications are prohibited during study treatment in the study (see Table 14-1 in Appendix 1, this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions):

- Strong and moderate inhibitors or inducers of CYP3A4/5.
- Substrates of CYP3A4/5 with a narrow therapeutic index.
- Medications with a known risk for QT prolongation.
- Other investigational and anti-neoplastic therapies, including chemotherapy, immunotherapy, target therapy, biological response modifiers, or endocrine therapy other than exemestane.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene).
- Prolonged systemic corticosteroid treatment (≥2 weeks), except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), dexamethasone mouthwash (provided by Novartis), eye drops or local injections (e.g. intraarticular) should not be given. A short duration of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease, LFT abnormality).
- Herbal preparations/medications (except for vitamins) or dietary supplements that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation,

[redacted]

including, but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using these preparations at least 7 days prior to first dose of study treatment.

6.5.3 Permitted concomitant therapy requiring caution and/or action while on study

Permitted medications to be used with caution combined ribociclib + everolimus + exemestane treatment in this study (Appendix 1, Table 14-2) are listed below. These medications should be excluded from patient use if possible. If they must be given based on the investigator's judgment, then use with caution and consider a ribociclib interruption if the concomitant medication is only needed for a short time:

- Moderate inhibitors or inducers of CYP3A4/5.
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index.
- Strong inhibitors of BSEP.
- Medications that carry a possible risk for QT prolongation.
- Sensitive substrates of the renal transporters, MATE1 and OCT2.
- Sensitive substrates of BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements)

6.5.3.1 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing ribociclib drug exposure to subtherapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic)

6.5.4 Drugs with QTc prolongation

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at www.qtdrug.org.and in Appendix 1. Medications with a known risk for QT prolongation are prohibited during study treatment.

[redacted]

6.6 Patient numbering, treatment assignment or randomization

6.6.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening (signs consent) and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of a 4 digit Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential 3 digit patient number, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator.

6.6.2 Treatment blinding

This study is open-label.

6.6.3 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Ribociclib will be supplied as capsules or tablets for oral use. The capsules or tablets will be packaged in bottles. Everolimus and exemestane will be supplied as tablets for oral use. Refer to Table 6-1 for ribociclib capsule/tablet and everolimus and exemestane tablet strengths. Ribociclib, everolimus and exemestane will be dosed on a flat scale of mg/day and not adjusted to body weight or body surface area. The dexamethasone mouthwash must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. The dexamethasone mouthwash should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in original, commercial container.

6.6.4 Study drug packaging and labeling

Ribociclib capsules/tablets are packaged in high density polyethylene (HDPE) bottles with child resistant closures. Everolimus tablets are packaged in blister packs (4 blisters per pack per strength). Exemestane tablets are packaged in high density polyethylene (HDPE) bottles with child resistant closures.

Medication labels will be in the local language and comply with the legal requirements of the United States. They will include storage conditions for the drug but no information about the patient. The medication will be supplied as open label supply to the sites in a way which allows the patient to take medication at home.

Ribociclib capsules/tablets, Everolimus and Exemestane tablets, and dexamethasone mouthwash will be supplied by Novartis.

[redacted]

6.6.5 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels, and in the (Investigator's Brochure for LEE011) and the package insert for everolimus,exemestane, and dexamethasone.

6.6.6 Study drug compliance and accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

On days of PK sampling and scheduled ECG visits to the clinic, the patient will take their assigned combination of drugs at the clinic. For all other study days, the patient will take their assigned combination at home. The time of dose administrations taken in the clinic must be recorded in the Dosage Administration Record eCRF.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the monitor or to the Novartis address provided in the investigator folder at each site.

6.6.7 Handling of other study treatment

Not applicable.

6.6.8 Disposal and destruction

The ribociclib, everolimus, exemestane and dexamethasone supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. If pre-arranged between Novartis and study site, destruction of used and unused ribociclib, everolimus, exemestane and dexamethasone will be performed at the study site if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Below is a list all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source

[redacted]

documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

The following are based on local lab results. Allowed visit windows are specified as follows:

- Screening assessments, apart from those listed below, must occur within 21 days before first dose of study treatment as per Table 7-1.
- Vital signs, physical exam, laboratory assessments and ECOG performance status that were completed within 3 days prior to Day 1 of each cycle (e.g. C1D1) do not need to be repeated on day 1 of that respective cycle.
- For all other visits, a ±3 day window is permitted on assessments to take into account scheduling, if not explicitly specified otherwise. For efficacy assessments there is a ±7 day window for those done within 12 months of C1D1. After 12 months, there is a ±14 day window, refer to Section 7.2

Radiological assessments must be performed as outlined in Table 7-2.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Reference to protocol section	Screening phase	Treatment phase							Post treatment follow-up phase			Survival phase
Visit name			Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent cycles	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up	End of post-treatment follow-up	Survival follow-up
Study days			-21 to -1	1	15	1	15	1	1	Within 15 days from last dose	Last dose + 30 days	Every 8 weeks (if applicable)		Every 6 months
Screening														
Study Informed Consent	D	7.1.1	X											
IRT Screening (after ICF signature)	S	7.1.1.1	X											
Disposition Assessment														
End of Phase Disposition	D	7.1.1.2	X							X			X	
Patient history														
Demography	D	7.1.1.3	X											
Inclusion/exclusion criteria	D	5.2	X											
Medical history and current medical conditions	D	7.2.2.1	X											
HER2 status	D	7.2.2.1	X											
Pregnancy test (if GnRH antagonist required)	D	5.3	X											

[redacted]

	Category	Reference to protocol section	Screening phase	Treatment phase							Post treatment follow-up phase			Survival phase
Visit name			Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent cycles	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up	End of post-treatment follow-up	Survival follow-up
Study days			-21 to -1	1	15	1	15	1	1	Within 15 days from last dose	Last dose + 30 days	Every 8 weeks (if applicable)		Every 6 months
Diagnosis and extent of cancer	D	7.1.1.3	X											
Prior antineoplastic therapy	D	7.1.1.3	X											
Prior / concomitant medications	D	6.5	Continuous – up to 30 days after last dose											
Assessments														
Physical examination	S	7.2.2.1	X	X[1]		X		X	X	X				
Performance status	D	7.2.2.3	X	X[1]		X		X	X	X				
Height	D	7.2.2.4	X											
Weight	D	7.2.2.4	X	X[1]		X		X	X	X				
Vital signs	D	7.2.2.2	X	X[1]	X	X	X	X	X	X				
Laboratory assessments														
Hematology	D	7.2.2.5.1	X	X[1]	X	X	X	X	X	X				
Chemistry	D	7.2.2.5.2	X	X[1]	X	X	X	X	X	X				
Fasting Lipid Panel	D	7.2.2.5.2	X					X	Every 3rd cycle	X				

[redacted]

	Category	Reference to protocol section	Screening phase	Treatment phase							Post treatment follow-up phase			Survival phase
Visit name			Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent cycles	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up	End of post-treatment follow-up	Survival follow-up
Study days			-21 to -1	1	15	1	15	1	1	Within 15 days from last dose	Last dose + 30 days	Every 8 weeks (if applicable)		Every 6 months
Coagulation	D	7.2.2.5	X		As clinically indicated					X				
Urinalysis	D	7.2.2.5.3	X	X[1]				X		X				
Tumor assessment														
Tumor evaluation (RECIST 1.1)	D	7.2.1.1	X	CT/MRI Chest, Abdomen, Pelvis +/- whole body bone scan +/- X-ray Every 8 weeks first day of study treatment for the first 12 months, and then every 12 weeks thereafter until disease progression										
Cardiac assessment														
ECG (standard 12-lead)	D	7.2.2.6.1	X (Must be completed between days -7 to -1)		X	X	X	X	X For all cycles up to Cycle 6	X				
				As clinically indicated										
ECHO or MUGA	D	7.2.2.6.2	X	As clinically indicated										
Safety														
Adverse events	D	8.1	X	Continuous						X	X			
Pharmacokinetics														
PK	D	7.2.3		X	X	X	X	X						

[redacted]

	Category	Reference to protocol section	Screening phase	Treatment phase						Post treatment follow-up phase			Survival phase
Visit name			Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent cycles	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up	End of post-treatment follow-up	Survival follow-up
Study days			-21 to -1	1	15	1	15	1	1	Within 15 days from last dose	Last dose + 30 days	Every 8 weeks (if applicable)		Every 6 months
[redacted]														
Study Drug administration														
ribociclib	D	6.2.4.1		Daily										
everolimus	D	6.2.4.1		Daily										
exemestane	D	6.2.4.1		Daily										
dexamethasone	D	6.3.1.1		TID through Cycle 2										
Discontinuation														
New antineoplastic therapies after discontinuation	D	7.1.6									X	X		

[redacted]

	Category	Reference to protocol section	Screening phase	Treatment phase						Post treatment follow-up phase			Survival phase
Visit name			Screening	Cycle 1		Cycle 2		Cycle 3	Subsequent cycles	End of study treatment (EOT)	Safety follow-up	Efficacy follow-up	End of post-treatment follow-up	Survival follow-up
Study days			-21 to -1	1	15	1	15	1	1	Within 15 days from last dose	Last dose + 30 days	Every 8 weeks (if applicable)		Every 6 months
Survival follow-up (phone call)	D	7.1.8												X
	[1] If performed within 3 days prior to day 1 of study treatment, will not need to be repeated on first day of cycle. Use of the same value in screening and C1D1 is allowed if done within 3 days of cycle 1 day 1.													

[redacted]

7.1.1 Screening

The Study IRB/IEC approved Informed Consent Form (ICF) must be signed and dated before any screening procedures are performed (procedures that are part of the clinical routine during the initial diagnostic work-up of the patient may be performed before signing the ICF). A copy of the ICF must be given to the patient or to the person signing the form. The Investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

After signing the study Informed Consent Form, the screening assessments will be done within 21 days prior to day one of study treatment for selected assessments (Table 7-1 and Table 7-2) for the list of assessments to be performed).

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to starting study treatment, including before signing the main study ICF can be considered as the baseline images for this study.

Re-screening of patients is allowed once per patient if the patient was not registered as entering the treatment phase. In this case the Subject Number assigned to the patient initially will be used and the patient will be identified with this number throughout his/her entire participation to the study.

For laboratory evaluations used to determine eligibility, repeated evaluation within the screening window are permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria

7.1.1.1 Eligibility screening

Following registration in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to start treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (Section 8.2 for SAE reporting details).

7.1.1.3 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics at screening includes:

- Demography (Date of birth and initials, sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)

[redacted]

- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- ER, PgR and HER2 status
- Rb status
- All prior antineoplastic therapies including surgical interventions and chemotherapy, biologic, immunologic and radiation therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded in the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, PT/PTT, INR, chemistry (including LFTs), lipid panel, HBV-DNA, HBsAg, HB Ag, HBc Ab, HCV-RNA-PDC, urinalysis, and FSH, LH and/or estradiol (if necessary)
- ECG
- ECHO/MUGA
- Radiological assessments (e.g. CT /MRI/bone scan)
- PK

7.1.2 Treatment period

During the treatment period, the patient must follow the Investigator's instructions with regards to contraception, concomitant medications, and dosing regimen (see Section 6). Patients will be treated with ribociclib + everolimus + exemestane until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow up, death, discontinuation from the study treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to Table 7-2, and Table 7-3.

If a patient remains on study after a dose interruption of >28 days, or after disease progression because the patient had experienced objective evidence of clinical benefit and in the opinion of the investigator it is in the best interest of the patient to remain on study, then this decision and report of a discussion with the sponsor must be reported in the source documentation and in a comment in the eCRF.

7.1.3 End of study treatment visit including safety completion and study treatment discontinuation

Patients who discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 15 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to Table 7-1. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of phase disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT eCRF page. The EOT visit is not considered the end of the study.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

If a patient discontinues study treatment, but continues study assessments, the patient remains

on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the End of Post Treatment Phase Disposition CRF page.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

7.1.4 Discontinuation of study treatment

Patients **may** voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse Event
- Lost to follow-up
- Physician decision
- Progressive Disease
- Protocol deviation
- Study terminated by sponsor
- Technical problems

Patients must be withdrawn from the study treatment if any of the following occur:

- Pregnancy

[redacted]

- Death
- Subject/Guardian decision

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation:

- Adjustments to study treatment that result in discontinuation. Please refer to Section 6.4.
- Use of prohibited medication. Please refer to Section 6.5 and Appendix 1.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.8.

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30 day safety follow-up.

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table. Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

7.1.6 Safety Follow-up

All patients must have safety evaluations for 30 days after the last dose of study treatment. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 30 days after the last dose of study drug. All AEs suspected to be related to study treatment should be followed up as clinically indicated, until resolution or stabilization. Data collected should be added to the Adverse Events CRF, Concomitant Medications CRF, and Anti-neoplastic treatment CRF.

[redacted]

7.1.7 Efficacy Follow-up

Patients enrolled in this study who discontinue study treatment for any reason other than disease progression will be followed up every 8 (±1 weeks) weeks via a phone call and CT/MRI scans as detailed in Table 7-1 and Section 7.2, until disease progression or until 15 months after last patient enrolled into the study, whichever comes first. Antineoplastic therapies beginning during this F/U period must be recorded on the Antineoplastic Therapies Since Discontinuation of Study Drug eCRF.

7.1.8 Survival Follow-up

All patients will be follow for survival status every 24 weeks, until death, lost to follow up or withdrawal of consent, for at least 15 months after last patient enrolled into the study. Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

7.1.9 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Imaging tumor assessments

Tumor response will be assessed locally and centrally according to RECIST Version 1.1 (Eisenhauer et al 2009). The decision regarding patient management will remain with the local investigator. Patients should have at least one documented measurable lesion (per RECIST v1.1) or in the absence of measurable disease, have at least one lytic or mixed (blastic/lytic) bone lesion at study entry.

Imaging assessments will be performed at screening within 21 days prior to first dose of study treatment and subsequently every 8 weeks (+/- 1 week) from day one of study treatment during the first 12 months and every 12 weeks (+/- 2 weeks) thereafter. See Table 7-2 for details of assessments. The 8-week (or 12 week) interval should be respected regardless of whether study treatment is temporarily withheld or modified.

After baseline, selected assessments should be performed on cycle 1 day 1(will not need to be repeated on day of treatment if performed within 3 days of C1D1) see Table 7-1.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed within 21 days. Efficacy

[redacted]

assessments should continue as per the scheduled visit per Table 7-1 and Table 7-2, Table 7-3, and Table 7-4.

To the extent possible, each lesion should be assessed using the same imaging method throughout the study.

All patients will undergo CT, PET CT or MRI of the chest, abdomen and pelvis at baseline and subsequent scheduled visits per Table 7-2. The preferred imaging methodology is CT with intravenous (i.v.) contrast. However, if at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT or PET CT is allowed. MRI plus contrast is allowed, however not recommended of the chest due to respiratory artifacts.

A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET) must be acquired at screening for all patients. Skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan must be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. If multiple bone lesions are identified, bone scans can be used to follow lesions throughout the study instead of localized CT, MRI or x-ray. They should be repeated every 8 weeks from C1D1 for the first 12 months, then every 12 weeks thereafter. If a new bone lesion is identified on bone scan, confirm with CT, MRI or X-ray. If previous lesion is no longer appreciated, confirm response with CT, MRI or X-ray. If no bone lesions are identified at baseline or if bone lesions can be followed with X-ray, CT or MRI, then bone scan need not be repeated unless clinically indicated.

Positron Emission Tomography (PET)/CT may be used in place of bone scan and CT only if the CT component is of similar diagnostic quality as a CT performed without PET. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all skin lesions present at baseline per instructions provided in the manual from the designated vendor. These should be followed throughout the study according to the schedule outlined in Table 7-2.

Other metastatic disease sites will be followed by CT or MRI, as clinically indicated. Chest X-ray or ultrasound should not be used to assess tumor lesions.

Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed no less than 4 weeks and after the criteria for objective response are first met. In case tumor assessment is performed <8 weeks from the first assessment of an objective response to confirm PR/CR, subsequent tumor assessments should revert back to the protocol schedule outlined in Table 7-2 .

If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy. Any pre-existing radiographic findings which may mimic metastatic disease and any prior radiotherapy should be recorded in the eCRF.

[redacted]

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to registration for treatment, including before signing the main study ICF can be considered as the baseline images for this study.

Results from tissue or body fluid collection should be recorded in the eCRF to complement radiographic findings.

All study imaging performed, (e.g., to fulfill a progression or response criterion), should be submitted to the designated imaging CRO within 2 weeks.

If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Physical exam tumor assessments, photography, pathology/histology and cytology results, as well as, information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at baseline/screening and on-study interventions should be captured in the appropriate eCRF's and will be transmitted to the imaging CRO for review by a medical oncologist.

Table 7-2 Imaging assessments

Procedure	Screening: Day −21 to Day 1	Treatment phase*	End of treatment*	Post-Treatment Phase
CT or MRI (Chest, Abdomen, Pelvis)[1]	Mandated	Every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks)	Mandated	Every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) until disease progression, withdrawal of consent, loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed
Brain CT or MRI	Mandated at screening if history of existing or suspected brain metastases	If brain lesion is present at screening: every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks)	Mandated only if brain lesion at screening	If brain lesion at screening: every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) until disease progression, withdrawal of consent, loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment

[redacted]

Procedure	Screening: Day −21 to Day 1	Treatment phase*	End of treatment*	Post-Treatment Phase
				even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed
Whole body bone scan[1,2]	Mandated	If multiple bone lesions at screening and cannot be followed by X-ray, MRI or CT then bone scans should be done every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) If any new lesions are identified, then confirm with X-ray, CT or MRI	Mandated only if multiple bone lesions identified at screening Or as clinically indicated.	If multiple bone lesions at screening and cannot be followed by X-ray, MRI or CT then bone scans should be done every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) until disease progression, withdrawal of consent, loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only as clinically indicated
Bone X-ray, CT or MRI[1]	Only if skeletal abnormalities identified at screening or by bone scan and are not visible in the chest, abdomen, pelvis CT/MRI.	If new bone lesion is identified with bone scan, confirm metastasis with bone X-ray, CT or MRI, if not visible in the chest, abdomen, pelvis CT/MRI.	Mandated only if bone lesion at screening	If bone lesion at screening, every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (±2 weeks) until disease progression, withdrawal of consent, loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only in this case a ±14 days window is allowed.
CT or MRI of any disease outside of Chest Abdomen Pelvis	Only if suspected lesion at screening	Every 8 weeks if lesion identified at screening. Of note, If multiple bone lesions at screening and cannot be followed	Mandated if lesion at screening	If lesion s are identified at screening, every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) until disease progression, withdrawal of consent,

[redacted]

Procedure	Screening: Day −21 to Day 1	Treatment phase*	End of treatment*	Post-Treatment Phase
		by X-ray, MRI or CT then bone scans should be done every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) If any new lesions are identified, then confirm with X-ray, CT or MRI		loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only as clinically indicated
Skin Color Photography	Only if lesions at screening	Every 8 weeks if lesion at screening	Mandated if lesion at screening	If lesion s are identified at screening, every 8 weeks (±1 week) during the first 12 months and every 12 weeks thereafter (± 2 weeks) until disease progression, withdrawal of consent, loss to follow-up, or subject/guardian decision (±1 week). In the absence of disease progression, continue the assessment even if a new anti-neoplastic therapy is started until disease progression, only as clinically indicated

[1] Positron Emission Tomography (PET)/CT may be used in place of bone scan and CT only if the CT component is of similar diagnostic quality as a CT performed without PET. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1

[2] A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)

All scans will be acquired and analyzed locally. For primary endpoint, scans should be sent centrally to the CRO designated by Novartis for central imaging interpretation within 2 weeks.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing the procedures listed below as well as collecting all adverse events at every visit. All safety assessments should be performed pre-dose unless specified otherwise.

[redacted]

7.2.2.1 Physical examination

A complete physical examination that evaluates all major organ systems will be performed at Screening/baseline. Subsequent physical exams may be limited and should be focused on sites of disease to explore clinical signs and symptoms.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

Physical exams to be performed are outlined in Table 7-1.

7.2.2.2 Vital signs

Vital signs (heart rate, blood pressure and temperature) will be obtained in the sitting position, or as appropriate prior to any blood collection.

Vital signs to be performed per Table 7-1.

7.2.2.3 Performance status

Assessment of ECOG Performance Status will be performed at screening and regularly throughout the whole study period irrespective of the time of dosing

Performance status to be performed per Table 7-1 and Table 7-3.

Table 7-3 ECOG performance status

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

7.2.2.4 Height and Weight

Height in centimeters (cm) and body weight in kilogram (kg). Height and weight to be performed per Table 7-1.

7.2.2.5 Laboratory evaluations

Sites will use their local laboratories for the analysis of all safety lab samples, collected at the time points indicated as per Table 7-1. More frequent assessments may be performed if clinically indicated, or at the investigator's discretion and these should be recorded on the Unscheduled Visit eCRF's.

Abnormal laboratory values that are clinically relevant (e.g., require an interruption or delay to study treatment, lead to clinical symptoms, or require therapeutic intervention) must be documented in the Adverse Event eCRF.

[redacted]

Novartis will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-4 Local Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	White blood cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), hemoglobin (Hgb) and platelet count.
Biochemistry with fasting glucose	Sodium, potassium, urea or BUN, creatinine, fasting glucose, calcium (or corrected calcium), magnesium, phosphorous, total protein and albumin. AST (SGOT), ALT (SGPT), total bilirubin, direct bilirubin, GGT and alkaline phosphatase, Amylase, lipase and LDH.
Fasting Lipid Panel	Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
Coagulation	PT/PTT, International normalized ratio [INR]
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If there are any significant findings on the dipstick then a microscopic evaluation should be measured: Microscopic Panel (WBC and RBC sediments, Casts, Crystals, Bacteria, Epithelial cells)

7.2.2.5.1 Hematology

Complete blood count (CBC) with differential - white blood count (WBC), neutrophil count (including bands], lymphocyte, monocyte, eosinophil, and basophil counts, hemoglobin, and platelet count. Hematology collections to be performed per Table 7-1. Hematology tests are to be performed according to the Visit Schedules outlined in Table 7-1. For details of the Hematology panel refer to Table 7-4.

7.2.2.5.2 Clinical chemistry

Sodium, potassium, chloride, bicarbonate, urea or BUN, creatinine, glucose, fasting glucose (at least 2 hours fasting), AST (SGOT), ALT (SGPT), total bilirubin (if a total bilirubin elevation

[redacted]

≥Grade 2 occurs then direct and indirect bilirubin should be measured), LDH, albumin, calcium (corrected for serum albumin), magnesium, phosphate, alkaline phosphatase and fasting lipid panel (at least 8 hours). Clinical chemistry visit schedules are outlined in Table 7-1. For details of the Chemistry panel refer to Table 7-4.

7.2.2.5.3 Urinalysis

Urinalysis is to be performed according to the Visit Schedules outlined in Table 7-1. For details of the urinalysis panel refer to Table 7-4.

7.2.2.5.4 HBV testing

Prior to enrollment, the categories of patients listed in Section 5.1.1 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab. HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in HCV testing.

Patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be tested for HCV RNA-PCR test at screening. For a list of hepatitis C risk factors, refer to Section 5.1.2. Follow-up testing will be performed, as per the visit schedule, only if the patient has a history or is positive at baseline, or both.

7.2.2.5.5 Hepatic safety markers

An additional blood sample is requested from patients in response to rise in ALT/AST or in total bilirubin (as described below) if this rise occurs outside of the scheduled collection dates:

- In patients with normal AST and ALT and total bilirubin at baseline that present a rise of AST or ALT ≥grade 2 with total bilirubin >2 x ULN without evidence of cholestasis (defined as: ALP elevation >2.0 x ULN with R value [ALT/ALP in x ULN] <2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis).

OR

- For patients with elevated baseline AST or ALT or total bilirubin that present [AST or ALT >2 x baseline AND >3.0x ULN] OR [AST or ALT 8.0x ULN]- whichever is lower-combined with [total bilirubin 2xbaseline AND >2.0 x ULN]

OR

- ALT or AST >8 x ULN without bilirubin increase

Analysis of samples will be performed based on results of ALT/AST and total bilirubin, with the aim to better understand the underlying mechanism of any observed hepatotoxicity.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

Standard triplicate 12-lead ECGs will be performed after the patient has been resting for 5-10 minutes prior to each time point indicated in Table 7-5.

Triplicate ECGs should be taken approximately 2-minutes apart. The combined QTcF values from these 3 ECGs will be averaged to provide a single value for each time point. Eligibility

[redacted]

will be based on the average of the triplicate ECG conducted at screening. In order for accurate evaluation of baseline QTcF, a total of three 12-lead ECGs will be performed within 7 days prior to registration (at screening between Day -7 and Day -1).

Note: All study ECGs, should be submitted to the designated CRO immediately.

Note: To ensure ECG evaluation is received for eligibility assessment, it is advisable to perform the ECG at least 24 hours prior the scheduled enrollment date as it takes at least 24 hours to receive central read.

If an abnormal ECG or QTcF value of ≥481 ms is obtained at any time after enrollment, management guidelines detailed in Table 6-7 must be followed.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate.

Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

In the event that a QTcF value of ≥501 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched blood sample for PK and record the time and date of the last study drug intake to determine plasma levels of ribociclib and any other identified metabolites.

Table 7-5 Central ECG Collection Plan

Cycle	Patients	Day	Sampling Time[a, b]	ECG Type
Screening	All	-7 to -1	Anytime	Triplicate 12 Lead
1	All	Day 15	pre-dose[d]	Triplicate 12 Lead
			2 h post-dose (± 15 min)	Triplicate 12 Lead
			4 h post-dose (± 15 min)	Triplicate 12 Lead
2	All	Day 1	pre-dose[d]	Triplicate 12 Lead
			2 h post-dose (± 15 min)	Triplicate 12 Lead
			4 h post-dose (± 15 min)	Triplicate 12 Lead
	All	Day 15	pre-dose[d]	Triplicate 12 Lead
			2 h post-dose (± 15 min)	Triplicate 12 Lead
			4 h post-dose (± 15 min)	Triplicate 12 Lead
3	All	Day 1	pre-dose[d]	Triplicate 12 Lead
4	All	Day 1	pre-dose[d]	Triplicate 12 Lead
5	All	Day 1	pre-dose[d]	Triplicate 12 Lead
6	All	Day 1	pre-dose[d]	Triplicate 12 Lead
9th and every 3rd cycle[c]	For patients with QTcF ≥481 ms at any time prior to cycle 7	Day 1	pre-dose	Single 12 Lead

[redacted]

Cycle	Patients	Day	Sampling Time[a, b]	ECG Type
Unscheduled			As clinically indicated	Triplicate 12 Lead
End of Treatment			Within 15 days of last dose	Triplicate 12 Lead

[a]. All measurement times are relative to dose of ribociclib unless otherwise specified.

[b]. If both ECG and PK sample are scheduled at the same time, the PK sample should be taken immediately (within 1 hour) after ECG assessment

[c]. Pre-dose ECG on the first day of every cycle. Additionally, 2 h post-dose in every 3rd cycle (i.e. Cycle 9, 12, 15, 18, etc.).

[d]. The exact date and time of dosing must be recorded on the appropriate eCRF.

All ECGs including unscheduled triplicate ECGs with clinically relevant findings, collected during the study should be transmitted to a central laboratory and will be centrally reviewed by an independent reviewer. Each ECG tracing should be labeled with the study number, patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening when the patient signs informed consent should be recorded on the relevant medical history/current medical conditions eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page

7.2.2.6.2 Cardiac imaging - ECHO (echocardiogram) or MUGA (multiple gated acquisition) scan

The left ventricular heart function will be evaluated by ECHO or MUGA at Screening and if clinically indicated during the study. The same procedure should be used throughout the study.

7.2.3 Pharmacokinetics

The blood sampling regimens for determining the PK of ribociclib (and its active metabolite, LEQ803) and everolimus after oral administration are given in the table below (Table 7-6).

An unscheduled PK blood sample may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion. If a patient discontinues from the study treatment due to toxicities related to study treatment, an unscheduled PK blood sample may be obtained as soon as possible after the last dose and the date and time of last dose recorded. In addition, an unscheduled blood sample may be collected if additional ECG measurements are conducted.

[redacted]

[redacted]

7.2.3.1 Pharmacokinetic blood sample collection and handling

7.2.3.1.1 Blood collection plan

Phase I and II: PK sampling will be performed in all subjects treated in the Phase I and Phase II parts of this study. Blood for PK profiling of ribociclib (and its metabolite) and everolimus will be collected on Cycle1 Day 15, Cycle 2 Days 1 and Day 15 and Cycle 3 Day 1 (see Table 7-6).

For subjects who were previously treated with a CDK 4/6 inhibitor within 30 days of starting study drug will require PK sample on Cycle 1 Day 1

Table 7-6 Schedule of blood sample collection for PK in phase I and II

Cycle	Day	Scheduled Time Point Relative to Dosing	Blood Volume (mL)
1	1	Pre-dose (if previously treated with a CDK 4/6 i)	3
	15	Pre-dose[a]	3
		2 h post-dose (± 30 min)	3
		4 h post-dose (± 30 min)	3
2	1	Pre-dose[a]	3
	15	Pre-dose[a]	3
		2 h post-dose (± 15 min)	3
		4 h post-dose (± 15 min)	3
3	1	Predose	3
Unscheduled		Anytime [b]	3

a. Collect Pre-dose PK sample immediately before drug administration (approximately 24-hrs after the last dose and immediately before the next dose)

b. Unscheduled PK blood samples may be collected at any time for measurement of plasma drug concentrations if clinically indicated or at the Investigator's discretion and will be uniquely, sequentially numbered.

7.2.3.1.2 Additional guidelines for PK sampling/ECG

On days with PK sampling and/or ECG testing (collection days are outlined in Table 7-6), the following additional guidelines must be followed:

- Pre-dose ECGs and/or PK samples should be collected before dosing of the study treatment.
- ECGs should be done prior to PK sampling.

[redacted]

- The time of PK collection and the time the study medication was taken must be precisely recorded in the eCRF.
- Sites must record the precise date and time of the last study treatment prior to PK collection in the eCRF.
- Post-dose ECGs and/or PK samples should be collected after dosing of the study treatment.

The date and exact time of dosing on PK collection days, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF pages. In addition, the exact time of dosing on the previous day must be precisely recorded.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed, and medication should resume on the next day. The occurrence and frequency of any vomiting must be noted in the adverse events section of the eCRF. In addition, the date and exact time of vomiting should only be recorded if it occurs within 4 hours of dosing on the days of PK sampling. If a vomiting episode occurs within the first 4 hours post-dosing during the day of the last dose prior to trough PK samples the exact time (whenever possible) must be noted on the eCRF.

PK parameters (eg. C_{max}, T_{max}, AUC_{0-6h}, etc.) will be estimated (when feasible) from individual plasma concentration-time profiles using appropriate methods and software; a detailed description of the planned analyses is given in Table 7-6.

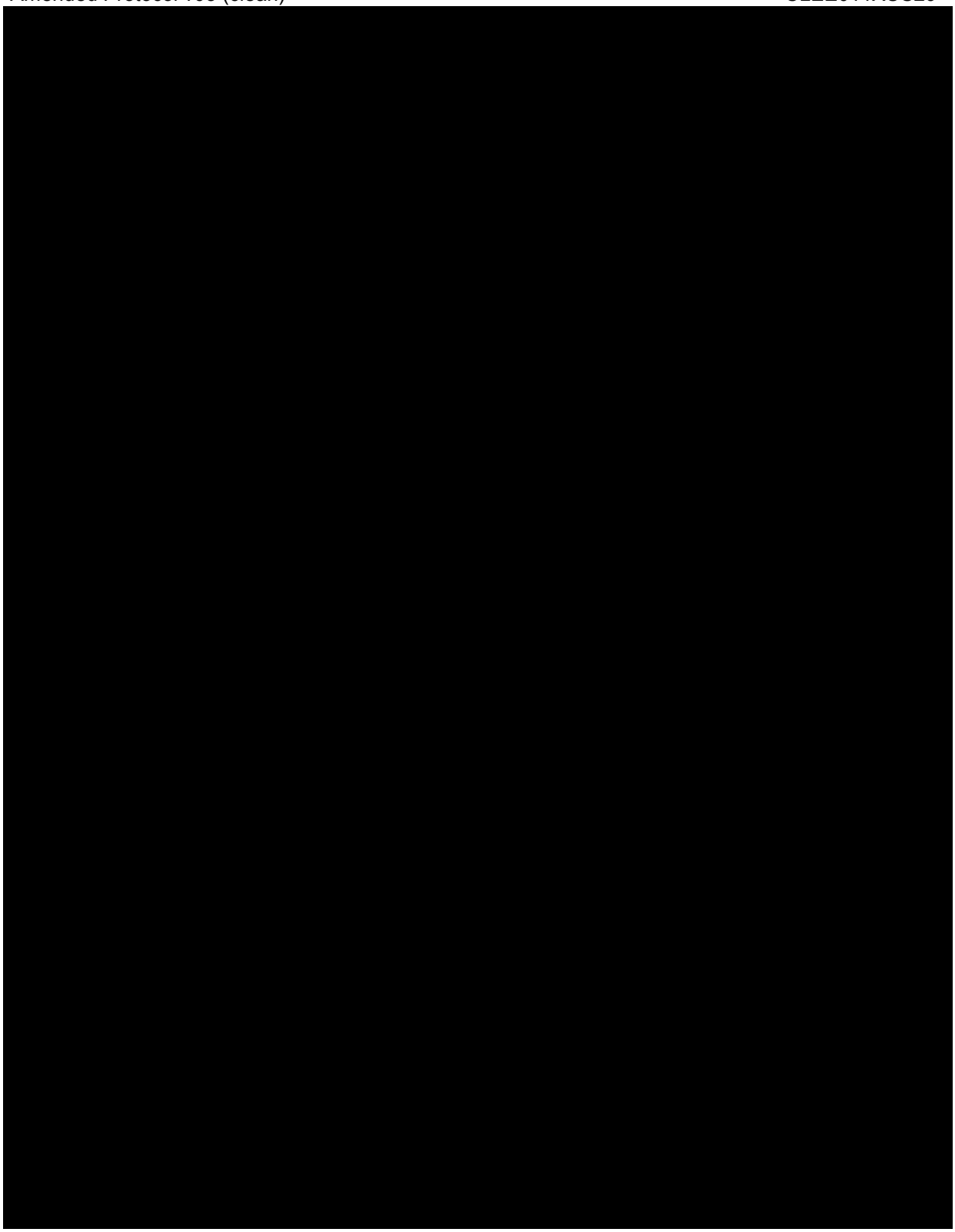
7.2.3.1 Pharmacokinetic blood sample collection and handling

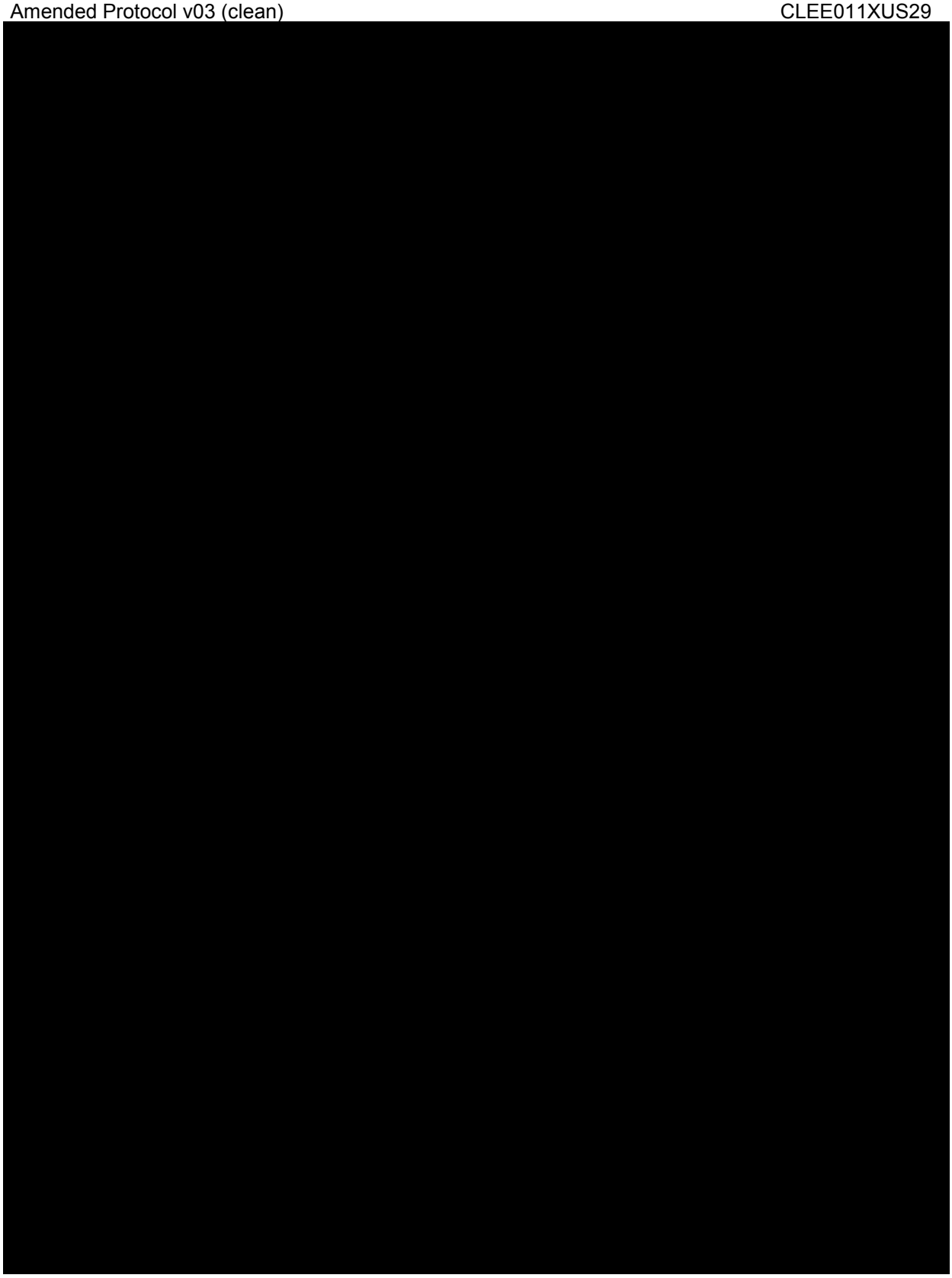
Blood samples will be obtained from all patients either by direct venipuncture or through an indwelling cannula (e.g., inserted in a forearm vein, or central venous line) for the analysis of plasma concentrations of ribociclib (and any relevant metabolites such as LEQ803), when feasible. At the specified time points described in Table 7-1 and Table 7-5, one single 3mL blood draw will be collected into a tube containing EDTA and gently inverted several times to thoroughly mix the anticoagulant. The blood tube will be centrifuged to separate the plasma. Plasma will immediately be split and transferred into separate pre-labeled tubes for ribociclib. Plasma samples will be stored frozen in an upright position until shipment.

Any sampling problems (e.g., patient took study drug before blood sample, scheduled sampling time is missed, sample is not drawn according to the schedule) should be noted as a comment on the eCRF. Refer to the Laboratory Manual for detailed instructions for the collection, handling, and shipment of PK samples

[redacted]

[redacted]





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8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose

of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its duration (Start and end dates) or Ongoing at End of Study.
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)

[redacted]

4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a SAE is defined as in Section 8.2.

If the event worsened the event should be reported a second time in the CRF noting the start date when the even worsens in toxicity. For Grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1 criteria), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Requires inpatient hospitalization or prolongation of existing hospitalization,
    - Note that hospitalizations for the following reasons should not be reported as serious adverse events:
        1. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
        2. Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        3. Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

For all patients who sign the study ICF, SAE collection starts at time of study informed consent whether the patient is a screen failure or not. To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period (or 5 half-lives, whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to

[redacted]

each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancy

This protocol will enroll only men and post-menopausal women (chemical ovarian suppression allowed).

If a female subject, or a female partner of a male subject should become pregnant, to ensure safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator's Brochure for ribociclib and the approved package inserts for everolimus and exemestane. Additional safety information collected between IB updates will be communicated in the form of INs. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.4 Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to assess the safety efficacy of ribociclib. The IDMC will be responsible for reviewing the efficacy and safety data

[redacted]

accruing in the trial at regular intervals of approximately every three months or when 25%, 50%, 75% and 100% of the patients are enrolled whichever occurs first. Also, if requested by the IDMC Chair, additional safety reviews may be performed.

The IDMC will consist of at least one oncologist, one hepatologist and one statistician and will be formed prior to the study treatment of the first patient. Detailed recruitment status and interim safety reports will be provided to the IDMC on a regular basis. Recruitment will not be interrupted during IDMC analysis. Details will be provided in the IDMC charter.

8.5 Steering committee

The SC will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team.

The SC will be an advisory board for the study according to the protocol through recommending modifications as circumstances require. The SC will be consulted for protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results. The details of the role of the SC will be defined in a SC charter.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRF's with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRF's, the adherence to the

[redacted]

protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRF's must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRF's are performed according to the study-specific monitoring plan.

9.3 Data collection

This study will use Electronic Data Capture (EDC). The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRF's have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRF's and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood and tumor samples for PK [redacted] assessments will be collected by sites and sent to the Novartis designated central laboratory for processing. The laboratory results and IRT data will be sent electronically to Novartis. Imaging and ECG data will be collected at the sites and the data will be transmitted to a designated CRO for centralized analysis, as well as further processing and data reconciliation.

Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRF's and laboratory paper requisition forms for accuracy and completeness and will instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff, and one copy will be retained at the investigational site.

9.4 Data management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the

[redacted]

investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data collected for all third party data such as ECG, PK [redacted] will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and data made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between Novartis and the CRO biostatistician and database management.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

Data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The study data will be analyzed and reported based on all patients' data up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study.

Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary Clinical Study Report will be reported once all patients have discontinued the study or at the end of the study, whichever occurs first.

Data will be summarized and listed by study group.

For safety endpoint, all patients will be analyzed for each phase and may be pooled for analysis. The efficacy data that will be analyzed for Phase I and Phase II of this study separately

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected, will not be included in any analysis, but will be reported in the CSR as separate listings.

[redacted]

The reason for discontinuation from study will be summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient. Other missing data will simply be noted as missing on appropriate tables/listings.

10.1 Analysis sets

10.1.1 Full analysis set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of the assigned combination of study drugs (ribociclib+ everolimus + exemestane).

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of any of the components from the investigational treatment, and have at least one valid post-baseline safety assessment. Investigational treatment/group refers to the triplet combination of ribociclib + everolimus + exemestane. The statement that a patient had no AEs (on the AE eCRF) constitutes a safety assessment.

10.1.3 DLT-determining analysis set

The DLT-determining set (DDS) includes all patients from the safety set in the dose escalation part who either completed a minimum exposure requirement and have sufficient safety evaluations in the first cycle or discontinued prematurely due to a dose limiting toxicity (DLT).

A patient is considered to have met the minimum exposure requirement if having received at least 75% of the planned combination doses (i.e. 21 out of 28 planned daily doses) for all compounds administered together (same day): ribociclib, everolimus and exemestane. The length of a cycle is 28 days.

Patients who do not experience a DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

10.1.4 Pharmacokinetic analysis set

The PK analysis set (PAS) consists of all patients who have at least one blood sample providing evaluable PK data. The PAS will be used for summaries of PK data (tables and figures) as well as for listings of derived parameters.

10.1.5 Per-protocol set

A subset of Full Analysis Set (FAS) excluding major protocol violations

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including age, gender, height, weight, medical condition, and disease characteristics will be summarized descriptively. Treatments (study treatment, concomitant therapies, compliance).

[redacted]

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of ribociclib, everolimus and exemestane as well as the dose intensity (based on actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity based on planned dose and planned duration), will be listed and summarized by means of descriptive statistics. The summary data will be presented for each treatment cycle individually, as well as for all study days as a single category. The total daily doses of ribociclib, everolimus and exemestane for each patient will be summarized using descriptive statistics (e.g. mean, median, maximum and minimum doses).

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized by ATC (Anatomical Therapeutic Chemical Classification System) term. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized by treatment group/study arm. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions).

10.4 Statistical hypothesis, model, and method of analysis

10.4.1 Study Design

This is a multi-center, open-label, Phase I/II study consisting of both Phase I dose escalation and dose de-escalation, and a Phase II. The dose escalation and de-escalation part of the trial will be conducted in men and postmenopausal women with HR+ HER2-negative advanced breast cancer that is endocrine resistant. Phase II will evaluate the antitumor activity of the combination of ribociclib +everolimus + exemestane combination in men and postmenopausal women with HR+HER2- advanced breast cancer that progressed on a CDK4/6 inhibitor.

10.4.2 Sample size and accrual

Phase I: In the phase I of the study, there will be 3-6 patients per dose level cohort (for a total of 3 cohorts). A RP2D will be based on safety profile of the dose escalation (cohort A&B) and the dose de-escalation (cohort C). RP2D will be defined as the optimal dose level at which 33% or less experience DLTs. Thus, including confirmation, at least 3-6 patients will be required for Phase I for each cohort.

[redacted]

Phase II:

The sample size is based on an exact test for single proportion to test the null hypothesis H0: $p \leq 0.10$ where p is the clinical benefit rate in 24 weeks. If the true rate is $p \geq 30\%$, then with one-sided alpha level of 0.05% and a power of 80%, a minimum of approximately 60 (30 per group) evaluable patients are required for the study.

Including drop out rate of 10%, to get 60 evaluable patients, a total of approximately 66 pateints (33 patients per group) will be enrolled for the phase 2 of the study for each group (group 1 and group 2). Thus, if fewer than 8 patients show clinical benefit at 24 weeks out of 33 patients within each group then the study will not show significant clinical benefit. Thus, approximately at least 66 patients (33 patients per group (group 1&2)) will be required to be enrolled for the Phase II of the study

10.5 Objectives

10.5.1 Primary objectives

Phase I: The primary objective of this dose escalation part of the study is to estimate the MTD(s) and/or RP2D of ribociclib in combination with everolimus and exemestane in postmenopausal women with HR+ HER2− advanced breast cancer.

Phase II: The primary objective is to evaluate efficacy measured by Clinical benefit rate (CBR) at 24 weeks for the triple combination of ribociclib + everolimus + exemestane among patients with HR+HER2- advanced breast cancer following the progression of CDK 4/6 inhibitors.

Demonstration of significant Clinical Benefit Rate (CBR) will be based on this study with at least an 80% power to test the null hypothesis that the clinical benefit rate in 24 weeks is at least 10% or less with an alternative hypothesis that this rate is above 10%.

The Clinical benefit rate will be presented together with an exact 95% Clopper-Pearson confidence interval. The null hypothesis will be rejected and successful clinical benefit will be demonstrated if the lower limit of the 95% confidence interval is greater than at least 0.10. Thus, if 8 or more patients show clinical benefit at 24 weeks then the null hypothesis will be rejected and significant clinical benefit will be demonstrated. Primary efficacy analysis will be performed on the FAS. For primary efficacy variable, the analysis time point is when all patients who are enrolled complete 24 weeks or discontinue from the study earlier. Phase 1 patients who had received the RP2D and are post CDK 4/6 completing 24 weeks or discontinue early will also be included in the final phase II analysis.

10.5.2 Secondary objective(s)

Progression-free survival (PFS), defined as the time from date of treatment to the date of first documented progression or death due to any cause.

PFS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who do not progress will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

[redacted]

Overall response rate (ORR) defined as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST 1.1. ORR will be calculated based on FAS according to the IIT principle; however, patients with only non-measurable disease at baseline will be included in the numerator if they achieved a complete response. ORR will be summarized by frequency and percentage. Disease Control Rate (DCR) in Phase I will be summarized by prior CDK 4/6 inhibitor treatment status with accompanying 95% confidence intervals.

Overall survival (OS) is defined as the time from date of first treatment to the date of death due to any cause. If a patient is not known to have died, survival will be censored at the last date of contact. OS will also be summarized by Kaplan-Meier Product-Limit method.

Duration of Overall Response (DOR) applies only to patients whose best overall response is CR or PR according to RECIST 1.1. The start date is the date of first documented response (CR or PR) and the end date is the date defined as first documented progression or death due to underlying cancer. In other words, the start date should be determined using the time that the response was first determined and not using the time the response was confirmed. If a patient had not had an event, duration will be censored at the date of the last adequate tumor assessment. DOR will be listed and summarized by treatment arm.

ECOG performance scale as described in Table 7-3 will be used to assess physical health of patients. An analysis of time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed. Deterioration is considered definitive if no improvements in ECOG PS status is observed at a subsequent time of measurement during treatment period following the time point where the deterioration is observed.

Adverse Events (AEs), serious AE (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions and dose intensity

To determine the PK profile of ribociclib and everolimus in the triplet combination. PK parameters including, but not limited to, $AUC_{0\text{-}6h}$, C_{trough}, C_{max}, accumulation ratio (R_{acc})

10.5.2.1 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and preferred term, severity (based on CTCAE grades), relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

10.5.2.2 Laboratory abnormalities

For laboratory tests covered by CTCAE version 4.03, the study's bio statistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

[redacted]

For laboratory tests where Grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

If the lower limits of normal ranges used in CTCAE definitions are missing, then they have to be replaced by a clinical meaningful limit.

The following summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment Grades 3 or 4.
- Shift tables using CTCAE Grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTCAE Grades are not defined, shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Listing of all laboratory data with values flagged to show the corresponding CTCAE Grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other [redacted] analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the Report and Analysis Plan (RAP).

10.5.2.3 Other safety data

Vital sign and ECG data will be summarized descriptively.

All safety information collected will be listed and notable values will be flagged. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.2.4 Supportive analysis for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the RAP Module 3 prior to DBL.

10.5.2.5 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized. Cumulative dose, dose intensity and relative dose intensity of ribociclib, everolimus and exemestane will be listed by patient and summarized. Categories for relative dose intensity for ribociclib, everolimus and exemestane will be specified as <0.5, ≥0.5 - <0.75, ≥0.75 - <0.9, ≥0.9 - <1.1 and ≥1.1. The number and proportion of patients within each category will be presented.

10.5.3 Pharmacokinetics

Ribociclib and everolimus concentrations for all PK-evaluable patients will be summarized based on timepoints (listed in Table 7-6). The LLOQ for ribociclib (and LEQ803) in plasma is approximately 1.00 ng/mL. The LLOQ for everolimus in whole blood is approximately 0.3 ng/mL. The LLOQ for exemestane in plasma is approximately 0.0200 ng/mL. All concentrations below the LLOQ or missing data will be labeled as such in the concentration

[redacted]

data listings. [redacted]

Table 10-1 Non-compartmental pharmacokinetic parameters

Parameter	Definition
C_{max}	Maximum observed drug concentration after drug administration (mass x volume^{-1})
C_{trough}	Minimum drug concentration at the end of a dosing interval (taken directly before next administration) (mass x volume^{-1})
T_{max}	Time to reach maximum plasma/blood/serum drug concentration (time)
AUC 0-6h	Area under the drug concentration-time curve during a dosing interval (mass x time x volume^{-1})
R_{acc}	Accumulation ratio calculated as AUC_{T} ,ss / AUC_{T},sd
$T_{1/2}$	Effective elimination half-life (time)
CL	Apparent total body clearance of drug (volume x time^{-1})

10.5.3.1 Data handling principals

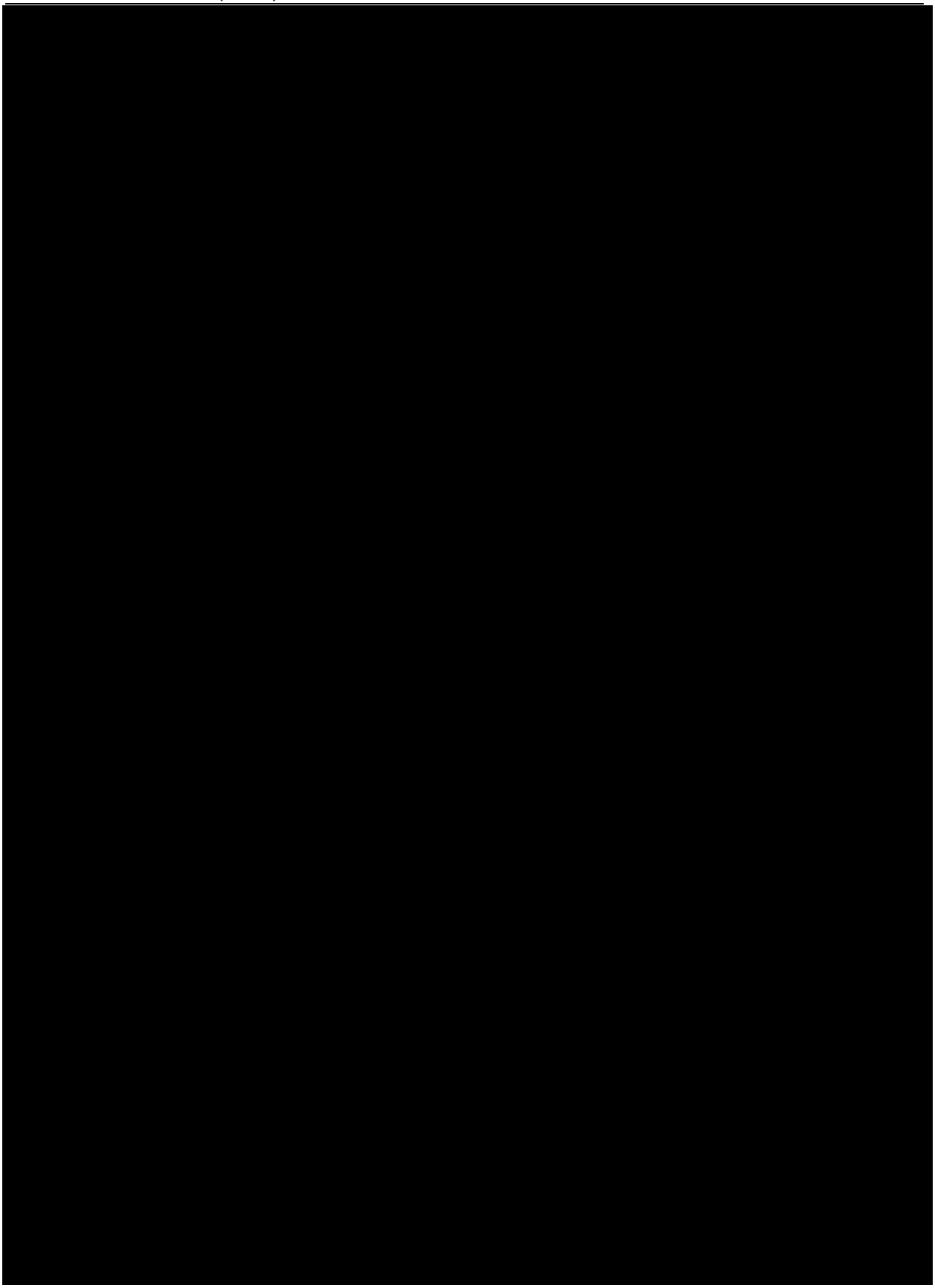
10.5.3.1.1 Basic tables, figures amd listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all PK parameters by treatment group and study day. When a geometric mean is presented, it will be stated as such. Only median values and ranges will be given for Tmax.

Descriptive graphical plots of individual plasma concentration by time will be generated, as will mean concentration-time profiles for ribociclib (and LEQ803) and everolimus. Details of PK analysis presented will be given in the Reporting and Analysis Plan (RAP). [redacted]

[redacted]

[redacted]



10.7 Interim analysis

No formal interim analysis is planned One interim statistical analysis will be done after completing Phase I part of the study. The final analysis will be after completing Phase II of the study.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written, IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed Informed Consent Form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

[redacted]

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations but not later than 10 working days.

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14 Appendices

14.1 Appendix 1- Concomitant medication

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ribociclib.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction and Co-Medication Considerations (v05 release date: 2015), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/clinpharm/ddis/main-table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsade's de pointes (TdP), refer to the CredibleMeds® website (www.qtdrugs.org/).

These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

Table 14-1 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavir, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Carbamazepine, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3], enzalutamide
CYP3A substrates with NTI[1]	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, lomitapide[5], lovastatin, nicardipine, nisoldipine, pimozide, quinidine, simvastatin, sirolimus, tacrolimus
Medications with a known risk for QT prolongation[4]	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin,bepridil chloroquine, cocaine chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, gatifloxacin, grepafloxacin, halofantrine, haloperidol, ibutilide, levofloxacin, levomepromazine, levosulpiride, levomethadyl, mesoridazine methadone, moxifloxacin, ondansetron, oxaliplatin, papaverine HCl (intra-coronary), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, terodiline, terfenadine, thioridazine, vandetanib,
Herbal preparations/ medications	Herbal preparations/medications known as strong inducers or inhibitors of CYP3A4/5 or those with a known risk of QT prolongation are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

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Category	Drug Name
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, hormonal therapy, including but not limited to all SERMS [inclduing raloxifene], biologic or radiation therapy [except for palliative radiotherapy as outlined in the protocol],and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must discontinue study drug.

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes), or drugs which have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood.

[2] Herbal product

[3] P-gp inducer

[4] The list provided is as of January 2018.Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list.

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of ribociclib or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at www.qtdrugs.org.

Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

Table 14-2 List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Aprepitant, amprenavir, asafoetida resin (Ferula asafoetida) cimetidine, crizotinib, diltiazem, faldaprevir, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, Schisandra sphenanthera (nan wu wei zi), verapamil
Moderate CYP3A4/5 inducers	Bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, telotristat, lopinavir[5]
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib,brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatininb, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutnib, isavuconazole, ivabradine, ivacaftor, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, perospirone, quetiapine, ridaforolimus, rivaroxaban, sildenafil, simeprevir, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin-
BSEP inhibitors	Alectinib, atorvastatin, bromocriptine, candesartan, clobetasol, clofaziminie, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone, pioglitazone, reserpine, rifamycin, simeprevir, telmisartan, timcodar, troglitazone, valinomycin, velpatasvir

[redacted]

Category	Drug Name
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, artenimol+piperaquine , asenapine, atazanavir, atomoxetine, bedaquiline, bendamustine, bortezomib, bosutinib, buprenorphine, cabozantinib, capecitabine, ceritinib, clomipramine, crizotinib, clozapine, cyamemazine (cyamepromazine), dabrafenib, dasatinib, degarilix, delamanid, desipramine, dexmedetomidine, dolasetron, efavirenz, eliglustat, epirubicin, eribulin mesylate, ezogabine(retigabine), famotidine, felbamate, fingolimod, flupentixol, gemifloxacin, granisetron, hydrocodone-ER, iloperidone, imipramine (melipramine), isradipine, ketanserin, lapatinib, lenvatinib, leuprolide, loperamide, lithium, melperone, midostaurin, mifepristone, mirabegron, mirtazapine, moexipril/HCTZ, necitumumab, , nilotinib, norfloxacin, nortriptyline, nusinersen, ofloxacin, lanzapineosimertinib, oxytocin, paliperidone, palonosetron, panabinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, quetiapine, ranolazine rilpivirine, risperidone, romidepsin, sertindole, sorafenib, sunitinib, tamoxifen, telavancin,tetrabenazine, tipiracil/trifluridine, tizanidine, tolterodine,oremifene,trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine, vorinostat, ziprasidone
MATE1/2 substrates[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topotecan, varenicline
OCT2 substrates[4]	Amantadine, 6-beta-hydroxycortisol, carboplatin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium,, and zidovudineAcyclovir,
BCRP substrates	Daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, sulfasalazine, sofosbuvir, tenofovir, topotecan, venetoclax..

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.
[2] The list provided is as of January 2018. Check https www crediblemeds.org/healthcare-providers/drug-list for the most updated list
[3]MATE1 and MATE2 share considerable substrate specificity.
[4]OCT1 and OCT2 share considerable substrate specificity.
[5] Lopinavir is prohibited when combined with ritonavir
Source: Novartis PK Sciences Memorandum: Drug-Drug Interactions (DDI) and Co-medication Considerations for Novartis Clinical Trials (January 2018), which is compiled from Indiana University "Clinically Relevant" Flockhart Table™, University of Washington Drug Interaction Database, and FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.2

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14.2 Appendix 2 - Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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Document status:	Version 3.1: 29-Nov-2011 Version 3:0: 19-Oct-2009 Version 2:0: 18-Jan-2007 Version 1:0: 13-Dec-2002
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Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

14.2.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.2.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.2.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

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14.2.3 Definitions

14.2.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.2.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to <15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.2.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study if she/he has bone only disease (if lytic or mixed) See section 5 eligibility criteria. Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.26.

14.2.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).

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- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.2.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

[redacted]

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.4.
- **Nodal target**: See Section 14.2.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.2.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-3) and non-target lesions (Table 14-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-5) as well as the presence or absence of new lesions.

14.2.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.2.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement

[redacted]

should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.2.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.2.12 Determination of target lesion response

Table 14-3 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to <10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.2.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present

[redacted]

and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-3 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the “merged lesion” should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the “merged lesion” should be recorded for the size of one of the original lesions while a size of “0”mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.

[redacted]

- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.2.13 Determination of non-target lesion response

Table 14-4 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (<10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. <10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

14.2.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.2.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.6.

14.2.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-5.

Table 14-5 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.2.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

[redacted]

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.2.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.2.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required

[redacted]

- SD = at least one SD assessment (or better) >6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

[redacted]

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.2.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.2.19 Progression-free survival

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.2.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.2.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

[redacted]

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.2.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment 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 time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.2.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.2.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.2.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

[redacted]

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.2.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.2.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

[redacted]

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-6.

Table 14-6 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.2.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.2.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.2.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 14-7 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.2.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

[redacted]

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-7 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.2.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.2.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.2.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 15 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision

[redacted]

- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.2.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.2.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the

[redacted]

RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.2.33 Programming rules

The following should be used for programming of efficacy results:

14.2.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.2.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation 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 outlined in Section 14.2.25). 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.

14.2.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.2.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.2.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.2.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

[redacted]

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up
- For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:
- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-7)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.2.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).

- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.2.40 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

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Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

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14.3 Appendix 3 - Bone Marrow Reserve in Adults

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

Table 14-8 Marrow distribution of the adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head: Cranium Mandible	 165.8 16.4	 0.75 0.75	136.6 124.3 12.3	13.1	13.1
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle : 2 Humerus, head & neck 2 Scapulae 2 Clavicles	 26.5 67.4 21.6	 0.75 0.75 0.75	86.7 20.0 50.5 16.2	8.3	**8.3**
STERNUM AND RIBS	Sternum Ribs: 1 pair 2 3 4 5 6 7 8 9 10 11 12	39.0 10.2 12.6 16.0 18.6 23.8 23.6 25.0 24.0 21.2 16.0 11.2 4.6	0.6 All 0.4	23.4 82.6 4.1 5.0 6.4 7.4 9.5 9.4 10.0 9.6 8.5 6.4 4.5 1.8	2.3 7.9	**10.2**
PELVIC BONES	Sacrum 2 os coxae	194.0 310.6	0.75 0.75	145.6 233.0	13.9 22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

[redacted]