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Clinical Development

Ribociclib (LEE011)

Oncology Clinical Protocol CLEE011AIT01 / NCT03439046

A phase IIIb, open-label, local, multicenter study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib plus letrozole and, in patients with a PIK3CA mutation, on second-line treatment with alpelisib plus fulvestrant (BioItaLEE)

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List of abbreviations

aBC	Advanced Breast Cancer
ADA	American Diabetes Association
ADME	Absorption Distribution Metabolism and Excretion
AE	Adverse Event
AESI	Adverse Events of Special Interest
AKT	Protein Kinase B
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
AUC0-6h	Area Under the Curve 0-6h
BAS	Biomarker Analysis Set
BCRP	Breast Cancer Resistance Protein
BSA	Body Surface Area
BSEP	Bile Salt Export Pump
CBR	Clinical Benefit Rate
CLRF	Central Laboratory Requisition Form
Cmax	Maximum Plasma Concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
ctDNA	Circulating tumor DNA
CDK 4/6	Cyclin-Dependent Kinases 4 and 6
CHF	Congestive Heart Failure
CV	Coefficient of Variation
CYP	Cytochrome P
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
PTA	Post-Trial Access
DTI	Direct Thrombin Inhibitor
EBV	Epstein-Barr Virus
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture

EGFR	Epidermal Growth Factor Receptor
EM	Erythema Multiforme
EoT	End of Treatment
ER	Estrogen Receptor
ERCP	Endoscopic Retrograde Cholangiopancreatography
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence In Situ Hybridization
FPFV	First Patient First Visit
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GGT	Gamma-glutamyl transpeptidase
HAV	Hepatitis A Virus
HbA1C	Glycosylated Hemoglobin
HbsAg	Hepatitis Surface Antigen
HDL	High Density Lipoprotein
HER2	Human Epidermal Growth Factor Receptor 2
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
HSV	Herpes Simplex Virus
IC50	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IRB	Institutional Review Board
INR	International Normalized Ratio
ISTAT	Italian National Institute for Statistics
IWRS	Interactive Web Response System
LDH	Lactase Dehydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LPFV	Last Patient First Visit
LVEF	Left Ventricular Ejection Fraction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume

medDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRP2	Multidrug Resistance Protein 2
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NCI-CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event
NSAI	Nonsteroidal Aromatase Inhibitors
NTI	Narrow Therapeutic Index
ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate
OS	Overall Survival
PBPK	Physiologically-Based Pharmacokinetic
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gp	P-glycoprotein
PHI	Protected Health Information
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog
PTT	Partial Thromboplastin Time
QTcF	QT corrected interval using Fridericia formula
Rb	Retinoblastoma protein tumor suppressor gene
RBG	Random Blood Glucose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SERM	Selective Estrogen Receptor Modulator
SD	Stable Disease
SmPC	Summary of Product Characteristics
[redacted]	
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TdP	Torsades de Pointe
Tmax	Time to Peak Concentration
[redacted]	
TME	Tumor Microenvironment
TTP	Time to Progression

TK1	Thymidine kinase 1
ULN	Upper Limit of Normal
WBC	White Blood Cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
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
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time, all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival.
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 patient permanently stops taking study treatment for any reason
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

Amendament 4 (19-Apr-2023)

Amendament rationale

The first core phase patient was screened on 1 Feb 2018, 332 patients have been screened and 287 have been enrolled. The core phase of the study is currently closed for enrollment. The first extension phase patient was screened on 4 September 2019 and, as of April 2023, 20 patients have been screened and enrolled.

The purpose of this amendment is to define post-trial access (PTA) to therapy for patients, given that the primary objective of the study, defined as "to identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome", has been satisfactorily explored. Since the primary objective has been reached before the *per protocol* LPLV, the primary aim of this amendment is to define the procedure for study exit and to establish the possible PTA for alpelisib.

Rationale for study closure:
Since BioItaLEE endpoints are not based on a statistical hypothesis to be verified (as explicated in 10.8 section "the study is descriptive in nature and no formal statistical testing is necessary or applicable."), but rather modelled after biomarker trials, their fulfillment relies on events rather than on statistical design. As of today, with more than 200 patients having reached EoT assessments and more than 50 months of follow up for ongoing patients, the information is enough to perform the analysis stated as primary endpoint satisfactorily. The dropout rate observed so far has progressively slowed down to nearly a patient a month, with projection, sustained by literature data, tending to even lower numbers: this would require a follow-up period to reach *per protocol* LPLV that would risk rendering obsolete the information collected so far. As such, Novartis has decided to terminate the trial. The present amendment will detail study procedure related to the final study visit and the mechanism to assure therapeutic continuity.

Changes to the protocol
Changes to specific sections of the protocol and corresponding paragraphs of the synopsis are shown in the track changes version of the protocol using strike through font for deletions and underlined for insertions.

- Paragraph 4.4.1
- Paragraph 7.1.3
- Paragraph 7.1.5
- Table 7-1
- Table 7-2
- Table 7-3
- Table 7-4
- Table 7-5

IECs
The changes herein affected Informed Consent. Sites will be required to update and submit for approval a revised Informed Consent Form that takes into account the changes described in this protocol amendment.

A copy of this amended protocol will be sent to the Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IEC approval prior to implementation.

Amendment 3 (11-Dec-2019)

Amendment rationale

The first core phase patient was screened on 1 Feb 2018, 332 patients have been screened and 287 have been enrolled. The core phase of the study is currently closed for enrollment. The first extension phase patient was screened on 4 September 2019 and, as of 3 December 2019, 6 patients have been screened and enrolled.

On 24 May 2019, based on the results of the pivotal Phase III study CBYL719C2301, the United States Food and Drug Administration (FDA) granted approval of alpelisib in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. Other global submissions are currently under review by other Health Authorities worldwide. The Investigator's Brochure (IB) Edition 13, dated 15-Oct-2019, included comprehensive assessments of SOLAR-1 safety data (with cutoff date 13 May 2019) and all other available safety data, which led to further defining the alpelisib safety profile and risks associated with alpelisib. Additionally, the IB was updated with new drug-drug interaction data that warrants an update of prohibited medications and concomitant medications to be used with caution. Accordingly, this amendment covers these updates along with updates for the existing guidelines for the management of adverse events associated with the use of alpelisib and follow-up on toxicities.

In summary, the purpose of this amendment is to provide a protocol update on the following based on the recently released alpelisib IB Edition 13:

- New clinical pharmacology data and Drug-Drug Interactions (DDI)
- Update of the inclusion /exclusion criteria
- Update on permitted concomitant medications to be used with caution, prohibited medications and the use of bisphosphonates/denosumab
- Update on guidance of dose interruption/modifications, management of AEs associated with the use of alpelisib, and guidance for follow-up on toxicities
- Other editorial changes to align with new alpelisib protocols in other indications
- Added AST/ALT/TBilirubin dose modifications in Table 6-10 [redacted] and section on follow-up of potential drug-induced liver injury (DILI) was updated
- Minor update for the guidelines of skin rash
- Added DRESS as one of possible manifestations of severe cutaneous skin reactions

This amendment also makes a few minor corrections/changes.

Changes to the protocol

Changes to specific sections of the protocol and corresponding paragraphs of the synopsis are shown in the track changes version of the protocol using strike through font for deletions and underlined for insertions. The changes are outlined in order of appearance:

- Updated List of abbreviations.
- Section 1.2.4: updated clinical experience and approval information of alpelisib. Added SOLAR-1 pharmacokinetic analyses and data on food effect.
- Section 5.3 Inclusion criteria for extension phase:
  - #8: updated total serum bilirubin to <2 x ULN (from ≤ULN) and added that any elevated bilirubin should be asymptomatic at enrollment. Updated AST and ALT from ≤ 2.5 x ULN to ≤ 3 x ULN.
  - #10: changed wording on dietary advice for patients with hyperglycemia.
- Section 5.5 Exclusion criteria for extension phase:
  - #2: added mTOR and AKT inhibitors to prohibited prior treatments.
  - #9: added that testing for hepatitis is not mandatory unless required by local regulations.
  - #10: corrected CYP3A4 (from CYP3A) and added inhibitors of BCRP as prohibited concomitant medications.
  - #13: added that exclusion due to impairment of gastrointestinal function is at the investigator's discretion.
  - #14: added interstitial lung disease as exclusion criteria.
  - #16: added and combined cardiac abnormalities leading to exclusion.
  - #18: added Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as severe cutaneous reactions.
  - #20: added unresolved osteonecrosis of the jaw prior to initiating study treatment based on observations within SOLAR-1 data.
- Section 6.1.2.2 - Alpelisib dosing: additional guidance on missed dose instructions.
- Section 6.3.1.3: updated follow-up on potential drug-induced liver injury (DILI).
- Section 6.3.2 - Table 6-10: updates of criteria for interruption and re-initiation of alpelisib as per IB.
- Section 6.3.2.1.1: added interstitial lung disease as a selected toxicity requiring close monitoring when treating with alpelisib.
- Section 6.3.2.1.2: updated the guidelines for the treatment of alpelisib-induced skin toxicity.
- Section 6.3.2.1.3 updated dietary advice and guidelines for alpelisib-induced hyperglycemia.
- Section 6.3.2.1.5: updated follow-up on potential drug-induced liver injury (DILI).

- Section 6.3.2.1.6: added guidelines for hypersensitivity.
- Section 6.4.1: added general information on managing concomitant medications.
- Section 6.5.1: added general information on managing concomitant medications.
- Section 6.5.1.1: updated oral anti-diabetics with hyperglycemia in relation to alpelisib and CYP2C9.
- Section 6.5.1.2: updated gastric protection agents used concomitantly with alpelisib.
- Section 6.5.1.5: added section on hematopoietic growth factor concomitant with alpelisib.
- Section 6.5.2: updated text for medications to be used with caution for CYP2C9, CYP2B6, CYP3A4 and herbal medications.
- Section 6.5.3 (new): additional information and guidance on the use of bisphosphonates based on SOLAR-1 study data and the incidence of osteonecrosis of the jaw with alpelisib in combination with fulvestrant.
- Section 6.5.4 (previously 6.5.3): Prohibited therapy concomitant with alpelisib:
  - Inclusion of strong CYP3A4 inducers based on additional data (as listed in Table 14.4).
  - Inclusion of BCRP efflux transporters.
  - Removal of risk of Torsades de pointes and drugs associated with QT prolongation and/or TdP.
- Section 14.2. (Appendices):
  - Section 14.2.1: changed Table 14-3 - List of CYP450 substrates to be used with caution – and added text concerning permitted medication to be used with caution.
  - Section 14.2.2: Added Table 14-4 (new) - List of prohibited strong inducers of CYP3A4 -and changed Table 14-5 – List of prohibited BCRP inhibitors. Deleted List of prohibited QT prolonging drugs and List of QT prolonging drugs to be used with caution.
  - Section14.5: updated liver event and laboratory trigger definitions and follow-up requirements.

IECs

A copy of this amended protocol will be sent to the Independent Ethics Committees (IECs) and Health Authorities. The changes described in this amended protocol require IEC approval prior to implementation.

The changes herein affect 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.

Amendment 2 (28-May-2019)

Amendment rationale

The first patient was screened on 1 Feb 2018 and as of 15 April 2019, 332 patients have been screened and 287 have been enrolled in the study.

The purpose of this amendment is to broaden the study's investigation of gene alterations to the second line in patients with HR+ HER2-negative and PIK3CA mutated tumors following discontinuation to ribociclib and letrozole to identify patterns of mutations, how they evolve, their association with treatment outcomes, and thus establish treatment strategies that are tailored to the genetic profile of each individual breast cancer patient.

Preclinical breast cancer cell lines with acquired resistance to palbociclib data indicate that acquired resistance to CDK4/6 inhibition occurs through a loss of independence to Rb signaling; therefore targeting PI3K/mTOR as an alternative pathway might be a viable strategy worthy of further clinical investigation (O'Brien 2017). Alpelisib is a drug specifically targeting PIK3CA mutant breast cancer. Alpelisib in combination with fulvestrant, is approved by the FDA for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

In the SOLAR-1 trial, 20 patients with a PIK3CA mutation and who had previously received a CDK4/6 inhibitor as first line treatment for aBC were enrolled. The patients treated with alpelisib in combination with fulvestrant (9 patients) showed a prolonged PFS respect to the ones treated in monotherapy with fulvestrant in the control arm. Therefore, with a PIK3CAPI3KCA mutated, alpelisib demonstrated efficacy in prolonging PFS. Even if sample size (20 patients) was small, a benefit was demonstrated but more data on efficacy and biomolecular evolution during this treatment sequencing should be collected (Juric, 2018).

Particularly in patients with a PIK3CA mutation, elucidating resistance mechanisms and defining an optimal treatment sequencing strategy by identifying the unique gene mutation pattern in each breast cancer subtype after CDK 4/6 inhibitor therapy remain unmet needs. Optimizing genomic information and identifying useful predictive markers of toxicity and efficacy may also help clinicians in selecting patients who may benefit more from each of these therapies (ribociclib + letrozole AND alpelisib + fulvestrant) and from a sequence of treatments (ribociclib + letrozole followed by alpelisib + fulvestrant).

To this aim, an extension phase has been added only for patients with PIK3CA mutations following treatment discontinuation with first-line ribociclib + letrozole (core phase). These patients will be treated in second line with alpelisib in association with fulvestrant, a combination that has demonstrated clinically relevant benefits and a manageable safety profile in this subgroup of patients (Juric, 2018). As in the core phase of the study, liquid biopsies will be collected to identify ctDNA alterations, how they evolve, and their association with outcomes and different patient profiles. Moreover the trial enrolled patients starting from first-line treatment and has been evaluating the biomolecular evolution of the disease since the beginning of advanced disease; the analyses will thus evaluate a population prospectively and help us develop an understanding of how the disease evolves, population with a PI3KCA mutation included, during selective treatment pressure.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol and corresponding paragraphs of the synopsis are shown in the track changes version of the protocol using strike through font for deletions and underlined for insertions.

Section 1: updated to include background information on alpelisib and fulvestrant.

Section 2: updated to provide the rationale behind the extension phase.

Section 3: Objectives and endpoints have not been changed but now include treatment with alpelisib + fulvestrant within their scope.

Section 4: study design has been updated to describe the added extension phase. The protocol also now states that liquid biopsies will be obtained at the end of ribociclib + letrozole treatment regardless of the reason for discontinuation.

Section 5: patient population has been updated to include the patient population of the added extension phase. Inclusion/exclusion criteria for the extension phase have been added.

Section 6: the treatment section has been updated with information concerning the dosing and dose modifications of alpelisib + fulvestrant, as well as the use of concomitant medications.

Section 7: study flow, visit schedule and details of assessments for the extension phase have been added. The protocol also now states that liquid biopsies will be obtained at the end of ribociclib + letrozole treatment regardless of the reason for discontinuation.

Section 8 now also contains the adverse events of special interest related to treatment with alpelisib.

Section 10: statistical methods and data analysis for the extension phase have been added.

Section 13: references have been added.

Appendix 1: information about medications administered concomitantly with ribociclib has been updated.

Appendix 2: information about medications administered concomitantly with alpelisib has been added.

Appendix 3: guidelines for the treatment of alpelisib-induced diarrhea have been added.

Appendix 4: guidelines for the treatment of study drug induced stomatitis/oral mucositis have been added.

IRB/IECs

The changes herein affected Informed Consent. Sites will be required to update and submit for approval a revised Informed Consent Form that took into account the changes described in this protocol amendment.

A copy of this amended protocol will be sent to the Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 1 (11 July-2018)

Amendment rationale

The first patient was screened on 1 Feb 2018 and as of 9 July 2018, 159 patients have been screened and 118 have been enrolled in the study.

Amendment 1 was mainly intended to update or clarify biological sample collection timelines and data analysis, inclusion-exclusion criteria, management of treatment cycles in case of drug interruption and timelines or frequency of some trial assessments.

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

- Number of patients and sites involved was adjusted to reflect that 48 sites have been involved and that the aim is to have in the trial approximatively 300 patients who can be analyzed for the biological endpoints.
- Biological samples collection planned on C24D1 was removed.
- Inclusion-Exclusion criteria section was updated to better clarify the eligible population. In particular it was clarified that patients need to have a baseline tumor sample and at least one tumor lesion (target or not target).
- The definition of End of Study was updated to capture that End of study will be declared after all patients have discontinued all components of the study.
- Recommendations for the adjustment of treatment cycles in the case of ribociclib dose interruptions were added.
- Visit Evaluation schedule was updated to clarify the frequency of visits after C6 (every 3 cycles) and the relative assessments and to allow the collection of antineoplastic therapies since discontinuation of study treatment in the safety follow-up visit.
- A post treatment follow-up visit, 3 months after the EOT, was added. Second line antineoplastic therapy will be collected.
- Phosphorus, FSH and estradiol were added to the local laboratory collection plan to align it with the protocol text and requirements.
- Further details about biological samples collection/assessment were added.
- The frequency of efficacy assessments was recommended every 12 weeks.
- Biomarker analysis set (BAS) was updated to capture all subjects of the Full Analysis set who have an evaluable biomarker profile (at least baseline samples) and who do not have violations of the main inclusion-exclusion criteria.
- Timeline of first interim analysis was removed to allow periodical analysis.
- Amendment 01 also included minor editorial changes, typo corrections, adaptation to the new Novartis protocol template and additional clarifications to address investigators' questions as described in the list of changes below:

Changes to the protocol

The changes are outlined as follows in order of appearance:

- Summary section of the protocol was updated to maintain consistency with the main body of the protocol.
- Throughout the document: typographical and grammatical corrections.
- Section 1.2.1.2.2: updated reference.
- Section 4.1: updated number of sites and patients.
- Section 4.2: added timing of interim analysis.
- Section 4.3: revised information about the definition of end of study.
- Figure 4.1: revised figure to clarify patient population and definition of end of study.
- Figure 4.2: revised figure to remove c24d1 timepoint and to clarify the biological sample collections.
- Section 5.1: updated definition of patient population.
- Section 5.2: Inclusion criteria #2 revised to clarify patient population definition.
- Section 5.2: Inclusion criteria #12 added to clarify that patients need to have at least one tumor lesion.
- Section 5.2: Inclusion criteria #6 revised to clarify that patients must have a baseline tumor tissue to be provided and the acceptable types.
- Section 5.3: Exclusion criteria #3 revised to clarify that also neo adjuvant therapy is allowed (previous typographic mistake).
- Section 6.1.3: revised to update the definition of treatment duration.
- Section 6.3.2: added to insert recommendations on adjustment of ribociclib treatment cycles in case of dose interruptions/reinitiation.
- Section 6.3.2.1.2: revised to insert phosphorous.
- Section 7.1: added timelines of screening ECG.
- Table 7-1: revised to add postmenopausal status to the medical history, to clarify timelines and assessments of cycles after C6D1, to update follow-up period/visits and relative assessments of the antineoplastic therapy since discontinuation of study treatment, to update table notes.
- Section 7.2.1.3: definition of acceptable baseline tumor tissue updated.
- Sections 7.2.3 and 7.2.5: updated to insert a 3 months post-treatment follow up visit.
- Section 7.3.1: revised to clarify biological assessments, to add table 7-2 containing the biological sample collection plan, to clarify the use of residual biological samples.
- Section 7.3.2 and Table 7-3: updated to clarify recommended timelines for imaging assessments.
- Table 7-5: updated to add hormones to confirm post-menopausal status (if needed).
- Section 10: removed c24d1, updated definition of BAS.
- Section 10.7: updated timing of interim analysis.
- Section 13: updated references.

IRB/IECs

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The changes herein affected Informed Consent. Sites were required to update and submit for approval a revised Informed Consent Form that took into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CLEE011AIT01
Title	A phase IIIb, open-label, local, multicenter study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib plus letrozole and, in patients with a PIK3CA mutation, second-line treatment with alpelisib plus fulvestrant
Sponsor and Clinical Phase	Novartis – Phase IIIb
Investigation/study type	Interventional
Purpose and rationale	Although the results of clinical studies assessing the efficacy of ribociclib appear impressive, some patients do not respond to therapy and others eventually progress, underscoring the need to discover the mechanisms of de novo or acquired resistance. Elucidating resistance mechanisms by identifying the unique gene mutation pattern in each breast cancer subtype following progression or prolonged benefit from CDK 4/6 inhibitor therapy remains an unmet need and is crucial for leveraging the efficacy of CDK4/6 inhibitors. Optimizing genomic information and identifying useful predictive markers of toxicity may also help clinicians in selecting patients who may benefit more from these therapies. The present study is divided into a core phase and an extension phase. In the core phase, postmenopausal women with HR+, HER2- advanced breast cancer who have not received any prior agent for treatment of advanced disease will be treated with ribociclib + letrozole and followed until discontinuation of treatment due to any cause. Discontinued patients with PIK3CA mutations will subsequently enter the extension phase and undergo treatment with alpelisib + fulvestrant. **Core phase** The main purpose of this local, multicenter study is to investigate genetic and gene alterations in tumor prior to and following progression on ribociclib and thus identify patterns of mutations, how they evolve, and their association with CDK4/6 inhibition and outcomes such as sustained response or early progression. [redacted] Ribociclib and other cyclin-dependent kinase 4/6 inhibitors, in combination with letrozole, will likely have an impact on first-line treatment of advanced breast cancer. In order to study the biological features of a homogeneous population, the trial will be conducted only in first-line postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC). **Extension phase – patients with a PIK3CA mutation**

	Alpelisib combined with fulvestrant demonstrated clinically relevant benefits and a manageable safety profile in Phase I and Phase III (SOLAR-1) studies of patients with HR-positive, HER2-negative advanced breast cancer with PIK3CA mutations. Alpelisib is an oral class I α-specific PI3K inhibitor and, in combination with fulvestrant, is approved by the FDA for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. A noteworthy finding of the SOLAR-1 study is the potential viability of using liquid biopsies to identify PIK3CA mutation status. While patients with PIK3CA mutations evaluated in tissue samples had a 35% reduction in risk for disease progression, the risk reduction was 45% for patients with PIK3CA mutations evaluated in circulating tumor DNA. The authors concluded that compared to tissue DNA, circulating tumor DNA was a very easily accessible and less invasive source of material for mutation profiling and resulted in an even larger clinical benefit compared to tissue biopsy. The main purpose of this extension phase is to identify and characterize patients who benefit from treatment with alpelisib + fulvestrant in second line following treatment discontinuation with first-line ribociclib + letrozole through evaluation of the patient's tumor genomic profile by means of liquid biopsies.
Primary Objective	The primary objective of this study is to identify circulating tumor DNA (ctDNA) alterations, how they evolve, and evaluate their possible association with clinical outcome in both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment (core and extension phases respectively).
Secondary [redacted] Objectives	The secondary objectives are as follows: **Core phase** • To evaluate serum thymidine kinase 1 (TK1) activity over time as blood marker of proliferation and its association with clinical outcome. • To identify the patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" (i.e. Time to Progression > 25 months) and to patients with early progression (i.e. progressed at first imaging evaluation). • To assess mutational and gene aberrations across different patient profiles. [redacted] • To evaluate correlations between blood and tissue samples. [redacted] • To evaluate the safety and tolerability of ribociclib + letrozole in postmenopausal women with HR+, HER2- advanced breast cancer on first-line treatment. • To assess the clinical efficacy of ribociclib + letrozole.

	Extension phase –patients with a PIK3Ca mutation • To identify patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" and to patients with early progression (i.e. progressed at first imaging evaluation). • To assess mutational and gene aberrations across different patient profiles. [redacted] • To evaluate correlations between blood and tissue samples. [redacted] • To evaluate the safety and tolerability of alpelisib + fulvestrant in postmenopausal women with HR+, HER2- advanced breast cancer. • To assess the clinical efficacy of alpelisib + fulvestrant as a single treatment combination, and as one of two subsequent-line therapies (ribociclib + letrozole followed by alpelisib + fulvestrant) (PFS2 - PFS on second line treatment). [redacted]
Study design	This is a local, multicenter, open-label, single-arm trial that has enrolled 287 patients at 47 Italian sites. During the study's core phase, patients will be treated with ribociclib and letrozole until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor or lost to follow-up, whichever occurs first. Following treatment discontinuation, patients with PIK3CA mutations will enter an extension phase and undergo treatment with alpelisib + fulvestrant in second line until treatment discontinuation due to any cause. Second line treatment is defined in this protocol as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression). Cycle 1-day 1 Visit of the extension phase has to be done at least 7 days after the discontinuation of ribociclib and letrozole assumed in the core phase. To investigate the mechanisms of response and resistance to therapy with ribociclib in combination with letrozole and to therapy with alpelisib in combination with fulvestrant, both blood and tumor samples will be collected as described below: **First-line treatment with ribociclib + letrozole (core phase)** • Blood samples for ctDNA and TK1 will be collected at baseline, and then at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, as well as at end of treatment (EOT). • Newly obtained tissue biopsies will be collected at baseline and upon progression of disease. A baseline tumor sample must be obtained

	during the screening process prior to starting treatment. If a new biopsy is not clinically feasible, archival tissue will be acceptable (it is recommended to provide a recent biopsy of the locoregionally recurrent or metastatic disease). The second tumor tissue sample (if clinically feasible) will be obtained at time of progression and prior to subsequent therapy. Tumor samples will be analyzed to assess mutational and gene aberrations across different patient profiles. • [redacted]. **Second-line treatment with alpelisib + fulvestrant in patients with PIK3CA mutations following discontinuation of treatment with ribociclib + letrozole (extension phase)** • A tumor tissue sample (if clinically feasible) will be obtained at EOT upon progression of disease. • Blood samples for ctDNA will be collected at extension screening (if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form), cycle 2-day 1, at first imaging evaluation and at EOT. Safety will be evaluated through the documentation and analysis of AEs and SAEs, events of special interest (ribociclib: hematologic disorders [neutropenia including febrile neutropenia, neutropenic infection and neutropenic sepsis], QT prolongation, arrhythmia, hepatic dysfunction, liver toxicity, renal failure; alpelisib: GI toxicity [nausea, vomiting and diarrhea], hyperglycemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis, pneumonitis, severe cutaneous reactions), AEs leading to permanent treatment discontinuation, vital signs, physical examinations, variations of ECOG performance status, and hematology/chemistry parameters at study visits and for 30 days after discontinuation. Tumor assessment will be performed by the Investigator using RECIST v1.1 criteria and expressed as Time to Progression (TTP), Overall Response Rate (ORR) and Clinical Benefit Rate (CBR). Tumor assessments should be performed every 12 weeks (recommended timeframe) and at end of treatment.
Population	Core phase: the patient population will be made up of women in post-menopausal status with HR+, HER2- advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer who have not received any prior agent for treatment of advanced disease. These patients will undergo treatment with ribociclib and letrozole. Extension phase: the patient population will be made up of patients with PIK3CA mutations who discontinue therapy with ribociclib + letrozole during the core phase and subsequently undergo treatment with alpelisib + fulvestrant in second line.
Inclusion criteria	**Core phase** 1. Patient is a female ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities.

	2. Patient has an advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer in first-line treatment (treatment naïve for the advanced setting). 3. Patient is in post-menopause, defined by one of the following: • Prior bilateral oophorectomy • Age ≥ 60 • Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range 4. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory. 5. Patient has a HER2-negative breast cancer 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. 6. Patient is willing to undergo blood and tumor sample collection for the biological assessments/objectives as scheduled in the protocol. Note: patient must have a baseline tumor sample. It is recommended to provide a newly obtained tissue biopsy, or an archival tumor tissue derived by a recent biopsy of the locoregionally recurrent or metastatic disease (bone biopsies are acceptable). In cases this is not clinically feasible, the submission of an archival tumor tissue of the primary tumor is acceptable 7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. 8. Patient has an adequate bone marrow and organ function as defined by ALL the following laboratory values (as assessed by local laboratory): • Absolute neutrophil count ≥ 1.5×10^9/L • Platelets ≥ 100×10^9/L • Hemoglobin ≥ 9.0 g/dL • Potassium, sodium, calcium (corrected for serum albumin), magnesium, and phosphorus within normal limits or corrected to within normal limits with supplements before first dose of the study medication • INR ≤ 1.5 • Serum creatinine < 1.5 mg/dl or creatinine clearance > 50 mL/min • In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below 2.5 x Upper Limit of Normal (ULN). If the patient has liver metastases, ALT and AST should be < 5 x ULN.

	• Total serum bilirubin < ULN except for patients with Gilbert's syndrome, who may only be included if total bilirubin is ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN. 9. Patients must have a 12-lead ECG with the following parameters at screening: • QTcF interval at screening < 450 msec (using Fridericia's correction) • Resting heart rate ≥ 50 bpm 10. Patient must be able to swallow ribociclib and letrozole capsules/tablets. 11. Patients must be able to communicate with the investigator and comply with the requirements of the study procedures. 12. Patient must have either: • Measurable disease i.e. at least one target lesion as per RECIST 1.1 criteria • OR • If no measurable disease is present, then at least one not target lesion as per RECIST 1.1 criteria must be present **Extension phase – patients with a PIK3CA mutation** Written informed consent must be obtained prior to any screening procedures. 1. Patient is an adult female ≥ 18 years old at the time of consent and has signed informed consent (ICF) before any trial related activities and according to local guidelines. 2. Postmenopausal women (see inclusion criteria 3 from core phase) with hormone receptor-positive, HER2-negative advanced breast cancer not amenable to curative therapy. 3. Patient has been discontinued (any reason allowed) from treatment with ribociclib + letrozole in the core phase and is deemed suitable for treatment with alpelisib + fulvestrant in second line. Ribociclib + letrozole must be the last treatment regimen before alpelisib + fulvestrant. 4. Patient has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory. 5. Patient has HER2-negative breast cancer 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. 6. Patient has PIK3CA mutation as determined in tumor tissue and/or plasma by a Novartis designated laboratory. Results of tissue samples obtained during the core phase (screening or EOT) are acceptable 7. Patient has adequate bone marrow and coagulation function as shown by the following laboratory values: • Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L

	• Platelets ≥ 100 x 10^9/L (For patients with lesions involving the bone marrow, platelet count ≥ 75 x 10^9/L may be acceptable) • Hemoglobin ≥ 9.0 g/dL • INR ≤ 1.5 (INR ≤ 2.0 will be allowed for those patients treated with vitamin K antagonist) 8. Patient has adequate liver function as shown by: • In absence of liver metastases, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN or ≤ 5 x upper limit of normal (ULN) if hepatic metastases are present, • Total serum bilirubin < 2 x ULN (any elevated bilirubin should be asymptomatic at enrollment) except for patients with Gilbert's syndrome who may be included only if total bilirubin is ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN 9. Patient has adequate renal function: • Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 35 ml/min using Cockcroft- Fault formula 10. Patient has fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) ≤ 6.4% (both criteria have to be met) For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥ 5.7% (i.e. threshold for pre-diabetes) at screening, recommend lifestyle changes according to ADA guidelines (https://professional.diabetes.org/content-page/practice-guidelines-resources) and dietary advice (i.e. controlled carbohydrate intake, high fiber, low processed food intake, three macronutrient balanced meals and 2 small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended. 11. Patient has potassium, magnesium and calcium (corrected for albumin), within normal limits, or ≤ Grade 1 severity according to NCI-CTCAE v4.03 if judged clinically not significant by the investigator, or correctable with supplements before entry of study; re-screen is allowed. 12. Fasting serum amylase ≤ 2 × ULN. 13. Fasting serum lipase ≤ ULN. 14. Patient has ECOG (Eastern Cooperative Oncology Group) Performance Status ≤ 2.
Exclusion criteria	**Core phase** 1. Patient has a known hypersensitivity to ribociclib or letrozole or to any of the excipients of ribociclib or letrozole. 2. Patient who received prior treatment with any CDK4/6 inhibitor. 3. Patient who received any prior systemic hormonal therapy or chemotherapy for advanced breast cancer. Note:

	• Patients who received (neo)adjuvant therapy for breast cancer are eligible. If the prior (neo)adjuvant therapy included letrozole or anastrozole, the disease-free interval must be greater than 12 months from the completion of treatment until study entry. • Patients who received ≤ 28 days of letrozole or anastrozole for advanced disease prior to inclusion in this trial are eligible. 4. Patient is concurrently using other anti-cancer therapy. 5. Patient has had a major surgery within 14 days prior to starting study drug or absence of recovery from major side effects. 6. Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). 7. Patient who has received extended-field radiotherapy ≤ 4 weeks or limited field radiotherapy for palliation ≤ 2 weeks prior to start of treatment, or lack of recovery to grade 1 or better from related side effects of such therapy (except for alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). Patients for whom ≥ 25% of the bone marrow has been previously irradiated are also excluded. 8. Patient has concurrent malignancy or malignancy within 3 years prior to starting study drug, except for adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer. 9. Patient with central nervous system (CNS) metastases unless ALL the following criteria are met: • At least 4 weeks from prior therapy for CNS disease completion (including radiation and/or surgery) to start of the study treatment. • Clinically stable CNS lesions at the time of treatment initiation and not receiving steroids and/or enzyme-inducing anti-epileptic medications for the management of brain metastases for at least 2 weeks. 10. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). 11. Patient has a known history of HIV infection (testing not mandatory). 12. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal bacterial or viral infections, etc.). 13. Patient has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including but not limited to any of the following:

	• History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening • History of documented congestive heart failure (New York Heart Association functional classification III-IV) • Documented cardiomyopathy • Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block) • Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following: – Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia – Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication – Inability to determine the QT interval on screening (QTcF, using Fridericia's correction) • Systolic blood pressure > 160 mmHg or < 90 mmHg at screening 14. Patient is currently receiving any of the following medications and cannot be discontinued within 5 half-lives or 7 days prior to Cycle 1, Day 1, whichever is longer: • Concomitant medications, herbal supplements, and/or fruit (grapefruit pummelo, star fruit, Seville oranges) and their juices which are known strong inducers or inhibitors of CYP3A4/5. • Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 15. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airway diseases), eye drops or local injections (e.g., intra-articular). 16. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer. **Extension phase – patients with a PIK3CA mutation** Patients eligible for the extension phase must not meet any of the following criteria: 1. Patient has a known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib, or fulvestrant.

	2. Patient has received prior treatment with any PI3K, mTOR or AKT inhibitor. 3. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria: • At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. • Clinically stable CNS tumor at the time of screening untreated or without evidence of progressions for at least 4 weeks after treatment as determined by clinical examination and brain imaging (MRI or CT) during screening period and stable low dose of steroids for 2 weeks prior to initiating study treatment. 4. Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II (based on FPG and HbA1c, see inclusion criterion 10). 5. Patient has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer. 6. Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to enrollment, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia). 7. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting treatment with alpelisib or has not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g., intra-articular), stable CNS tumor on consistent low dose of steroids. 8. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not mandatory. 9. Any concurrent severe and/ or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic active hepatitis [testing is not mandatory unless required by local regulations], severe hepatic impairment, etc.). 10. Patients being concurrently treated with drugs recognized as being strong inducers of isoenzyme CYP3A or inhibitors of BCRP; switching to different medications prior to entry of treatment phase is allowed within the last 7 days prior to study treatment or within 5 half-lives, whichever is longer (see Appendix 14.2.2 for a complete list). 11. Patient has a history of noncompliance to medical regimens. 12. Patient with severe liver impairment (Child Pugh score B/C). 13. 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) based on investigator discretion.

	14. Patient has documented active pneumonitis / interstitial lung disease that requires treatment (chest CT scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present). 15. Patient has had major surgery within 14 days prior to starting treatment with alpelisib or has not recovered from major side effects. 16. Patient has any of the following cardiac abnormalities: • Symptomatic congestive heart failure i. History of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy ii. Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO) • History of angina pectoris, coronary artery bypass graft, symptomatic pericarditis or myocardial infarction ≤ 6 months prior to enrollment • Clinically significant cardiac arrhythmia (e.g., ventricular tachycardia), complete left bundle branch block, high grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block without pacemaker in place) • Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fredericia QT correction formula (QTcF) > 470msec at screening • Bradycardia (heart rate < 50 bpm at rest) by ECG or pulse 17. History of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis. 18. Patient has a history of severe cutaneous reactions such as Stevens-Johnson Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophils and Systemic Symptoms (DRESS). 19. Patient is concurrently using other anti-cancer therapy. Ribociclib and letrozole used in the core phase must be discontinued at least 7 days prior to day one of the extension study treatment. All drugs with overlapping toxicities must be discontinued within 7 days and AE resolved to NCI CTCAE v4.03 Grade ≤ 1 prior to study treatment. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study. 20. Patients with unresolved osteonecrosis of the jaw.
Investigational therapy	Ribociclib 600 mg oral daily (3 weeks on/1week off) in combination with letrozole 2.5 mg oral once daily.

	Alpelisib 300 mg oral daily on a continuous dosing schedule in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28 days cycle.
Assessments	**Biological assessments** **Ribociclib+ letrozole (Core phase)** • **Assessments in tumor tissue** Tumor tissue samples acquired at baseline and upon progression of disease (if clinically feasible) will be analyzed to assess mutational aberrations across different patient profiles. The analysis will include, but is not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN*. Tissue samples will also be used to evaluate changes over time, and to study tumor microenvironments and protein biomarkers. • **Assessments in blood** Blood samples will be collected at baseline, and then at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, as well as at EOT. Blood samples will be used to perform multiple gene assessments of ctDNA such as, but not limited to, *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN* and their association with resistance and clinical outcomes across different patient profiles. The findings will then be compared to those obtained on tissue biopsy. Serum samples will be used to measure TK1 activity. • [redacted] [redacted] [redacted] **Alpelisib + fulvestrant (Extension phase)** A tumor tissue sample (if clinically feasible) will be obtained at EOT upon progression of disease. Blood samples will be collected at extension screening (if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form), and then at Cycle 2-Day 1, at first imaging evaluation, as well as at EOT to perform multiple gene assessments of ctDNA. **Efficacy assessments** Tumor response will be assessed locally according to RECIST 1.1. **Safety assessments** • Physical examinations • ECOG performance status • Weight and vital signs • 12 lead ECGs (assessed locally)

	• Cardiac Imaging (MUGA or ECHO) (for extension phase only) • Laboratory assessments including hematology, chemistry, (assessed by local lab) • Adverse Events (AEs) collections
Data analysis	Data will be summarized with respect to demographic and baseline characteristics, safety observations and efficacy measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Analysis of primary endpoint: The proportions of patients with ctDNA alterations (i.e. such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN*) will be provided over time, separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases, to characterize the biological evolution of the disease in each patient. The association of these alterations with clinical outcomes will be also provided. In particular, the alterations will be analyzed at scheduled sample collections to define potential patterns of response, and at progression of disease to define potential mechanisms of resistance to CDK4/6 inhibitors and to alpelisib. Analysis of secondary endpoints: • Descriptive statistics of serum TK1 concentrations will be provided over time (i.e. as both absolute value and change from baseline value) for the ribociclib + letrozole treatment phase. The association of serum TK1 concentrations with clinical outcomes will also be provided. • The proportions of patients with ctDNA alterations (i.e. such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN*) will be provided over time, according to the scheduled sample collections, in the subsets of long responder patients (i.e. Time to Progression > 25 months) and those with early progression (i.e. patients progressed at first imaging evaluation). This analysis will be performed separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases.  • The proportions of patients with mutations as assessed at baseline by means of ctDNA sample and tissue biopsy will be provided and compared between the following patient profiles defined according to disease history (i.e. newly diagnosed vs. recurrent disease). This analysis will be performed separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases. • The proportions of patients with alterations detected at baseline and at disease progression will be compared between the two different

	procedures of detection (i.e. detection through liquid biopsy vs. tissue biopsy). This analysis will be performed separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases. [redacted] • Descriptive statistics of Time-to-Progression (TTP), defined as the time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer, will be provided. This analysis will be performed separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases. • Descriptive statistics of Overall Response Rate (ORR) and Clinical Benefit Rate (CBR) as defined by RECIST 1.1 for patients with measurable disease will be also provided. This analysis will be performed separately for the ribociclib + letrozole and alpelisib + fulvestrant treatment phases. • Descriptive statistics of Progression Free Survival on the second line treatment (PFS2), defined as the time from date of start of treatment to the date of event defined as the first documented progression on second-line treatment or death from any cause, will also be provided.

1 Background

1.1 Overview of breast cancer

Women in Italy account for 30 out of 59 million inhabitants, thus representing more than 50% of the entire population. According to the Italian National Institute for Statistics (ISTAT), women's life expectancy at birth increased by a rate of 4 months per year from 1950 to 2002, reaching 86.6 years. (Annuario statistico italiano, 2002). After cardiovascular diseases, tumors represent the first cause of death among women in Italy, each year killing 119 and 38 per 10,000 women in the 55–74 and ≥ 75 age groups, respectively (AIRT Working Group, 2006; Parkin et al., 2001). Breast cancer is the leading tumor among women in Italy. Official data from the Italian Ministry of Health estimated the total breast cancer incidence at 37,300 new cases in year 2005, with an overall prevalence of 416,000 cases (Grande, 2007). The incidence per age group was estimated to exceed 100 new cases every 100,000 women ≥ 40 years of age, rising to 200 new cases and to over 300 cases in women ≥ 50 and ≥ 60 years old, respectively. The number of deaths due to breast cancer in the Italian female population represented about 18% of the total cancer mortality rate in 1998, but the mortality rate has been reduced by 20% in the last 10 years (AIRT Working Group, 2006; ISTAT, 2005). In 2008, a total of 11,000 deaths were attributable to breast cancer among Italian women (AIRT Working Group, 2006; Piscitelli et al., 2009).

1.2 Introduction to investigational treatments

In approximately 70% of cases, women with breast cancer have hormone receptor-positive (HR+) tumors (Lim et al., 2012). Endocrine therapy is therefore standard treatment for either early or advanced HR+ cancer. Third-generation nonsteroidal aromatase inhibitors (NSAIs; e.g., anastrozole and letrozole) are among the preferred adjuvant therapy for postmenopausal women with HR+ advanced breast cancer and are widely used in a metastatic setting also (De placido et al., 2015). However, virtually all patients on NSAIs ultimately experience progression of disease, either as early failure of therapy or as relapse/progression after an initial response.
Studies of ER+ breast cancer cell lines indicate that estrogens and antiestrogens act in early to mid-G1 phase via cyclin D1 expression. G1/S transition is under the control of CDKs, particularly CDK4, CDK6 and CDK2. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase. The interplay between the ER pathway and the cell cycle control machinery – particularly the control of G1-S transition mediated by cyclin d and CDK 4/6 – provides a strong rational for the combined use of interventions designed to control both nodes as a way to stop the HR+ breast cancer proliferation. This mechanistic approach is corroborated by preclinical evidence of synergistic activity of CDK inhibitors and hormonal agents against HR+ breast cancer in cell lines and animal models and also clinical superiority with the combination (CDKi +hormonal agents) vs. endocrine therapy alone in recent phase II/III trials (PALOMA -1/2 with palbociclib; MONALEESA-2 with ribociclib) (Finn et al., 2009; Finn et al., 2015; Finn et al., 2016; Hortobagyi et al., 2016; Hortobagyi et al, ASCO 2017).

Ribociclib is a cyclin-dependent kinase 4/6 inhibitor and, in combination with an aromatase inhibitor, is approved by the FDA and EMA as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.
Alpelisib is an oral class I α-specific PI3K inhibitor and, in combination with fulvestrant, is approved by the FDA for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

1.2.1 Overview of ribociclib

Ribociclib is an orally bioavailable and highly selective small molecule inhibitor with highly specific nanomolar inhibitory activity against CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with half maximal inhibitory concentrations (IC50) of 0.01 and 0.039 μM in biochemical assays, respectively.

1.2.1.1 Non-clinical data

Ribociclib inhibits the phosphorylation of Rb at CDK4/6-binding sites with an average IC50 of 60 nM in Jeko-1 MCL cells that overexpress cyclin D1. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of ribociclib requires the presence of functional pRb.

Cardiac safety studies in vivo demonstrated QT prolongation with the potential to induce premature ventricular contractions (PVCs) at higher exposure levels. The effects of ribociclib

on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), kidney (concurrent degeneration and regeneration of tubular epithelial cells), 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. The hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) was identified as an additional target of toxicity that is not likely related to the primary pharmacology of ribociclib. Generally, all these effects of ribociclib demonstrated either reversibility or a clear trend towards reversibility. Ribociclib did not show an indication for a genotoxic potential. Reproductive studies in animals have demonstrated that ribociclib is embryotoxic, fetotoxic and teratogenic.

In vitro, ribociclib was a reversible inhibitor of human cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. Under therapeutic conditions, inhibition of CYP3A4 is likely to occur, while inhibition of CYP1A2 or CYP2E1 is not expected. The in vitro inhibitory potency of ribociclib for the transporters breast cancer resistance protein (BCRP), organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein-1 (MATE1), and bile salt export pump (BSEP) may translate into clinically relevant inhibition at therapeutic doses.

Elimination of ribociclib is prevalently by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). 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.

Refer to the most recent ribociclib Summary of Products Characteristics (SmPC) for additional details.

1.2.1.2 Clinical experience

Ribociclib is currently being investigated in patients with breast cancer in multiple clinical trials at different phases of development. Refer to the most recent ribociclib SmPC for details on clinical studies with ribociclib.

1.2.1.2.1 Clinical safety of ribociclib

The clinical safety of ribociclib with endocrine agents such as letrozole, tamoxifen, exemestane and fulvestrant has been evaluated in several phase I and III combination trials. The recommended dose of ribociclib in combination with these agents was declared as 600 mg qd on a 3 weeks on/1 week off schedule.

The safety profile of ribociclib in combination with letrozole was investigated in a randomized clinical trial of ribociclib and letrozole versus placebo and letrozole (CLEE011A2301) in 668 treatment-naive postmenopausal women with HR-positive, HER2- negative, advanced BC. The most common treatment-emergent AEs reported in the ribociclib arm in this study occurring in >30% of patients were neutropenia (74.3%), nausea (51.5%), infections (50.3%), fatigue (36.5%), diarrhea (35.0%), alopecia (33.2%) and leukopenia (32.9%). The most common grade 3 or 4 AEs reported in ≥5 % of patients in the ribociclib arm were neutropenia (59.3%), leukopenia (21.6%), hypertension (9.9%), increased alanine aminotransferase (9.3%), lymphopenia (6.9%) and increased aspartate aminotransferase (5.7%). Febrile neutropenia occurred in 1.5% of the patients in the ribociclib arm. Blood creatinine increases were reported

in 6.9% of patients. Four patients (1.2%) met the biochemical and clinical criteria for Hy's Law with 3 reported as treatment-related and all 4 returning to normal values after treatment discontinuation. Eleven patients (3.3%) presented on treatment QTcF prolongation >480 msec. Serious AEs were reported in 21.3% of patients in the ribociclib arm with 7.5% of serious AEs deemed by investigators as treatment-related. There were 3 fatal events in the ribociclib arm (disease progression, sudden death, unknown cause) with 1 AE (sudden death) reported as treatment-related in a patient that had grade 3 hypokalemia and grade 2 QTcF prolongation (483 msec). Neutropenia, QT interval prolongation and hepatobiliary toxicity are considered to be important identified risks for ribociclib and appear to be manageable and reversible with adequate monitoring, interruption and/or reduction of ribociclib dosing.

For a comprehensive review of the safety profile of ribociclib in combination with endocrine agents, refer to the most recent ribociclib SmPC.

1.2.1.2.2 Clinical efficacy with ribociclib

In a phase III randomized clinical trial of ribociclib and letrozole versus placebo and letrozole (CLEE011A2301) in 668 treatment-naive postmenopausal women with HR-positive, HER2-negative, advanced BC, ribociclib improved Progression Free Survival (PFS) (hazard ratio 0.56, 95% CI: 0 .43-0.72, p=0.00000329). The investigator-reported overall response rate was 40.7% (95% CI: 35.4%- 46.0%) in the ribociclib arm and 27.5% (95% CI: 22.8%-32.3%) in the placebo arm (p=0.000155) in the full analysis set; and 52.7% (95% CI: 46.6%, 58.9%) and 37.1% (95% CI: 31.1%, 43.2%) (p=0.00028) in patients with measurable disease at baseline (Hortobagyi et al., 2016).

An update to this study with an additional 11 months of follow-up reported a consistent improvement in PFS in comparison with the interim analysis. Median PFS was prolonged by 9.3 mo, from 16.0 mo (95% CI: 13.4–18.2) in the placebo + letrozole arm to 25.3 mo (95% CI: 23.0–30.3) in the ribociclib + letrozole arm (hazard ratio 0.568, 95% CI: 0. 457-0.704, p=0.0000000963). 24-mo PFS rates were 54.7% vs 35.9%. The investigator-reported overall response rate was 42.5% (95% CI: 37.2%-47.8%) in the ribociclib arm and 28.7% (95% CI: 23.9%-33.6%) in the placebo arm (in the full analysis set); and 54.5% (95% CI: 48.4%, 60.6%) and 38.8% (95% CI: 32.7%, 44.9%) in patients with measurable disease at baseline (Hortobyagi et al., Annals of Oncology, 2018).

Refer to the most recent ribociclib SmPC for additional details on the efficacy profile of ribociclib.

1.2.1.2.3 Clinical pharmacokinetics of ribociclib

Following oral dosing of the capsule formulation at 600 mg, ribociclib is rapidly absorbed with median Tmax of 2.40 h (range: 0.683 to 7.82 h). Steady-state plasma Cmax ranges from 606 to 6170 ng/mL (geometric mean: 1820 ng/mL or 4.1 μM) and AUC0-24h ranges from 6770 to 90600 ng*h/mL (geometric mean: 23800 ng*h/mL). The effective T1/2 of ribociclib is 32.0 h (range: 8.06 to 97.9 h). Inter-patient variability in Cmax and AUC is 62% and 66%, respectively, as assessed by geometric coefficient of variation. LEQ803, an active metabolite of ribociclib, has similar Pharmacokinetic (PK) characteristics as the parent drug. At the 600 mg dose level, LEQ803 accounts for approximately 8% of parent exposure after single and multiple doses.

Neither ribociclib nor LEQ803 accumulate substantially following repeated daily administration.

Ribociclib undergoes extensive hepatic metabolism via CYP3A in humans based on in vitro and in vivo studies. Ribociclib is mainly eliminated via hepatic clearance, with renal clearance playing a lesser role in humans. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Ribociclib accounted for approximately 23% of the total radioactivity in plasma. The most prominent metabolites in plasma are CCI284 (N-hydroxylation), LEQ803 (N-demethylation), and M1 (secondary glucuronide), each representing <10% of total radioactivity. The clinical activity (pharmacological and safety) of ribociclib is primarily due to the parent drug, with a negligible contribution from circulating metabolites.

Concomitant use of ribociclib with strong CYP3A4 inhibitors or strong CYP3A4 inducers should be avoided as ribociclib exposure may be markedly affected. Co-administration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib AUC by 3.2-fold following a single oral dose of 400 mg ribociclib (CLEE011A2101). Co-administration of a strong CYP3A4 inducer (rifampicin) decreased ribociclib AUCinf by 89% following a single oral dose of 600 mg ribociclib ([CLEE011A2101]).

Ribociclib is a moderate to strong inhibitor of CYP3A4 but did not have a substantial effect on CYP1A2 substrates in humans (CLEE011A2106). Co-administration of midazolam (CYP3A4 substrate) with multiple doses of ribociclib (400 mg) increased midazolam exposure by 3.8-fold. Co-administration of caffeine (CYP1A2 substrate) with multiple doses of ribociclib (400 mg) increased caffeine exposure by 20% (1.2-fold). Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided. Concurrent use of CYP1A2 substrates is not expected to lead to clinically important Drug-drug Interactions (DDI).

Food does not affect the PK of ribociclib administered as a capsule or tablet formulation; ribociclib capsules or tablets can therefore be taken without regard to meals ([CLEE011A2111], [CLEE011A2103]).

Refer to the most recent ribociclib SmPC for additional details.

1.2.2 Overview of letrozole

Letrozole (Femara®) is a nonsteroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens to estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces a 75% to 95% decrease of estrogen levels after two weeks of treatment using daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities nor changes in levels of other hormones of the endocrine system as shown in early phase I (Lipton 1995; Trunet 1996). It is indicated for the adjuvant treatment of women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy. It is also indicated for the treatment of advanced HR+ breast cancer, both in the first-line setting as well as in patients who have disease progression following anti-estrogen therapy. Letrozole was compared with tamoxifen in a phase III trial in the first-line setting in ER+/HER2+ breast cancer. Letrozole was superior to tamoxifen for time

to progression (median, 9.4 v. 6.0 months) and median Overall Survival (OS) trended superior for letrozole (median, 34 versus 30 months) but this difference was not statistically significant (Mouridsen 2001). Trials recently reported – where single-agent letrozole was studied as control arm - demonstrated a median PFS with this agent in 1st line ranging from 14.4 to 15.6 months (Dickler et al 2016; Martin et al 2015; Finn et al 2016).

Letrozole is administered orally once daily at a dose of 2.5 mg and is rapidly and completely absorbed from the gastrointestinal tract. Concomitant intake of food has no effect on the extent of letrozole absorption and only a minor effect on the rate of absorption, which is considered to be of no clinical relevance. The terminal elimination half-life of letrozole is 2 days and steady-state plasma concentration with daily dosing at the standard dose is reached in 2-3 weeks. Letrozole is metabolized via CYP3A4 to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzonitrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. In addition, CYP2A6 forms the carbinol metabolite as well as its ketone analog [Femara® Prescribing Information, Novartis].

The most frequently reported adverse events that were significantly different from placebo for letrozole in the adjuvant and extended adjuvant setting include hot flashes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flashes, nausea and dyspnea and incidences of adverse events were similar for tamoxifen in this setting. In general, the observed adverse reactions are mild to moderate in nature [Femara® Prescribing Information, Novartis].

1.2.3 Low potential for interaction between ribociclib and letrozole

Letrozole is not expected to affect the metabolism of ribociclib, which is mainly metabolized by CYP3A4 with a 15-26% contribution by the polymorphic enzyme FMO3 (flavin-containing monooxygenase 3) based on in vitro data. Letrozole inhibits CYP2A6 (Ki = 4.6 μM) and CYP2C19 (Ki = 42 μM) in vitro (Jeong 2009; Femara® Prescribing Information) but is not an inhibitor of CYP3A4 or FMO3 and is therefore not expected to affect ribociclib metabolism.

Ribociclib may increase the exposure of co-medications that are substrates of CYP3A4 due to time-dependent inhibition of this enzyme. In vitro studies indicate ribociclib is a reversible inhibitor of CYP3A4 (Ki = 35 μM) and a time-dependent inhibitor of CYP3A4 (KI = 5.06 μM, kinact = 0.0245 min-1). Letrozole is metabolized via CYP3A4 and CYP2A6 (Femara® Prescribing Information) and hence letrozole concentrations could be affected by coadministration with ribociclib. Preliminary PK data for the combination of ribociclib (600 mg) and letrozole (2.5 mg) indicate ribociclib and letrozole exposures are within the range of values for the respective single agent and the combination is safe and tolerable.

1.2.4 Overview of alpelisib

Alpelisib is an oral alpha-specific class IA PI3K inhibitor belonging to the 2-aminothiazole class of compounds. Alpelisib potently inhibits p110α in its wild-type form as well as when constitutively activated by somatic mutations, and inhibits less strongly the β, δ, and γ isoforms of PI3K.

Alpelisib has demonstrated anti-tumor activity in preclinical in vitro and in vivo tumor models. In vitro, alpelisib has been shown to preferentially inhibit the proliferation of cell lines

harboring PIK3CA mutations (Fritsch 2014). In vivo, alpelisib has demonstrated dose-dependent tumor growth inhibition in various subcutaneous tumor transplant models.

For further details on clinical and non-clinical experience, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.4.1 PI3K pathway

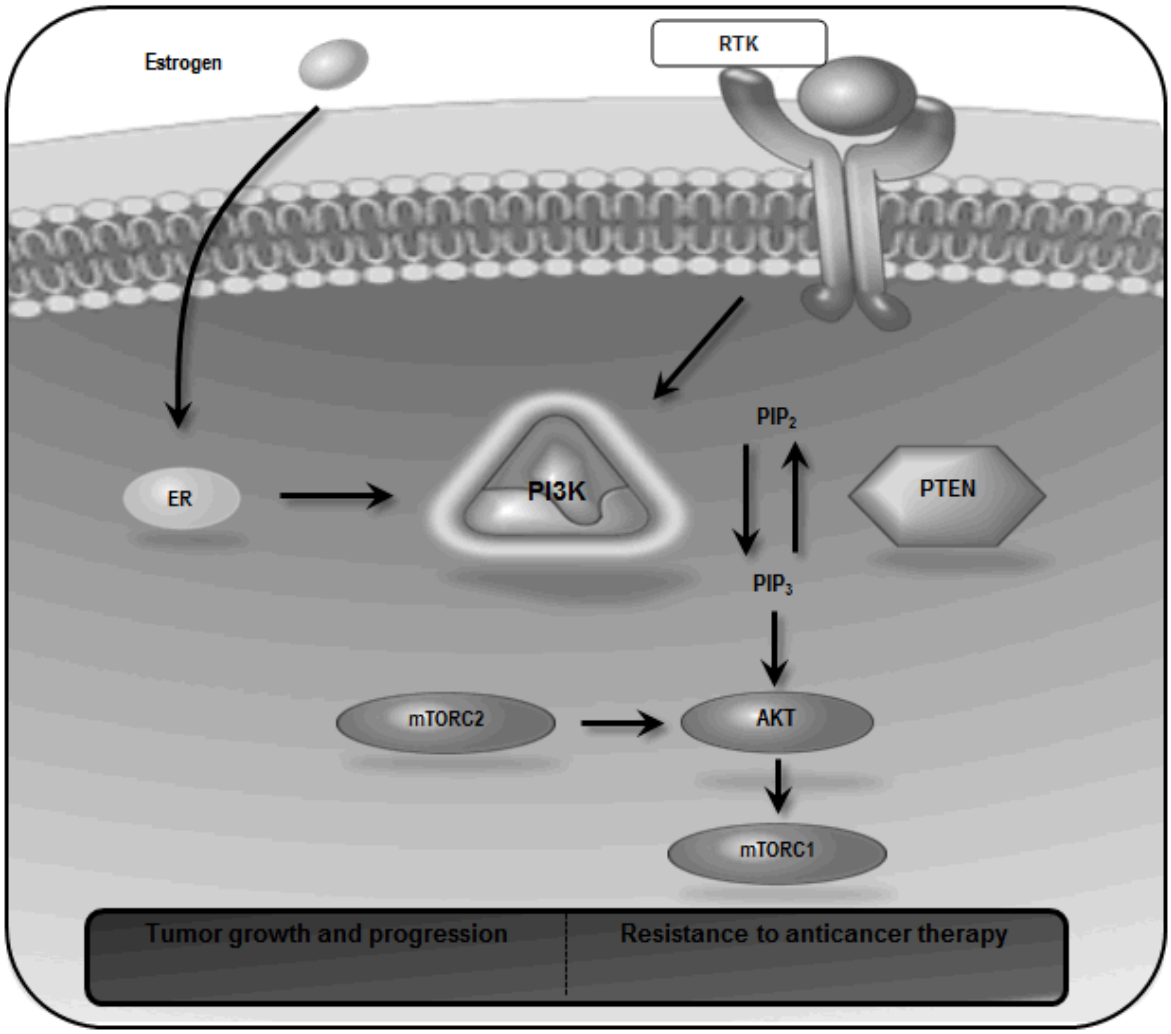
The phosphatidylinositol-3-kinase (PI3K) signaling regulates diverse cellular functions, including cell proliferation, survival, translational regulation of protein synthesis, glucose metabolism, cell migration, and angiogenesis (Katso 2001). PI3K signaling also serves a central role in the pathogenesis of numerous forms of neoplasia. Constitutive activation of PI3K signaling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors and in many tumor types (Liu 2009). Resistance to a variety of therapeutic interventions, including chemotherapy, hormonal therapy and anti-HER2 therapies, can also be linked to constitutive activation of the PI3K pathway (McCubrey 2006).

Molecular changes leading to constitutive activation of the PI3K pathway are diverse and include, but are not limited to:

- Gain-of-function mutations of PI3K subunits (PIK3CA encoding the PI3K catalytic subunit p110α; genes encoding the p85 regulatory subunit) or oncogenes encoding positive regulators of PI3K (e.g., HER2, EGFR, RAS, Src-family proteins) or
- Loss-of-function mutations or epigenetic alterations affecting negative regulators of PI3K signaling (e.g., loss of Phosphatase and Tensin Homolog (PTEN) expression or function) (Chow 2006; Cully 2006).

A schematic representation of these PI3K components is shown below:

Figure 1-1 Schematic representation of the PI3K pathway



Somatic missense mutations of PIK3CA that increase the kinase activity of PIK3α protein have been identified in tumor tissues and have been linked to cellular transformation in many different human cancers (Samuels 2004). The majority of somatic mutations were identified in mutational hotspots affecting the helical (exon 9) and kinase (exon 20) domains of the protein (Karakas 2006). However, some mutations were also identified in other domains of PI3K, such as the C2 domain (Bader 2005; Samuels 2004). Mutations affecting the helical or kinase domains were shown to enhance PI3K lipid kinase activity, to up-regulate the pathway downstream (increasing intracellular levels of phospho-AKT and phospho-S6), to drive cellular transformation in vitro and in vivo, and to enhance cell survival (Zhao 2008, Mankoo 2009). Mutations in the C2 domain were shown to induce or facilitate conformational changes leading to an increased activity of PI3Kα (Burke 2012, Hon 2012). Overall, the majority of gain-of function mutations identified in the PIK3CA gene were reported to occur in the mutational hotspots from exons 7, 9 and 20 which affect the C2, helical and kinase domains of PI3Kα respectively (Mankoo 2009).

1.2.4.2 PI3K pathway in HR+ breast cancer

The PI3K pathway is frequently altered in HR+ breast cancer. Gain-of-function mutations in PIK3CA have been observed in about up to 45% of HR+ breast cancer patients using next generation sequencing (NGS) approach (see Table below).

Table 1-1 PI3K signaling pathway mutations and alterations in breast cancer

	PIK3CA mutation	PTEN mutation/loss
All breast tumors	36%	NR
HR+ HER2-	45%	13%
Triple negative	9%	35%
HER2- positive	39%	4%
Cancer Genome Atlas Network 2012		

Pre-clinical data suggest that the ER pathway interacts with the PI3K pathway with extensive crosstalk between ER and growth factor pathway (Miller 2011; Osborne and Schiff 2011).

For example, estrogen deprivation leads to hyperactivation of the PI3K/mTOR pathway, which induces in turn an increase in cell proliferation and survival (Bjornsti 2004; Crespo 2002; Huang 2004; Mita 2003; Wullschleger 2006). This mechanism is linked to de novo or acquired resistance to endocrine therapy (Campbell 2001), including AI resistance (Shoman 2005; Crowder 2009; Miller 2011). Treatment with PI3K inhibitors in absence of estrogen can inhibit proliferation of long-term estrogen deprived cell lines supporting the concept of using combination of a PI3K inhibitor with an endocrine therapy in breast cancer.

More specifically, inhibition of the PI3K pathway has been shown to induce a unique synthetic lethality in the context of estrogen deprivation (Crowder 2009).

1.2.4.3 Non-clinical experience

1.2.4.3.1 Pharmacodynamics of alpelisib

In biochemical assays, alpelisib specifically inhibits the p110α sub-unit [redacted] more potently than the p110δ and γ isoforms. Alpelisib is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α. The biological activity of alpelisib correlates with inhibition of various PI3K/AKT downstream signaling pathway components commonly used as indicators of pharmacodynamics. Please refer to the [Alpelisib Investigator's Brochure] for further details.

In vivo, alpelisib shows dose and time-dependent inhibition of the PI3K/AKT pathway in relevant tumor xenograft models (p110α-mechanistic model and p110α-mutant xenograft models) in nude mice and rats. In vivo analyses of tumor tissues, upon acute dose or after repeated dosing, show a good correlation between compound exposure and PI3K pathway blockade (Fritsch 2014).

Finally, in breast cancer xenograft models, treatment with alpelisib led to a significant decrease in AKT phosphorylation, further supporting the observation of effective inhibition of PI3K signaling.

In vitro and in vivo non-clinical studies with alpelisib in combination with fulvestrant demonstrated a synergistic effect of the two drugs. The combination of alpelisib with fulvestrant demonstrated an increased anti-tumor effect compared to fulvestrant alone in ER+ breast cancer xenograft models (Fritsch 2014).

1.2.4.3.2 Nonclinical PK and metabolism of alpelisib

Alpelisib has low plasma clearance, a moderate volume of distribution at steady state and good absolute oral bioavailability in all preclinical species tested. The compound is moderately bound to plasma proteins with no major species difference and this binding is independent of concentration [redacted] Alpelisib showed rapid distribution to almost all rat tissues except the brain (rat Absorption Distribution Metabolism and Excretion study [ADME]). Results from 4-week Good Laboratory Practice (GLP) toxicology studies in dogs showed a roughly dose-proportional increase in exposure, while in rats exposure increased up to a dose of [redacted] beyond which no further increase was noted following single dose administration. The toxicology studies provided no clear evidence of increase in exposure following multiple dosing. No gender differences in exposure were observed in rats or dogs.

***In vitro* metabolism and transport**

The overall metabolic turnover of alpelisib was very low in dog and human hepatocytes (as well as microsomes) and slightly higher in the rat. CYP3A4 was found to be the major P450 enzyme involved in hepatic oxidative metabolism *in vitro* with small contribution by other enzymes. While UGT phenotyping showed that UGT1A9 could be involved in the glucuronidation of alpelisib in human liver microsomes, the turnover rate of phase II metabolism in vitro was very low. No covalent drug protein adduct formation was noted in human microsomes or hepatocytes. The main biotransformation pathway that was observed consistently *in vitro* and *in vivo* (see below) across species was amide hydrolysis to BZG791, a pharmacologically inactive product which – based *on vitro* experiments – can be produced both chemically and enzymatically by ubiquitously expressed, high-capacity enzymes (esterases, amidases, choline esterase) unlikely to become fully inhibited by drug interactions.

Alpelisib was found to be a time-dependent inhibitor of CYP3A4 ([redacted]. Reversible inhibition of CYP2C8 [redacted] CYP2C9 [redacted] and CYP2C19 [redacted] was also observed. Alpelisib may inhibit metabolic clearance of co-medications metabolized by CYP3A4, CYP2C8, CYP2C9 and CYP2C19 if sufficiently high concentrations are achieved in vivo. A risk assessment based on the mechanistic static model (or a "net effect model") (Fahmi 2008), assuming a very sensitive substrate (fm =1) and no gut metabolism (FG = 1), predicted an AUCR to be <1.1 with the lowest measured Ki for CYP2C9 at the calculated unbound hepatic inlet concentration (1.2 µM) at Maximum Tolerated Dose (MTD) level dose. Hence it is unlikely that inhibition of CYP2C9 or other CYP2C-family enzymes, which showed an even less inhibitory potential, translates into a clinically relevant interaction.

While clinically significant pregnant X receptor-(PXR)-mediated induction of CYP3A4 or aromatic hydrocarbon receptor-mediated induction of CYP1A2 by alpelisib has not been expected based on the negative result from in vitro nuclear activation assays, there has been recent growing evidence from a hepatocyte induction assay that alpelisib can induce CYP3A4 [redacted] likely via activation and crosstalk with

the constitutive androstane receptor. [redacted]

Alpelisib is a substrate of the Breast Cancer Resistance protein (BCRP) and has low affinity for P glycoprotein (P-gp/MDR1). Alpelisib does not inhibit BCRP or Multi-drug resistance protein-2 but showed very weak inhibition of P-gp [redacted] As the maximal inhibition of P-gp was only about 32% with respect to positive control, the overall interaction potential is expected to be low. Uptake of alpelisib in human hepatocytes was not influenced by inhibitors of the organic cation transporter, organic anion transporter, organic anion-transporting polypeptide and sodium taurocholate co-transporting polypeptide. Assessment of the hepatobiliary disposition mechanisms of alpelisib in sandwich cultured rat and human hepatocytes showed that it is actively transported into bile pockets.

Disposition of alpelisib

At the current stage of knowledge, elimination of alpelisib *in vivo* appears to be a three-parted pathway consisting of CYP450-mediated oxidative metabolism, hydrolysis to BZG791 (enzymatic or chemical, currently unknown) and biliary elimination. Recent results from the human ADME trial [CBYL719X2107] have shown that the contribution of oxidative metabolism to the overall clearance of alpelisib can be considered minor, in line with *in vitro* metabolism results. [redacted] In terms of excretion, the bulk of the dose was excreted in feces (78.8% of the dose) and urine (13.1 % of the dose) with only ~2% of unchanged alpelisib in urine indicating that renal clearance is negligible. [redacted] As alpelisib is a substrate for human BCRP *in vitro,* there is strong evidence for a hepatobiliary excretion, which is also supported by rat and human sandwich-cultured hepatocyte experiments.

For further details on nonclinical PK and metabolism experience, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.4.3.3 Safety pharmacology and toxicology of alpelisib

PI3 kinase is involved in various cellular processes such as proliferation, metastasis and energy metabolism. Therefore, toxic effects are not expected when cellular test systems or animals are exposed to an inhibitor of this pathway. In accordance with current guidance, repeated-dose toxicity studies of up to 13 weeks duration with daily oral treatment were conducted. In the 4-

and 13-week studies, reversibility of toxicity findings was assessed for a 4-week treatment-free recovery period (8 weeks in the 13-week rat study). This package was complemented by *in vitro* and *in vivo* safety pharmacology studies to investigate effects on respiratory, neuronal and cardiovascular functions, an ICH-compliant genotoxicity battery and the evaluation of a phototoxic potential *in vitro*.

Alpelisib was relatively well tolerated in the 4- and 13-week repeated-dose toxicity studies at exposure levels at which tumor growth control was achieved in mouse or rat tumor models. Alpelisib affected rapidly dividing tissues resulting in pharmacologically relevant observations only in animals exposed to an alpelisib dose close to or at MTD. The most frequently affected organs were the bone marrow and lymphoid tissue (spleen, thymus), and the epithelia of the alimentary tract, while other tissues like the vagina and uterus in rats, or prostate in dogs were also affected at higher doses.

Abnormal clinical chemistry and histopathology (pancreatic islets) findings indicated an altered glucose metabolism, correlating with a clear effect towards insulin insensitivity. In both rats and dogs, histopathology and clinical pathology findings were generally observed at higher doses that were also associated with reduced body weight development (in growing animals) and reduced food intake. All toxic events were reversible or showed a tendency to reversibility after a 4-week or 8-week treatment-free recovery period.

Cardiac safety studies, conducted *in vitro* and *in vivo*, did not indicate an electrophysiological risk. Furthermore, alpelisib in the rat safety pharmacology studies showed no effect on neuronal or pulmonary function, and no evidence of a phototoxic potential was found in a 3T3 neutral red uptake test *in vitro*.

The majority of the observed toxicological effects of alpelisib were related to the pharmacological activity of alpelisib as a p110α specific inhibitor of the PI3K pathway, such as an influence on insulin (and potentially glucose) homeostasis and the risk of increased blood pressure. Pharmacologically relevant toxicity was mainly observed at dosages close to or at MTD with the bone marrow and lymphoid tissue, pancreas, and some reproductive organs of both genders being the main target organs of the toxic effects.

For further details on safety pharmacology and toxicology, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.4.3.4 Genotoxicity status of alpelisib and metabolites

There is no evidence of a potential to induce reverse gene mutations or numerical or structural chromosome aberrations. For further details on genotoxicity data, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.4.4 Clinical experience

As of the cut-off date of 13 May 2019, approximately 3100 patients have been enrolled in alpelisib studies.

Alpelisib (Piqray®) was first approved in May 2019 in the United States and is indicated in combination with fulvestrant for the treatment of postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative PIK3CA

mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

Alpelisib has been investigated both as a single agent and as combination therapy in 25 clinical studies and as of 13 May 2019, 17 studies have been completed and 8 are ongoing. The safety profile of alpelisib is well characterized and manageable with generally reversible AEs.

The most common adverse events observed with treatment of alpelisib alone or in various combinations are hyperglycemias, rash or GI disorders (nausea, vomiting and diarrhea). Other reported adverse events include but are not limited to hypersensitivity, pneumonitis, and severe cutaneous reactions.

In summary, current data indicate a favorable clinical safety profile for alpelisib.

Study [CBYL719X2101] was a phase IA, multicenter, open-label, dose-escalation study with a dose expansion arm of single-agent alpelisib in patients with PIK3CA-altered advanced solid tumors, PIK3CA-altered or wildtype ER+ breast cancer. Alpelisib was administered orally as a tablet using doses ranging from 30 to 450 mg q.d., and 120 to 200 mg b.i.d. The trial enrolled 132 patients with advanced solid tumors and the single agent MTD was established as 400 mg q.d., and the recommended phase II dose (RP2D) was determined to be 350 mg q.d. The most frequent observed AEs were hyperglycemia (47%), nausea (46%), diarrhea (38%), decreased appetite (37%), fatigue (29%) and vomiting (27%). The most common drug-related Grade 3 or 4 adverse event was hyperglycemia (24%). Other Grade 3 or 4 AEs occurred in three patients, in all cases maculopapular rash. Among the 131 evaluable patients, confirmed partial response (PR) was observed in 7 patients (5.3%), with 8 (6.0%) that achieved an unconfirmed PR. Stable disease (SD) was observed in 68 patients (52%) with a disease control rate (CR/PR/SD) of 53%. All tumor responses were observed at alpelisib doses of 270 mg or higher (Juric 2014).

Overall, 20 patients with ER+, PIK3CA-altered metastatic breast cancer received alpelisib as part of the phase I study (Juric 2016). Sixteen out of 20 patients had received some form of chemotherapy and most patients had received multiple prior lines of hormonal therapy, including AIs, tamoxifen and fulvestrant. Hyperglycemia was observed in 13/20 patients (65%), with Grade 3 or 4 in 5/20 (25%) of patients. Rash was observed in 11/20 patients (55%), with Grade 3 or 4 in 3/20 (15%) of patients. GI events and fatigue/asthenia were also among the most commonly reported AEs. Overall, the safety profile of alpelisib in patients with advanced breast cancer was comparable to that seen in patients with other solid tumors. Eighteen of the 20 patients received doses of ≥ 270 mg/day. Among the 18 patients evaluable for radiologic response, 6 patients achieved tumor shrinkage >20%, with 2 patients demonstrating a PR (1 confirmed, 1 unconfirmed). Among the 11 patients who received study treatment for ≥16 weeks, 2 patients had PR and 9 had SD. Median PFS for the 20 breast cancer patients was 166 days (5.5 months); 95% CI: 110–286 days.

For further details on clinical experience please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.4.5 Clinical pharmacokinetics

Clinical PK data of alpelisib after single dosing in 108 patients and multiple daily dosing (as single agent) in 26 patients is available from the first-in-human trial [CBYL719X2101]. Plasma concentrations of alpelisib generally declined in a mono-exponential manner, suggesting

limited distribution towards peripheral tissues. Median terminal T1/2 generally appeared to be independent of dose and time, ranging between 6.1 and 10.5 hours at steady state. Half-life after a 400 mg q.d. dose was approximately 7 to 8 hours. Steady-state alpelisib plasma levels after daily dosing can be expected to be reached at 2 to 3 days following onset of therapy in most patients. The median accumulation ratio (Racc) of alpelisib across all dose levels and regimens ranged between 1.0 and 2.0, which is in agreement with the short T1/2 of alpelisib. At 400 mg q.d. the median Racc was 1.2 after 1 week.

In adult subjects who received alpelisib 300 mg once daily in the SOLAR-1 trial, mean steady-state alpelisib (coefficient of variation [%CV]) Cmax was [redacted] No clinically significant differences in alpelisib AUC were observed between low-fat low-calorie and high-fat high-calorie meals. Alpelisib can be co-administered with acid reducing agents as long as it is taken after food, since food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH.

Alpelisib is primarily metabolized by chemical and enzymatic hydrolysis to form its metabolite BZG791 and to a lesser extent by CYP3A4 in vitro. [redacted] Excretion of unchanged alpelisib occurs primarily via hepatobiliary export and/or intestinal secretion of alpelisib. As alpelisib is a substrate of BCRP, its elimination may be affected when co-administered with BCRP inhibitors.

Alpelisib inhibits CYP3A4 in a time-dependent manner and induces CYP2B6, CYP2C9 and CYP3A4 *in vitro*. Alpelisib is an inhibitor of P-gp. No clinically significant differences in the pharmacokinetics of everolimus (a substrate of CYP3A4 and P-gp) were however observed when coadministered with alpelisib. Alpelisib has a low potential to inhibit BCRP (Breast Cancer Resistance Protein), MRP2, BSEP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, OCT2, MATE1, and MATE2K at clinically relevant concentrations.

For further details on clinical pharmacokinetics, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.5 Overview of fulvestrant

Fulvestrant (Faslodex®) is the first-in-class unique ER down-regulator with no known agonist effects (Addo 2002). In fact, the fulvestrant mechanism of action is distinct from other endocrine agents (Wakeling 2000) as it binds, blocks and, unlike tamoxifen or other Selective estrogen receptor modulator (SERM), degrades the ER and completely inhibits ER signaling.

As a result, there is less chance of the ER being activated by alternative pathways that are believed to cause resistance (e.g. growth factor–mediated mechanisms) (Nicholson 2005).

Fulvestrant is approved for the treatment of HR+ mBC in postmenopausal women with disease progression following anti-estrogen therapy (USA, Europe). However, current clinical practice and treatment guidelines also include fulvestrant as treatment option for postmenopausal women without symptomatic visceral disease after recurrence or progression to an aromatase inhibitor (NCCN 2017).

The most common clinically significant adverse reactions occurring in ≥5% of patients receiving fulvestrant 500 mg were: injection site reactions, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremities, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Pooled safety analysis (SmPC) identified Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or alkaline phosphatase increases in approximately 15% of the treatment population with grade 3 increases seen in 1-2%. There was no difference in rates of AST, ALT and AP elevations between groups treated with 250 mg and 500 mg doses. For further details please refer to the latest [Faslodex® Prescribing Information].

The phase III FALCON trial demonstrated superior median PFS for fulvestrant 500 mg q.d. compared to anastrozole 1 mg in the 1st line treatment of postmenopausal women with locally advanced or metastatic breast cancer who have not had prior hormonal treatment for hormone receptor positive (HR+) breast cancer. The results show that median PFS was 2.8 months longer with fulvestrant than with anastrozole (Hazard ratio 0.797; 95% CI: 0.637-0.999; p=0.0486). Median PFS was 16.6 months in the fulvestrant arm, compared with 13.8 months in the anastrozole arm. The most commonly reported adverse events in the fulvestrant and anastrozole arms were arthralgia (16.7% vs 10.3%), hot flashes (11.4% vs 10.3%) and nausea (10.5% vs 10.3%), respectively (Robertson 2016). Fulvestrant has since (2017) received approval for first line indication in the US and Europe.

1.2.5.1 Clinical pharmacokinetics of fulvestrant

The recommended dose (intramuscular injection) is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. Fulvestrant is slowly absorbed reaching maximum plasma concentrations after about 5 days. Steady-state is achieved within the first month of dosing. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40-50 days. An in vitro inhibition study showed no relevant inhibition of CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. CYP3A4 is the only P450 isoenzyme involved in the oxidation of fulvestrant; however, non-P450 routes appear to be more predominant in vivo as interaction studies with rifampicin (CYP3A4 inducer) and ketoconazole (CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. The relative contribution of P-450 and non-P-450 routes in vivo is unknown [Faslodex® Prescribing Information]. The potential for interaction with fulvestrant therefore appears to be low.

Increased exposure to fulvestrant was observed in patients with moderate hepatic impairment (Child-Pugh class B); therefore a dose of 250 mg is recommended in these cases. Fulvestrant has not been administered to patients with severe hepatic impairment (Child-Pugh class C). For further details on the clinical pharmacokinetics of fulvestrant, please refer to the latest [Faslodex® Prescribing Information].

1.2.6 Overview of the combination of alpelisib and endocrine treatments

Pre-clinical data showing potential for cell death in addition to decreased proliferation have been observed when PI3K inhibitors are given in combination with hormonal therapy. In vitro combination of letrozole or fulvestrant with alpelisib in a PIK3CA mutant cell line of ER+ breast cancer (MCF7) displays synergy (O'Brien 2014) in line with the concept of synthetic lethality seen previously when PI3K was inhibited in an estrogen deprived cell line (Crowder 2009). For further details on preclinical experience, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.6.1 Experience with alpelisib and fulvestrant in metastatic breast cancer

The combination of alpelisib with fulvestrant was investigated as part of study [CBYL719X2101] in 87 patients with heavily pre-treated HR+ metastatic breast cancer in two groups: patients with a PIK3CA mutation (52 patients, 59.8%) and patients with wild-type PIK3CA (33 patients, 37.9%). For two patients (2.3%), PIK3CA mutational status was unknown. The MTD was established at alpelisib 400 mg QD and fulvestrant 500mg q28 days, with DLTs in 4 patients (diarrhea, vomiting, decreased appetite, abdominal distension and fatigue). Alpelisib doses of 350 mg and 300 mg QD were also investigated and mainly 300 mg QD emerged as the best tolerated dose in this combination. Overall, the most frequent AEs (>20%), regardless of grade, causality and alpelisib dose, suspected of being drug related were diarrhea (56.3%), nausea (42.5%), hyperglycemia (48.3%), decreased appetite (37.9%), fatigue (29.9%), vomiting (25.3%), stomatitis (27.6%) and fatigue (29.9%). The preliminary clinical efficacy of alpelisib + fulvestrant was demonstrated across all dose levels. Best overall response (BOR) achieved was confirmed PR for 13 (26.5%) patients and SD for 26 (53.1%) patients with PIK3CA mutant tumors versus PR for 0 (0%) patient and SD for 15 (46.9%) patients with PIK3CA non-mutant tumors. The disease control rate was 79.6% (95% CI: 65.7–89.8) and 46.9% (95% CI: 29.1–65.3) in the PIK3CA mutant and PIK3CA non-mutant groups, respectively. Estimated median PFS was longer in the PIK3CA mutant group vs PIK3CA non-mutant group (9.1 months vs 4.7 months) (Juric 2016). This data led to a design of a phase III randomized, double-blind, placebo-controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer that progressed on or after aromatase inhibitor treatment (SOLAR-1, [CBYL719C2301]).

The SOLAR-1 trial randomly selected 572 postmenopausal women or men with HR-positive, HER2-negative advanced breast cancer; 341 had PIK3CA mutations when tumor tissue was tested. The patients had received one or more prior lines of hormonal therapy but no chemotherapy for advanced breast cancer. They had not previously received fulvestrant (Faslodex) or any PI3K, Akt, or mTOR inhibitor, and were not on concurrent anticancer therapy. Patients were randomly assigned to receive oral alpelisib (300 mg/d) or placebo plus intramuscular fulvestrant (500 mg every 28 days and on days 1 and 15 of treatment cycle 1). The primary endpoint was locally assessed progression free survival in patients with PIK3CA mutations detected in tumor tissue. Results showed that PFS was nearly twice as long in patients with PIK3CA mutations randomly assigned to receive alpelisib compared to the placebo group. Median PFS was 11.0 months in the alpelisib arm compared to 5.7 months in the placebo group (HR 0.65, 95% CI 0.50–1.25, P = .00065) at a median follow-up of 20.0 months. Just over one-

third (36%) of patients with measurable PIK3CA-mutated advanced breast cancer (n = 262) responded to alpelisib plus fulvestrant, whereas the overall response rate in the placebo/fulvestrant group was 16% (*P* = .0002). The secondary endpoint of locally assessed progression-free survival in patients without PIK3CA mutations did not meet the predefined proof of concept endpoint (hazard ratio = 0.85, 95% confidence interval = 0.58–1.25, median = 7.4 vs 5.6 months) The Most frequent all-grade adverse events (AEs; ≥40% in either arm by single preferred term; ALP+FUL vs PBO+FUL) were hyperglycemia (65% vs 9%), diarrhea (54% vs 11%), nausea (46% vs 20%), and rash (40% vs 6%). Grade 3/4 AEs in ≥10% pts in either arm were hyperglycemia (fasting plasma glucose >250mg/dL; 37% vs <1%) and rash (13% vs <1%); discontinuations of ALP+FUL/PBO+FUL due to AEs were 3% vs 2% (ESMO 2018). In the SOLAR-1 trial, 20 patients with a PIK3CA mutation and who had previously received a CDK4/6 inhibitor as first line treatment for aBC were enrolled. The patients treated with alpelisib in combination with fulvestrant (9 patients) showed a prolonged PFS respect to the ones treated in monotherapy with fulvestrant in the control arm. Therefore, a benefit was demonstrated but more data on efficacy and biomolecular evolution during this treatment sequencing should be collected (Juric, 2018).

For further details on clinical experience, please refer to the latest version of the [Alpelisib Investigator's Brochure].

1.2.6.2 Potential for drug interactions

Based on the fulvestrant prescribing information and current compound and class related risks identified for alpelisib, the following overlapping toxicities might occur:

- Nausea, vomiting, diarrhea
- Skin alterations/rash

The potential for a drug-drug interaction between fulvestrant and co-administered drugs is considered to be low. There are no known drug interactions with fulvestrant. *In vitro* studies showed no relevant inhibition of the major CYP enzymes, including CYP1A2, 2C9, 2C19, 2D6 or 3A4 by fulvestrant. The lack of inhibition of CYP3A4 was confirmed in an *in vivo* interaction study with midazolam. In addition, interaction studies with rifampicin (strong CYP3A4 inducer) and ketoconazole (strong CYP3A4 inhibitor) demonstrated no effect on fulvestrant pharmacokinetics. Therefore, a DDI involving fulvestrant and alpelisib is unlikely to occur [Faslodex® Prescribing Information].

2 Rationale

2.1 Study rationale and purpose

The present study is divided into a core phase and an extension phase. In the core phase, postmenopausal women with HR+, HER2- advanced breast cancer who have not received any prior agent for treatment of advanced disease will be treated with ribociclib + letrozole and followed until discontinuation of treatment due to any cause. Discontinued patients with PIK3CA mutations will subsequently enter the extension phase and undergo treatment with alpelisib + fulvestrant in second line. Second line treatment is defined in this protocol as the

second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression).

2.1.1 Core phase

Although the results of the MONALEESA 2 study appear impressive, some patients do not respond to therapy and others eventually progress, underscoring the need to discover mechanisms of de novo or acquired resistance to ribociclib/letrozole. Among the various strategies to adopt, a better understanding of the molecular and genetic characteristics of each tumor is critical for defining the best choice of drugs to be given, depending on the expression or the mutational status of the targets at the tumor level (Cicciolini et al., 2015).

A review of clinical trials by Garrido-Castro and Goel evaluated potential biomarkers that may predict response and resistance to CDK4/6 inhibitors (Garrido-Castro et al., 2017). The following biomarkers were identified:

Potential biomarkers of response

- Estrogen receptor (ER) positivity: Given the biologic rationale for using CDK4/6 inhibitors in ER+ tumors (ER-driven cyclin D1 expression and higher Rb levels), ER positivity is a useful and approved clinical marker to identify potential candidates for CDK4/6 inhibitor therapy. It however remains unclear as to whether this is the only subgroup of tumors that derive benefit from these agents. For example, results from the PALOMA-3 trial indicate that fulvestrant + palbociclib is associated with a significant and consistent improvement in progression-free survival compared with fulvestrant + placebo irrespective of the degree of endocrine resistance and hormone-receptor expression level (Cristofanilli et al., 2016).

- Luminal pattern of gene expression: in a study determining the effects of palbociclib in human breast cancer cell-lines, Finn et al. noted that almost all sensitive cell lines showed a luminal pattern of gene expression. These cell lines also showed higher levels of Rb1 and CCND1 mRNA compared to the resistant group. Interestingly, some of the sensitive cell lines were ER negative (Finn et al., 2009). Human breast cancers with a determined luminal gene-expression pattern might therefore show sensitivity to CDK4/6 inhibition, irrespective of ER status. This hypothesis remains to be tested in clinical trial samples.

- CCND1 amplification and/or loss of p16 (INK4A or CDKN2A): Loss of the retinoblastoma protein tumor suppressor gene (Rb) coding for a nuclear phosphoprotein that regulates the cell cycle is found in many human cancers and probably leads to disruption of the p16-cyclin D1-CDK4/6-RB pathway. Cyclin D1 is known to activate CDK4, which then phosphorylates the RB protein, leading to cell cycle progression. p16 inhibits CDK4, keeping RB hypophosphorylated and preventing cell-cycle progression. The significance of these three markers, cyclin D1, CDK4 and p16 for breast cancer and carcinogenesis is nevertheless still controversial. Preclinical data suggest that tumors with higher levels of cyclin D1 or lower levels of p16 might be more sensitive to CDK4/6 inhibitors (Finn et al., 2009).

Peurala et al. analyzed 102 formalin-fixed human breast cancer samples, in which cyclin D1, CDK4 and p16 expression was evaluated immunohistochemically. Cyclin D1 was associated with a good breast cancer prognosis but functioned independently of CDK4. p16 correlated with a better prognosis and function without CDK4. The study concluded that cyclin D1, CDK4 and p16 function independently in human breast cancer (Peurala et al., 2013).

In the phase II PALOMA-1 study, two sequential cohorts were designed in an attempt to identify biomarkers of response. In the first cohort, only ER positivity and HER2-negative status were considered for enrolment. In the second, central confirmation of CCND1 amplification and/or p16 loss in the tumor specimen was required. Ultimately, patient selection based on CCND1 amplification or p16, compared to ER/HER2 status alone, did not predict for benefit from palbociclib (Finn et al., 2015). In the Phase III MONALEESA-2 study the assessment of baseline tumors by protein levels of Rb, p16 and cell proliferation marker Ki-67, and by gene expression levels of CDKN2A (p16) and CCND1 was performed. A consistent benefit from ribociclib + letrozole vs. placebo + letrozole was observed irrespective of baseline Rb, p16, and Ki67 levels or CDKN2A and CCND1 gene expression levels (Campone, 2017). Similarly, immunohistochemical staining for cyclin D1 and p16 on the PALOMA-2 specimens did not show differential benefit from palbociclib in patients with tumors with different degrees of expression for either of these proteins (Finn et al., 2016).

Potential biomarkers of resistance

- Loss of Rb function: Given that CDK4/6 inhibitors function primarily by suppressing Rb phosphorylation, tumors lacking functional Rb should be resistant to these agents. In the laboratory, chronic loss of Rb has been associated with the development of resistance to CDK4/6 inhibitors in breast cancer cell-lines. The same was true in explants derived from human breast tumors (Dean et al., 2010). Malorni et al. analyzed data from The Cancer Genome Atlas to develop an 87-gene expression signature of Rb loss (RBsig) (Malorni et al., 2016). The RBsig was able to predict with reasonable accuracy the likelihood of breast cancer cell-lines being sensitive to palbociclib (high RBsig correlated with palbociclib resistance). Notably, the RBsig scores were lowest in luminal A breast cancers and highest in basal-like breast cancers, in keeping with the notion that ER-positive tumors in general retain greater Rb functionality. This raises the question of whether the most meaningful biomarker for CDK4/6 inhibitor resistance might in fact be loss of Rb function rather than ER negativity (Garrido-Castro et al., 2017).

- Hyperactivity of the cyclin E-CDK2 axis: Aside from CDKs 4 and 6, CDK2 can also phosphorylate Rb, and in the presence of sustained CDK4/6 inhibition can substitute for CDK4/6 to a mechanism of escape from cell cycle arrest (Dean et al., 2010). In cell lines, this can be mediated by CCNE1 amplification, which may play an important role in early adaptation and acquired resistance to CDK4/6 inhibitors (Hererra-Abreu et al., 2016).

- Other genomic aberrations (ESR1, PIK3CA, TP53): The PALOMA-3 study was analyzed to determine the predictive role of mutations in the ER gene ESR1, which often occur in the setting of resistance to aromatase inhibitor therapy. ESR1 mutations in ctDNA were found in approximately 25% of the patients. Although an ESR1 mutation was associated with a worse outcome compared to ESR1 wild-type status in the overall population, ESR1 mutant and wild-type patients derived similar PFS benefit with palbociclib (Fribbens et al., 2016). Similarly, mutations in PIK3CA in plasma were also not associated with palbociclib treatment effect (Cristofanilli et al., 2016).

In summary, the only validated marker for response to a cyclin-dependent kinase 4/6 inhibitor is hormone receptor positivity and, as in the case of palbociclib, new biomarker analyses of treatment with ribociclib plus letrozole have not shed light on this issue. Researchers who ran the MONALEESA-2 study used archival or fresh tumor specimens at baseline and analyzed six

biomarkers of response to investigate how they correlated with progression-free survival. The Investigators examined total Rb expression in 479 patients, p16 expression in 405 patients, expression of CDKN2A, CCND1 and ESR1 in 386 patients, Ki67 protein expression in 463 patients, and PIK3CA status in 417 patients. The Investigators concluded that the benefit of progression-free survival was seen in all subgroups regardless of biomarker status (Andrè, 2017).

Discontinuation of recommended therapies is not uncommon in oncology. Nearly 20–30% of patients receiving adjuvant therapies for early breast cancer discontinue endocrine therapy before the completion of 5 years of standard of care. Adverse Events (AE) are the most common reason for discontinuing endocrine treatments (Ruddy et al., 2009). Predicting which patients will develop intolerable symptoms through genomic tests is therefore relevant. A study by Sini et al. reviewed genetic variations mainly related to the onset of adverse events during aromatase inhibitors in early breast cancer. [redacted]

In conclusion, elucidating resistance mechanisms by identifying the unique gene mutation pattern in each breast cancer subtype following progression or prolonged benefit from CDK 4/6 inhibitor therapy remains an unmet need and is crucial for leveraging the efficacy of CDK4/6 inhibitors. Optimizing genomic information and identifying useful predictive markers of toxicity may also help clinicians in selecting patients who may benefit more from these therapies.

The main purpose of this local, multicenter study is to investigate genetic and gene alterations in tumor prior to and following progression on ribociclib and thus identify patterns of mutations, how they evolve, and their association with CDK4/6 inhibition and outcomes such as sustained response or early progression. [redacted]

Ribociclib and other cyclin-dependent kinase 4/6 inhibitors, in combination with letrozole, will likely have an impact on first-line treatment of advanced breast cancer. In order to investigate the biological features of a homogeneous population, the trial will be conducted only in first-line postmenopausal women with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (aBC).

2.1.2 Extension phase

About 40% of patients with HR-positive breast cancer have PIK3CA mutations that activate the PI3K pathway and lead to cancer progression and resistance to endocrine therapy. These tumors may thus be particularly suited to treatment with the alpha-specific PI3K inhibitor alpelisib. Unlike other PI3K inhibitors that have activity spanning the alpha, beta, gamma, and delta isoforms of PI3K, alpelisib is specific for only the alpha isoform, giving it a safety profile that

compares favorably with other agents in its class (André et al., 2019). Alpelisib combined with fulvestrant demonstrated clinically relevant benefits and a manageable safety profile in Phase I and Phase III studies of patients with HR-positive, HER2-negative advanced breast cancer with PIK3CA mutations (CBYL719X2101, CBYL719C2301 [SOLAR-1]) (see Section 1.2.6.1). Alpelisib in combination with fulvestrant, is approved by the FDA for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen.

A noteworthy finding of the SOLAR-1 study is the potential viability of using liquid biopsies to identify PIK3CA mutation status. Juric et al. analyzed data from 341 patients with PIK3CA mutations, as determined by tissue biopsy, who had received prior endocrine therapy. In addition to tissue-based analysis, the researchers evaluated progression-free survival by PIK3CA mutational status as measured in circulating tumor DNA (liquid biopsy). While patients with PIK3CA mutations evaluated in tissue samples had a 35% reduction in risk for disease progression, the risk reduction was 45% for patients with PIK3CA mutations evaluated in circulating tumor DNA. The authors concluded that PFS was significantly prolonged in patients with plasma ctDNA-determined mutational status, demonstrating the clinical utility of the ctDNA test in selecting patients with a PIK3CA mutation and confirming the robustness of the primary endpoint results (Juric, 2018).The next step now is to understand how the disease evolves after treatment with ribociclib plus letrozole and, in PIK3CA mutated tumors, during subsequent therapy with alpelisib and fulvestrant.

The main purpose of this extension phase is to identify and characterize patients who benefit from treatment with alpelisib + fulvestrant in second line following treatment discontinuation with first-line ribociclib + letrozole through evaluation of the patient's tumor genomic profile by means of liquid biopsies. Second line treatment is defined in this protocol as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression).

2.2 Rationale for the study design

This study provides the opportunity to investigate the various mutations in post-menopausal women with HR+/HER2- advanced breast cancer on first-line treatment with ribociclib + letrozole, and on those with a PIK3CA mutation subsequently on second-line treatment with alpelisib + fulvestrant following discontinuation of treatment with ribociclib + letrozole, in order to better understand the mechanisms of response and resistance to therapies.

Liquid biopsy is a diagnostic concept consisting in the analysis of therapeutic targets and drug resistance-conferring gene mutations on cell-free circulating tumor DNA (ctDNA) released into peripheral blood (Alix-Panabières et al., 2013). Liquid biopsy is a less invasive approach that detects diagnostic, prognostic and theranostic biomarkers before and during treatment, and at progression of disease. It can easily be repeated during follow-up of cancer patients to control treatment efficiency and detect genomic alterations occurring as a result of resistance to targeted therapy. In theory, this approach can promote a change in therapy, even before detection of tumor progression or relapse (Ilie et al., 2014).

Thymidine kinase 1 (TK1) is a cellular enzyme involved in DNA precursor synthesis, and its activity has been used as a proliferation marker for monitoring malignant diseases (Jagarlamudi

et al., 2015). Here, serum TK1 activity and its association with clinical outcome will be evaluated as blood marker of proliferation in breast cancer patients.

Tumor tissue samples will be collected at baseline to identify biomarkers that may be predictive of benefit from the treatment under study and to understand the heterogeneity of mutations across diverse patient profiles. Tumor samples will also be collected at progression/end of treatment to understand the mechanisms of resistance to treatment.

The tumor microenvironment (TME) is increasingly recognized as a key factor in multiple stages of disease progression, particularly local resistance, immune-escaping, and distant metastasis, thereby substantially impacting the future development of frontline interventions in clinical oncology. An appropriate understanding of the TME promotes evaluation and selection of candidate agents to control malignancies at both the primary sites as well as the metastatic settings. Targeting the TME is a critical strategy to overcome acquired resistance, prevent metastasis, and improve therapeutic efficacy (Chen et al., 2015).

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 and Table 3-2 below. Primary biological objective ("to identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome") and related endpoint of the core phase have been extended also to treatment phase with alpelisib and fulvestrant. Moreover all the secondary objectives of the core phase, with the exception of TK-1 evaluation, have been extended to the treatment phase with alpelisib and fulvestrant. Objectives and endpoints are reported in two separated tables below only to better clarify.

Table 3-1 Objectives and related endpoints of Core phase

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome in the ribociclib + letrozole phase of treatment.	Multiple gene assessments such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN* and their association with clinical outcome in the ribociclib + letrozole phase of treatment.	
Secondary		Refer to Section 10.5
To evaluate serum thymidine kinase 1 (TK1) activity over time as blood marker of proliferation and its association with clinical outcome in the ribociclib + letrozole phase of treatment.	Measurement of TK1 activity in serum and its correlation with clinical outcome in the ribociclib + letrozole phase of treatment.	
To identify the patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" (i.e. Time to progression > 25 months) and to patients with early progression (i.e. progressed at first imaging evaluation) in the ribociclib + letrozole phase of treatment.	Multiple gene assessments such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN* in "long responder" patients and in those with early progression and their differences in the ribociclib + letrozole phase of treatment.	
To assess mutational and gene aberrations across different patient profiles in the ribociclib + letrozole phase of treatment.	Differences in mutations and gene alterations will be assessed based on baseline samples (ctDNA and tissue) and compared across different patient profiles (i.e. newly diagnosed vs. recurrent disease) in the ribociclib + letrozole phase of treatment.	
[redacted]		

Objective	Endpoint	Analysis
To evaluate correlations between blood and tissue samples in the ribociclib + letrozole phase of treatment.	Comparison between alterations detected through liquid biopsy and through tissue biopsy at baseline and at progression in the ribociclib + letrozole phase of treatment.	
[redacted]		
To evaluate the safety and tolerability of ribociclib + letrozole in postmenopausal women with HR+, HER2- advanced breast cancer on first-line treatment.	Adverse Events (AE), Grade 3/4 AEs & Serious Adverse Events (SAE) during treatment with ribociclib + letrozole.	
To assess the clinical efficacy of ribociclib + letrozole	Time-to-Progression (TTP) (RECIST 1.1), based on investigators' assessment. Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease. Clinical Benefit Rate (CBR) as defined by RECIST 1.1, including patients with Complete Response (CR), Partial response (PR), Stable Disease (SD) and Non-CR/Non-Progressive Disease (PD) > 24 weeks.	
[redacted]		

Table 3-2 Objectives and related endpoints of Extension phase (patients with a PIK3CA mutation)

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome in the alpelisib + fulvestrant phase of treatment.	Multiple gene assessments such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN* and their association with clinical outcome in the alpelisib + fulvestrant phase of treatment.	
Secondary		Refer to Section 10.5
To identify patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" and to patients with early progression (i.e. progressed at first imaging evaluation) in the alpelisib + fulvestrant phase of treatment.	Multiple gene assessments such as but not limited to *RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53* and *PTEN* in "long responder" patients and in those with early progression and their differences in the alpelisib + fulvestrant phase of treatment.	
To assess mutational and gene aberrations across different patient profiles in the alpelisib + fulvestrant phase of treatment.	Differences in mutations and gene alterations will be assessed based on baseline samples (ctDNA and tissue) and compared across different patient profiles in the alpelisib + fulvestrant phase of treatment.	
[redacted]		
To evaluate correlations between blood and tissue samples in the alpelisib + fulvestrant phase of treatment.	Comparison between alterations detected through liquid biopsy and through tissue biopsy at baseline and at progression in the alpelisib + fulvestrant phase of treatment.	

Objective	Endpoint	Analysis
[redacted]		
To evaluate the safety and tolerability of alpelisib + fulvestrant in postmenopausal women with HR+, HER2- advanced breast cancer.	Adverse Events (AE), Grade 3/4 AEs & Serious Adverse Events (SAE) during treatment with alpelisib + fulvestrant.	
To assess the clinical efficacy of alpelisib + fulvestrant as a single treatment combination and as one of two subsequent-line therapies (ribociclib + letrozole followed by alpelisib + fulvestrant) (PFS2 - PFS on second line treatment).	Time-to-Progression (TTP) (RECIST 1.1), based on investigators' assessment. Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease. Clinical Benefit Rate (CBR) as defined by RECIST 1.1, including patients with Complete Response (CR), Partial response (PR), Stable Disease (SD) and Non-CR/Non-Progressive Disease (PD) > 24 weeks. Progression Free Survival on the second line treatment (PFS2), based on investigators' assessment using RECIST 1.1.	
[redacted]		

4 Study design

4.1 Description of study design

This is a multicenter, local, open-label, single-arm trial that has enrolled 287 patients in the core phase at 47 Italian sites.

During the study's core phase, patients will be treated with ribociclib and letrozole in first line until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor or lost to follow-up, whichever occurs first. Following treatment discontinuation, patients with PIK3CA mutations will enter an extension phase and undergo treatment with alpelisib + fulvestrant in second line until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor or lost to follow-up, whichever occurs first. Second line treatment is defined in this protocol as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression).

In order to investigate the mechanisms of response and resistance to therapy with ribociclib in combination with letrozole, and to therapy with alpelisib in combination with fulvestrant, biological samples will be collected as described below:

First-line treatment with ribociclib + letrozole (core phase)

- Blood samples for ctDNA and TK1 will be collected at baseline, and then at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, as well as at EOT

  Newly obtained tissue biopsies will be collected at baseline and upon progression of disease. A baseline tumor sample must be obtained during the screening process prior to starting treatment. If a new biopsy is not clinically feasible, archival tissue will be acceptable (it is recommended to provide a recent biopsy of the locoregionally recurrent or metastatic disease). The second tumor tissue sample (if clinically feasible) will be obtained at time of progression and prior to subsequent therapy. Tumor samples will be analyzed to assess mutational and gene aberrations across different patient profiles.

- [redacted]

Second-line treatment with alpelisib + fulvestrant in patients with PIK3CA mutations following discontinuation of treatment with ribociclib + letrozole (extension phase)

- Blood samples for ctDNA will be collected at extension screening (if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form), cycle 2-day 1, at first imaging evaluation and at EOT.
- A tumor tissue sample (if clinically feasible) will be obtained at EOT upon progression of disease.

4.2 Timing of interim analyses and design adaptations

Interim analyses may be performed periodically to fulfill safety updates, analysis of different endpoints or for publication purposes.

4.3 Definition of end of study

End of study will be declared after all patients have discontinued all components of the study, including both core and extension phase (for eligible patients).

4.4 Early study termination

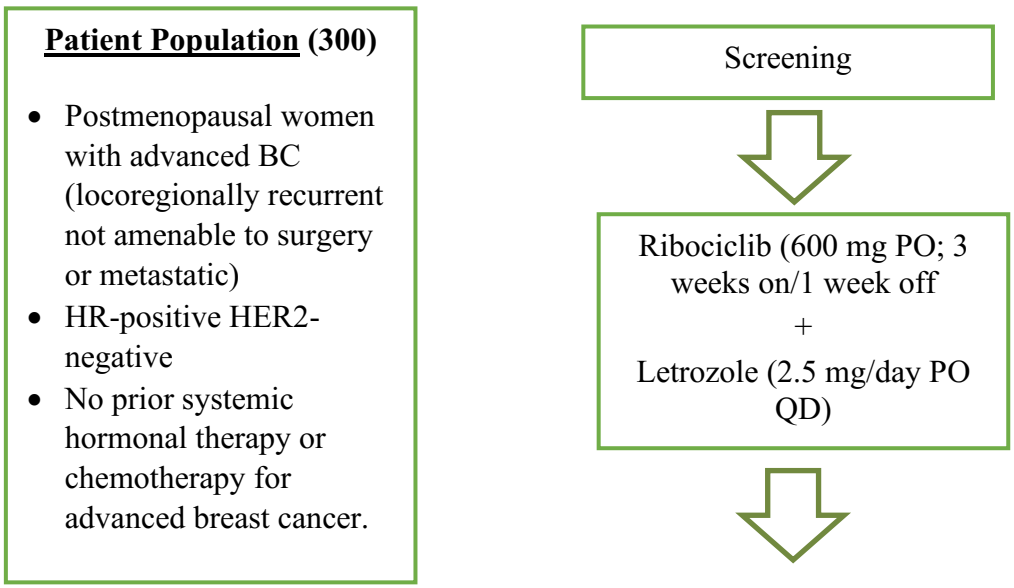
The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients will continue to be followed as described in Section 7 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Independent Ethics Committees (IEC) of the early termination of the trial.

4.4.1 Ensuring therapeutic continuity for ongoing patients in case of early study termination by sponsor

In case of early study termination by sponsor, therapeutic continuity will be granted to all patients, irrespectively of the phase of the trial. In detail:

- For those patients in the extension phase, alpelisib plus fulvestrant will be provived through a PTA program.
- For those patients in the core phase, the EMA and AIFA label applies so they can receive the treatment with ribociclib through the National Healthcare System.
    - For those patients in the core phase at study termination, access to alpelisib plus fulvestrant upon ribociclib discontinuation will be granted through a PTA program, provided they have a validated test demonstrating a PIK3Ca mutation on tumor tissue or plasma AND they meet the inclusion criteria aligned with those applied by the trial.

Figure 4-1 Study design of core phase



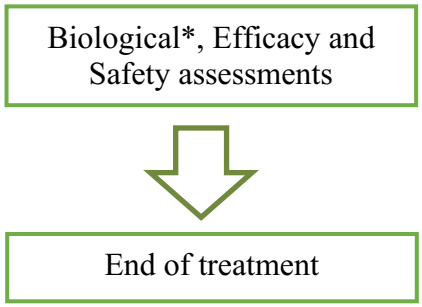
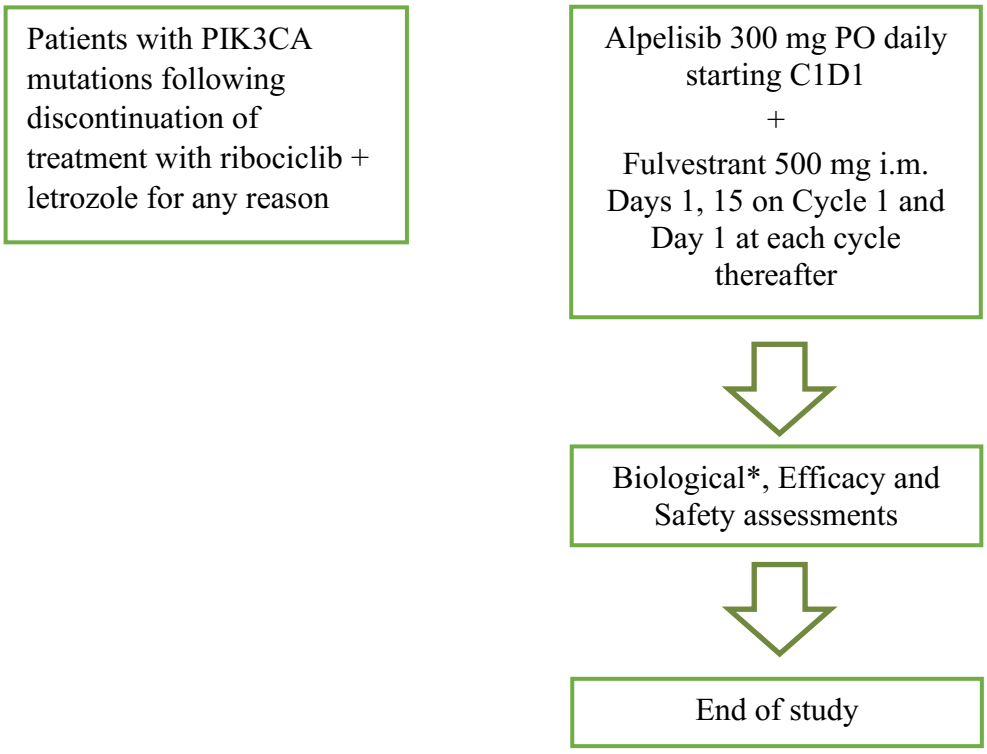
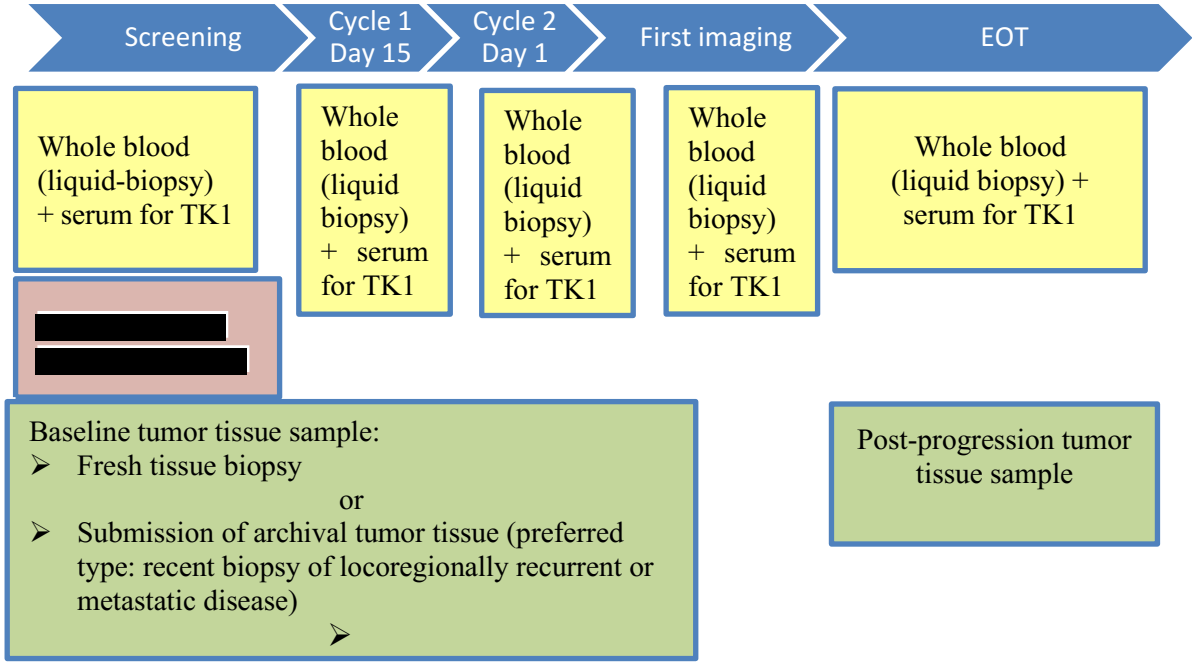

Biological*, Efficacy and Safety assessments
End of treatment

Figure 4-2 Study design of extension phase

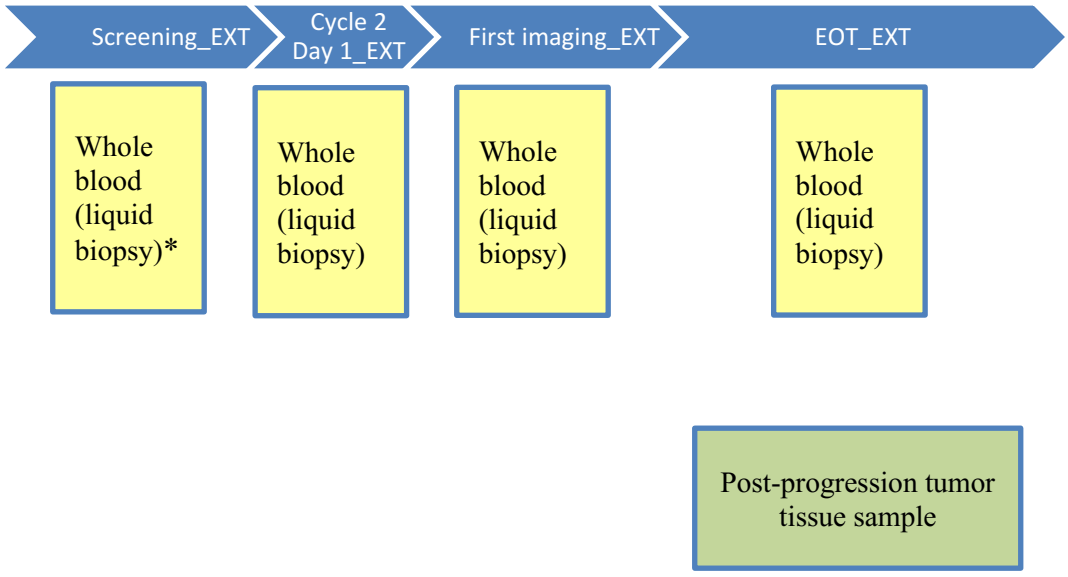


*See Figure 4.3 for details

Figure 4-3 Biological assessments
Core phase



Extension phase (patients with a PIK3CA mutation)



* if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form

5 Population

5.1 Patient population

Core phase: the patient population will be made up of women in post-menopausal status with HR+, HER2- advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer who have not received any prior agent for treatment of advanced disease. These patients will undergo treatment with ribociclib and letrozole.

Extension phase: the patient population will be made up of patients with PIK3CA mutations who discontinue therapy with ribociclib + letrozole during the core phase and subsequently undergo treatment with alpelisib + fulvestrant in second line. Second line treatment is defined in this protocol as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression).

The investigator must ensure that the patient meets all the inclusion criteria and none of the exclusion criteria for enrollment in the study.

5.2 Inclusion criteria (core phase)

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is a female ≥ 18 years old at the time of informed consent and has signed informed consent before any trial related activities.
2. Patient has an advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer in first-line treatment (treatment naïve for the advanced setting).
3. Patient is in post-menopause, defined by one of the following:
    - Prior bilateral oophorectomy
    - Age ≥ 60
    - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.
4. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory.
5. Patient has an HER2-negative breast cancer 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.
6. Patient is willing to undergo blood and tumor sample collection for the biological assessments/objectives as scheduled in the protocol.

    Note: patient must have a baseline tumor sample. It is recommended to provide a newly obtained tissue biopsy or an archival tumor tissue derived by a recent biopsy of the locoregionally recurrent or metastatic disease (bone biopsies are acceptable). In cases this is not clinically feasible, the submission of an archival tumor tissue of the primary tumor is acceptable.

7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
8. Patient has an adequate bone marrow and organ function as defined by ALL the following laboratory values (as assessed by local laboratory):
    - Absolute neutrophil count ≥ 1.5×10^9/L
    - Platelets ≥ 100×10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Potassium, sodium, calcium (corrected for serum albumin), magnesium, and phosphorus within normal limits or corrected to within normal limits with supplements before first dose of the study medication
    - INR ≤ 1.5
    - Serum creatinine < 1.5 mg/dl or creatinine clearance > 50 mL/min
    - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below 2.5 × Upper Limit of Normal (ULN). If the patient has liver metastases, ALT and AST should be < 5 × ULN.
    - Total serum bilirubin < ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN.
9. Patients must have a 12-lead ECG with all of the following parameters at screening:
    - QTcF interval at screening < 450 msec (using Fridericia's correction)
    - Resting heart rate ≥ 50 bpm
10. Patient must be able swallow ribociclib and letrozole capsules/tablets.
11. Patients must be able to communicate with the investigator and comply with the requirements of the study procedures.
12. Patient must have either:
    - Measurable disease i.e. at least one target lesion as per RECIST 1.1 criteria

      OR
    - If no measurable disease is present, then at least one not target lesion as per RECIST 1.1 criteria must be present.

5.3 Inclusion criteria (extension phase- patients with a PIK3CA mutation)

Patients eligible for the extension phase of this study have to meet **all** of the following criteria:

Written informed consent must be obtained prior to any screening procedures.

1. Patient is an adult female ≥ 18 years old at the time of consent and has signed informed consent (ICF) before any trial related activities and according to local guidelines.

2. Postmenopausal (see inclusion criteria 3 from core phase) women with hormone receptor-positive, HER2-negative advanced breast cancer not amenable to curative therapy.

   Patient has been discontinued (any reason allowed) from treatment with ribociclib + letrozole in the core phase and is deemed suitable for treatment with alpelisib + fulvestrant in second line. Ribociclib + letrozole must be the last treatment regimen before alpelisib + fulvestrant.

   Second line treatment is defined in this protocol as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e. even in absence of progression).

3. Patient has a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.
4. Patient has HER2-negative breast cancer 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. Patient has PIK3CA mutation as determined in tumor tissue and/or plasma by a Novartis designated laboratory. Results of tissue samples obtained during the core phase (screening or EOT) are acceptable
6. Patient has adequate bone marrow and coagulation function as shown by the following laboratory values:
   - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L (for patients with lesions involving the bone marrow, platelet count $\geq 75 \times 10^9$/L may be acceptable)
   - Hemoglobin ≥ 9.0 g/dL
   - INR ≤ 1.5 (INR ≤ 2.0 will be allowed for those patients treated with vitamin K antagonist)
7. Patient has adequate liver function as shown by:
   - In absence of liver metastases, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN or $\leq 5 \times$ upper limit of normal (ULN) if hepatic metastases are present
   - Total serum bilirubin $< 2 \times$ ULN (any elevated bilirubin should be asymptomatic at enrollment) except for patients with Gilbert's syndrome who may be included only if total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN
8. Patient has adequate renal function:
   - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 35 ml/min using Cockcroft- Fault formula
9. Patient has fasting plasma glucose (FPG) $\leq$140 mg/dL (7.7 mmol/L) and glycosylated hemoglobin (HbA1c) $\leq 6.4\%$ (both criteria have to be met).

For patients with FPG ≥ 100 mg/dL and/or HbA1c ≥ 5.7% (i.e. threshold for pre-diabetes) at screening, recommend lifestyle changes according to ADA guidelines (https://professional.diabetes.org/content-page/practice-guidelines-resources) and dietary advice (i.e. controlled carbohydrate intake, high fiber, low processed food intake, three macronutrient balanced meals and 2 optional small snacks rather than one large meal) and exercise. A consultation with a diabetologist is highly recommended.

10. Patient has potassium, magnesium and calcium (corrected for albumin), within normal limits , or ≤ Grade 1 severity according to NCI-CTCAE v4.03 if judged clinically not significant by the investigator, or correctable with supplements before entry of study; re-screen is allowed.
11. Fasting serum amylase ≤ 2 × ULN.
12. Fasting serum lipase ≤ ULN.
13. Patient has ECOG (Eastern Cooperative Oncology Group) Performance Status ≤ 2.

5.4 Exclusion criteria (core phase)

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

1. Patient has a known hypersensitivity to ribociclib or letrozole or to any of the excipients of ribociclib or letrozole.
2. Patient who received prior treatment with any CDK4/6 inhibitor.
3. Patient who received any prior systemic hormonal therapy or chemotherapy for advanced breast cancer.

   Note:

   - Patients who received (neo)adjuvant therapy for breast cancer are eligible. If the prior (neo)adjuvant therapy included letrozole or anastrozole, the disease-free interval must be greater than 12 months from the completion of treatment until study entry.
   - Patients who received ≤ 28 days of letrozole or anastrozole for advanced disease prior to inclusion in this trial are eligible.
4. Patient is currently using other anti-cancer therapy.
5. Patient has had major surgery within 14 days prior to starting study drug or absence of recovery from major side effects.
6. Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
7. Patient who has received extended-field radiotherapy ≤ 4 weeks or limited field radiotherapy for palliation ≤ 2 weeks prior to start of treatment, or lack of recovery to grade 1 or better from related side effects of such therapy (except for alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion). Patients

for whom ≥ 25% (Ellis RE 1961) (see Appendix 14.6) of the bone marrow has been previously irradiated are also excluded.

8. Patient has concurrent malignancy or malignancy within 3 years prior to starting study drug, except for adequately treated, basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
9. Patient with central nervous system (CNS) metastases unless ALL the following criteria are met:
    - At least 4 weeks from prior therapy for CNS disease completion (including radiation and/or surgery) to start of the study treatment.
    - Clinically stable CNS lesions at the time of treatment initiation and not receiving steroids and/or enzyme-inducing anti-epileptic medications for the management of brain metastases for at least 2 weeks.
10. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (uncontrolled ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
11. Patient has a known history of HIV infection (testing not mandatory).
12. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal bacterial or viral infections, etc.).
13. Patient has clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormalities, including but not limited to any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) or symptomatic pericarditis within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia

- Concomitant use of medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued (within 5 half-lives or 7 days prior to starting study drug) or replaced by safe alternative medication
- Inability to determine the QT interval on screening (QTcF, using Fridericia's correction)

- Systolic blood pressure >160 mmHg or < 90 mmHg at screening

14. Patient is currently receiving any of the following medications and cannot be discontinued within 5 half-lives or 7 days prior to Cycle 1, Day 1, whichever is longer:
    - Concomitant medications, herbal supplements, and/or fruit (grapefruit pummelo, star fruit, Seville oranges) and their juices which are known strong inducers or inhibitors of CYP3A4/5 (see Appendix 14.1)
    - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
15. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airway diseases), eye drops or local injections (e.g., intra-articular).
16. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product, whichever is longer.

5.5 Exclusion criteria (extension phase - patients with a PIK3CA mutation)

Patients eligible for the extension phase must not meet **any** of the following criteria:

1. Patient has a known hypersensitivity to alpelisib or fulvestrant, or to any of the excipients of alpelisib, or fulvestrant.
2. Patient has received prior treatment with any PI3K, mTOR or AKT inhibitor.
3. Patients with central nervous system (CNS) involvement unless they meet ALL of the following criteria:
    - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
    - Clinically stable CNS tumor at the time of screening untreated or without evidence of progressions for at least 4 weeks after treatment as determined by clinical examination and brain imaging (MRI or CT) during screening period and stable low dose of steroids for 2 weeks prior to initiating study treatment.
4. Patients with an established diagnosis of diabetes mellitus type I or uncontrolled type II (based on FPG and HbA1c, see inclusion criterion 10).

5. Patient has a concurrent malignancy or malignancy within 3 years of study screening period, with the exception of adequately treated, basal or squamous cell carcinoma, non-melanoma skin cancer or curatively resected cervical cancer.
6. Patient has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to enrollment, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia).
7. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting treatment with alpelisib or has not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops or local injections (e.g., intra-articular), stable CNS tumor on consistent low dose of steroids.
8. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not mandatory.
9. Any concurrent severe and/or uncontrolled medical conditions that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic active hepatitis [testing is not mandatory unless required by local regulations or requirements], severe hepatic impairment, etc.).
10. Patients being concurrently treated with drugs recognized as being strong inducers of the isoenzyme CYP3A4 or inhibitors of BCRP; switching to different medications prior to entry of treatment phase is allowed within the last 7 days prior to study treatment or within 5 half-lives, whichever is longer (see Appendix 14.2.2 for a complete list).
11. Patient has a history of noncompliance to medical regimens.
12. Patient with severe liver impairment (Child Pugh score B/C).
13. 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) based on investigator discretion.
14. Patient has documented active pneumonitis/interstitial lung disease that requires treatment (chest CT scan performed at baseline for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
15. Patient has had major surgery within 14 days prior to starting treatment with alpelisib or has not recovered from major side effects.
16. Patient has any of the following cardiac abnormalities:

    - Symptomatic congestive heart failure

      i. History of documented congestive heart failure (New York Heart Association functional classification III-IV), documented cardiomyopathy

      ii. Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)

- History of angina pectoris, coronary artery bypass graft, symptomatic pericarditis or myocardial infarction ≤ 6 months prior to enrollment
- Clinically significant cardiac arrhythmia (e.g., ventricular tachycardia), complete left bundle branch block, high grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block without pacemaker in place)
- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening
- Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or Fredericia QT correction formula (QTcF) > 470 msec at screening
- Bradycardia (heart rate < 50 bpm at rest) by ECG or pulse

17. History of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.
18. Patient has a history of severe cutaneous reactions such as Stevens-Johnson Syndrome (SJS), Erythema Multiforme (EM), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
19. Patient is concurrently using other anti-cancer therapy. Ribociclib and letrozole used in the core phase must be discontinued at least 7 days prior to day one of the extension study treatment.

    All drugs with overlapping toxicities must be discontinued within 7 days and AE resolved to NCI CTCAE v4.03 Grade ≤ 1 prior to study treatment. Exception to this criterion: patients with any grade of alopecia are allowed to enter the study.
20. Patients with unresolved osteonecrosis of the jaw.

6 Treatment

6.1 Study treatment

For this protocol, the term “investigational drug” refers to the Novartis study drugs ribociclib and alpelisib. The other drugs to be used in this study are letrozole and fulvestrant. “Study treatment” in this protocol refers to the combinations of investigational drug (ribociclib) + letrozole and investigational drug alpelisib + fulvestrant.

Ribociclib (200 mg tablets) and alpelisib (50 mg and 200 mg tablets) will be supplied by Novartis as individual patient supply in packaged boxes. Letrozole (Femara) and fulvestrant will be provided by Novartis. Storage conditions will be detailed in the package. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record in the electronic Case Report Form (eCRF).

6.1.1 Dosing regimen

6.1.1.1 Ribociclib + letrozole (core phase)

Ribociclib (LEE011) is given orally once a day on days 1-21 of each 28-day cycle. On days 22-28, ribociclib is not given ("rest days"). Letrozole is given orally as per Summary of Product Characteristics (SmPC) once a day on a continuous daily schedule (days 1-28 of each 28-day cycle). There is no "rest" in the letrozole schedule.

Table 6-1 Dose and treatment schedule: ribociclib +letrozole

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Ribociclib	Tablet for oral use	600 mg (3 tablets of 200 mg)	Daily on D1-D21 (28 day cycles)
Letrozole	Tablet for oral use	2.5 mg	Continuous daily

Study treatment is administered as a flat-fixed dose (starting doses: ribociclib 600 mg QD 3 weeks on/1 week off; letrozole 2.5 mg QD continuously), and not by body weight or body surface area. The investigator or responsible site personnel should instruct the patient to take the study treatment as per protocol (emphasizing the importance of compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study treatment to the site at the end of each cycle. Site personnel will ensure that the appropriate dose of each study treatment is provided at each visit.

6.1.1.2 Alpelisib + fulvestrant (extension phase- patients with a PIK3CA mutation)

Alpelisib is administered orally at a dose of 300 mg once daily on a continuous dosing schedule starting on Cycle 1 Day 1 in combination with fulvestrant 500 mg intramuscular on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28 days cycle.

Table 6-2 Dose and treatment schedule: alpelisib + fulvestrant

Study treatments	Pharmaceutical form and route of administration	Dose[1]	Frequency and/or Regimen
Alpelisib	Film coated tablets for oral use	300 mg (e.g. 2 x 50 mg tablets + 1 x 200 mg tablet)[2]	Daily (continuous) starting on C1D1
Fulvestrant	Injection for i.m. administration	500mg	Days 1, 15 on Cycle 1 and Day 1 at each cycle thereafter

[1] Dose reduction levels for alpelisib will be administered accordingly. For example, alpelisib 250 mg should preferentially be administered as 1 x 50 mg tablets + 1 x 200 mg tablet.

[2] In case of patient supply difficulties, any combination of alpelisib may be taken to consume the total dose.

Alpelisib is dosed on a flat scale of mg/day and not by weight or body surface area. There are no breaks between dosing cycles. The investigator or responsible site personnel should instruct the patient to take the study treatment as per protocol (emphasizing the importance of

compliance). Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study treatment to the site at the end of each cycle. Site personnel will ensure that the appropriate dose of each study treatment is provided at each visit.

6.1.2 Dosing

6.1.2.1 Ribociclib and letrozole

Ribociclib and letrozole should be taken as follows:

- Ribociclib is dosed for the first 21 days of the 28-day cycle.
- Patients should be instructed to take the study treatment together with a large glass of water (~250 mL) at the same time each day. Evening doses are strongly not recommended.
- Ribociclib and letrozole can be administered with or without food.
- Patients should be instructed to swallow the ribociclib and letrozole tablets whole and not chew, crush or open them.
- If vomiting occurs, re-dosing is not allowed before the next scheduled dose. Vomiting during a treatment cycle must be recorded in the adverse events section of the eCRF.
- Any missed doses (not taken with 6 hours of intended time) should not be replaced or made up on a subsequent day.
- Grapefruit, grapefruit hybrids, pummelos, star fruit, Seville oranges or products containing their juice should be avoided during the entire study and preferably for 7 days before the first dose of study medication since these foods are known CYP3A4 inhibitors and may increase exposure to ribociclib. Orange juice is allowed.
- Herbal or dietary supplements known to be strong inhibitors or inducers of CYP3A4 are not permitted. If the potential for interaction is unknown, the supplement should be avoided. Multivitamins are permitted.

6.1.2.2 Alpelisib + fulvestrant

The following general guidelines should be followed for alpelisib administration:

- Patients should be instructed to take the dose of alpelisib once daily at approximately the same time each day after a meal (preferably in the morning after breakfast) except on the days blood collection is scheduled at the clinic, at which time the patients should take their doses at the clinic at any later point of time.
- Alpelisib must be taken within 1 hour after a meal or snack. If, for any reason, a breakfast (or other meal) was not consumed, the patient should take study treatment with a glass of water within 1 hour after a snack at any later point in time.
- If a dose of alpelisib is missed, it can be taken immediately after food and within nine hours after the time it is usually administered. After more than nine hours, the dose should be skipped for that day. On the next day alpelisib should be taken at the usual time.

- Alpelisib should be taken with a glass of water. Patients should swallow the tablets whole and not chew them.
- 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 during a treatment cycle must be noted in the adverse events section of the eCRF.

On days with pre-dose fasting (overnight) glucose and/or amylase/lipase and/or c peptide and/or lipid profile samples as described in Table 7-2, the patient must be fasting overnight for 8-12 hours prior to the blood collection but can freely drink water. After this blood sample, the patient should have a light breakfast. Alpelisib must be taken within 1 hour after the meal in the clinic.

6.1.3 Rescue medication

Not applicable

6.1.4 Treatment duration

Patients may continue study treatment with ribociclib + letrozole and, in patients with PIK3CA mutations, subsequently with alpelisib + fulvestrant until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor, lost to follow-up, technical problems, whichever event occurs first.

6.2 Dose escalation guidelines

Not applicable

6.3 Dose modifications

6.3.1 Ribociclib + letrozole

6.3.1.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or required to allow patients to continue the study treatment. These dose modifications are summarized in Table 6.3, Table 6.4, Table 6.5, Table 6.7 and Table 6.8. No dose re-escalation is permitted.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring discontinuation in Table 6.4, Table 6.5, Table 6.7, and Table 6.8, treatment must be discontinued. If dosing was interrupted for > 28 days due to ribociclib related toxicity, ribociclib must be discontinued.

Dose reductions are not permitted for letrozole.

Any changes to ribociclib dose or interruption of the study treatment must be recorded on the Dosage Administration Record eCRF.

6.3.1.1.1 Letrozole

The established clinical dose of letrozole (2.5 mg/day) will be used and no dose modification is planned in this study. The letrozole SmPC should be consulted regarding full prescribing information, monitoring, and management of adverse events.

In cases where letrozole is required to be permanently discontinued, the patient must be discontinued from the study.

6.3.1.1.2 Ribociclib

Ribociclib should not be used as monotherapy.

The management of severe or intolerable adverse reactions requires dose reduction, temporary interruption, and/or discontinuation of ribociclib therapy. See Table 6.3 for guidance

Table 6-3 Ribociclib dose modifications guidelines

	Ribociclib	
	Dose	**Number of tablets and strength**
Starting dose	600 mg	3 x 200 mg tablets
First dose reduction	400mg	2 x 200 mg tablets
Second dose reduction	200 mg	1 x 200 mg tablets

Recommendations for dose reduction, interruption or discontinuation of ribociclib in the management of study drug related adverse reactions are summarized in Table 6.4, Table 6.5, Table 6.7 and Table 6.8.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring a discontinuation in Table 6.4, Table 6.5, Table 6.7 and Table 6.8 or listed in Section 7.1.3, treatment must be discontinued.

If a patient inadvertently doses ribociclib on a rest day (e.g. days 22-28 of any given cycle), ribociclib should be interrupted to ensure 7 consecutive rest days and avoid overdose. The visit schedule will be adjusted accordingly.

6.3.1.2 Recommendations on adjustment of ribociclib treatment cycles in the case of dose Interruptions/ reinitiation

Delayed start of a cycle:

In the case of ribociclib being withheld at Cycle (x) D1 based on investigator's judgement, the patient should reinitiate ribociclib on a 3-week ON/ 1-week OFF schedule once the assessment(s) are within acceptable levels according to Section 6.3 Dose Modifications. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Mid-cycle dose interruption:

In the case of ribociclib being withheld for < 7 days during any cycle, patient should reinitiate ribociclib to complete the 21-calendar-day treatment (3 weeks ON) followed by 1-week OFF schedule.

In the case of ribociclib being withheld for ≥ 7 days during any cycle, patient should reinitiate ribociclib to a new 28 calendar day treatment schedule (3 weeks ON/ 1 week OFF) once the assessment(s) are within acceptable levels according to Section 6.3 Dose Modifications. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Table 6-4 Ribociclib dose reduction/interruption and management recommendations for hematological adverse drug reactions

Toxicity/Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	
Grade 1 (≥ 75 x 10^9/L)	No dose adjustment required.
Grade 2 (≥ 50 - < 75 x 10^9/L)	Dose interruption until recovery to grade ≤ 1. Re-initiate ribociclib at the same dose.
Grade 3 (≥ 25 - < 50 x 10^9/L)	Dose interruption until recovery to grade ≤1. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤ 1 and reduce ribociclib to the next lower dose level.
Grade 4 (< 25 x 10^9/L)	Dose interruption until recovery to grade ≤ 1. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 4: discontinue ribociclib.
Absolute Neutrophil count	
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 until recovery to ≥1.0 x 10^9/L. Re-initiate ribociclib at the same dose level. If toxicity recurs at grade 3: temporary dose interruption until recovery to ≥ 1.0 x 10^9/L. If resolved in ≤ 7 days, maintain dose level. If resolved in >7 days, reduce ribociclib dose to the next lower dose level. For Grade 3 neutropenia without fever or signs of infection on Day 14 of the first 2 cycles: Consider continuing ribociclib at current dose level to complete cycle. Repeat complete blood count on Day 21. Consider dose reduction based on the neutropenia recovery (<7 days / > 7 days).
Grade 4 (< 0.5 x 10^9/L)	Dose interruption until recovery to ≥ 1.0 x 10^9/L. Re-initiate ribociclib at the next lower dose level.
Febrile neutropenia	
Grade 3 ANC < 1.0 x 10^9/L with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than one hour	Dose interruption 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 ribociclib.
Grade 4	Discontinue ribociclib.

Life-threatening consequences; urgent intervention indicated	
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 until recovery to grade ≤ 2. Re-initiate ribociclib at the same dose.
Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue ribociclib.

Table 6-5 Ribociclib dose reduction/interruption and management recommendation for hepatic toxicities

Hepatotoxicity (bilirubin, SGPT/ALT, SGOT/AST)	
Total bilirubin without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later)	Maintain dose level with LFTs monitored bi-weekly.
Grade 2 (≥ 1.5 – <3.0 x ULN)	Dose interruption of ribociclib. If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level. If resolved to ≤ grade 1 in > 21-28 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 ≤ grade 1 is > 28 days, discontinue ribociclib.
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of ribociclib, until resolved to ≤ grade 1, then lower 1 dose level of ribociclib. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If resolved to ≤ grade 1 in > 28 days or toxicity recurs, discontinue ribociclib.
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 liver metastases 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, other 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.	
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 (confirmed 48 – 72 h later).	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. If resolved to ≤ baseline grade in ≤ 21 days, then maintain dose level. If resolved to ≤ baseline grade 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 ribociclib.
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN).	Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib. Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption. If recovery to ≤ baseline grade is > 28 days, discontinue ribociclib. If toxicity recurs, discontinue ribociclib.

Increase from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN).	Dose interruption of ribociclib until resolved to ≤ baseline grade, then lower 1 dose level of ribociclib. Repeat liver enzyme and bilirubin tests twice weekly for 2weeks after dose resumption. If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue ribociclib.
Grade 4 (> 20.0 x ULN)	Discontinue ribociclib
AST or ALT and concurrent Bilirubin	
For patients with normal ALT and AST and total bilirubin at baseline: AST or ALT >3.0 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 ribociclib.
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.	

6.3.1.3 Follow up on potential drug-induced liver injury (DILI) cases

Transaminase increase combined with total bilirubin (TBIL) increase may be indicative of drug-induced liver injury (DILI) and should be considered as a clinically important event.

In general, any increase of serum aminotransferases to > 3 x ULN should be followed by repeat testing within 48 to 72 hours. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required.

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], 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. It denotes the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$) or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and Liver Function Tests (LFT) testing should be repeated 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.

Upon presentation:

- Perform comprehensive medical history including cardiac disease, blood transfusions, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc.
- History of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
- Exclude other causes of liver disease.

Subject monitoring:

- Repeat liver chemistry tests within 48-72 hours.

- Retest frequency can decrease to weekly or less if abnormalities stabilize, drug has been discontinued, and the subject is asymptomatic.

As drug-induced liver injury (DILI) is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed (see Table 6-6). Liver biopsy has limited value in the diagnosis of DILI as histopathological findings in DILI can resemble many other liver conditions. However, biopsy can be useful to establish an alternative diagnosis especially if other tests are inconclusive.

If DILI is confirmed, permanently discontinue.

If DILI is unlikely, interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of study treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen should be discussed with the Novartis medical safety team.

Table 6-6 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, gammaGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Following appropriate causality assessments as outlined above, the causality of the drug is estimated as "probable" i.e. > 50% likely if it appears greater than all other causes combined. The term "drug-induced" indicates probably caused by the drug, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

6.3.1.4 Additional follow-up for QTc prolongation

Table 6-7 Ribociclib dose reduction/interruption and management recommendation for QTcF prolongation

Grade	Dose Modification
For all grades	1. Check the quality of the ECG and the QT value and repeat if needed. 2. Perform analysis of serum electrolytes (K+, Ca++ correct for albumin, Phosphorus, Mg++). If outside of the normal range, interrupt ribociclib administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal.

	3. Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. 4. Check compliance with correct dose and administration of ribociclib.
Grade 1: QTcF 450-480 ms	Perform steps 1-4 as directed in "For All Grades." No dose adjustments required.
Grade 2: QTcF 481-500 ms	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms. Repeat ECG as clinically indicated until the QTcF returns to < 481 ms, Restart ribociclib with dose reduced by 1 dose level. Refer to Table 6.3 for dosing schedule. If QTcF ≥ 481 ms recurs, ribociclib should be reduced again by 1 dose level. Refer to Table 6.3 for dosing schedule. Repeat ECG 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms.
Grade 3: QTcF ≥ 501 ms on at least two separate ECGs	Interrupt ribociclib. Perform steps 1-4 as directed in "For All Grades." 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, ribociclib will be reduced by 1 dose level. Refer to Table 6.3 for dosing schedule. • If QTcF remains ≥ 481 ms after performing steps 1-4 as directed in "For All Grades," discontinue ribociclib. Repeat ECG 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms. If QTcF of ≥ 501 ms recurs, discontinue ribociclib.
Grade 4: [QT/QTcF ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	Discontinue ribociclib. Perform steps 1-4 as directed in "For All Grades." Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms.

6.3.1.5 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus and magnesium for all adverse reactions that are potentially associated with electrolyte imbalance. If electrolyte values are outside of normal range, interrupt ribociclib administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes. For all other adverse events, please follow recommendations in Table 6.8.

Table 6-8 Ribociclib dose reduction/interruption and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management recommendations
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the same dose.

	If the same toxicity recurs at grade 2, interrupt ribociclib until recovery to grade ≤ 1. Re-initiate ribociclib at the next lower dose level.
3	Dose interruption until recovery to grade ≤ 1. Initiate appropriate medical therapy and monitor. Re-initiate ribociclib at the next lower dose level. If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤ 1 and reduce ribociclib dose the next lower dose level. If toxicity recurs at grade 3, discontinue ribociclib.
4	Discontinue ribociclib and treat with appropriate medical therapy.

6.3.2 Alpelisib + fulvestrant

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. All dose modifications must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria [NCI-CTCAE v4.03]. If the administration of alpelisib is interrupted for reasons other than toxicity, then treatment with alpelisib may be resumed at the same dose.

A maximum of 2 dose reductions of alpelisib from the recommended starting dose may be allowed before considering discontinuation of alpelisib.

Please refer to Table 6.9 and Table 6.10 for guidance.

Table 6-9 Dose reduction sequential steps for alpelisib

Alpelisib dose level	Dose and schedule	Number of tablets and strength
Starting dose	300 mg/day continuously	1 x 200 mg tablet and 2 x 50 mg tablets
Dose level -1	250 mg/day continuously	1 x 200 mg tablet and 1 x 50 mg tablet
Dose level -2	200 mg/day continuously	1 x 200 mg tablet

Recommendations for dose reduction or dose interruption of alpelisib in the management of adverse reactions are summarized in Table 6.10. Clinical judgment of the treating physician and confirmation of lab values should guide the management plan of each patient based on individual benefit/risk assessment. However, treatment must be discontinued as indicated in Table 6.10.

After treatment is resumed at a lower dose:

- If the same toxicity recurs with the same severity, then the next treatment re-initiation must resume at a lower dose irrespective of duration.
- Once the alpelisib dose has been reduced, re-escalation is not permitted, even upon resolution of AEs.

If administration of alpelisib dosing is held for more than 28 days, then alpelisib must be permanently discontinued. Grade 4 adverse events will lead to permanent discontinuation,

irrespective of recovery time, unless otherwise specified. Patients requiring more than 2 dose reductions for alpelisib should be permanently discontinued.

Table 6-10 Criteria for interruption and re-initiation of alpelisib treatment

Dose Modifications for alpelisib as specified below. Fulvestrant may be continued while alpelisib dose is being held at the investigator's discretion.	
Worst toxicity -CTCAE Grade (value)	**Dose Modifications for alpelisib**
Investigations (Fasting Plasma Glucose)	
Hyperglycemia (see also Section 6.3.2.1.3) Always consider consultation with a diabetologist and recommend/reinforce lifestyle changes as per ADA (https://professional.diabetes.org/content-page/practice-guidelines-resources), i.e. exercise and dietary advice (e.g. controlled carbohydrate intake, high fiber, low processed food intake. Three macronutrient balanced meals and 2 optional small snacks rather than one large meal). Note: This table provides dose management recommendations based on FPG or RBG measurements. FPG should be performed as clinically indicated. The preferred option for treating alpelisib-induced hyperglycemia is metformin given its wide availability and well characterized safety profile. However, in case of intolerance to metformin, investigator's judgment should be exercised and other oral hypoglycemics such as SGLT2 inhibitors, thiazolidinediones or dipeptidyl peptidase-4 inhibitors can be used.	
Grade 1 FPG > ULN - 160 mg/dL [> ULN - 8.9 mmol/L] or RBG > 140 - 200 mg/dl [> 7.8 mmol/L - 11.1 mmol/L]	Maintain dose level and remind patient on lifestyle changes*. • If FPG < 140 mg/dl or RBG < 160 mg/dl, consider adding metformin as per guidance below or in cooperation with diabetologist. • If FPG 140 - 160 mg/dl or RBG 160 - 200 mg/dl, start/intensify metformin as per guidance below or in cooperation with diabetologist. Metformin 500 mg once daily with dinner. If no gastrointestinal (GI) intolerance after several days, increase to 500 mg bid with breakfast and dinner. If tolerated, increase to 500 mg with breakfast and 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated, reduce to prior tolerated dose. Monitor blood glucose as clinically indicated and at least weekly for 8 weeks, then continue checking at least every two weeks until blood glucose levels are within baseline values.
Grade 2 FPG > 160 - 250 mg/dL [> 8.9 - 13.9 mmol/L] or	Maintain dose level and remind patient of lifestyle changes*. Exclude confounding factors such as urinary tract infection, consider consultation with a diabetologist and start oral-antidiabetic treatment, e.g. metformin 500 mg bid with breakfast and dinner. If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner. If tolerated, 1000 mg bid with breakfast and dinner. If not tolerated,

RBG > 200 - 250 mg/dL [> 11.1 - 13.9 mmol/L]	reduce to prior tolerated dose. Titrate to the maximum tolerated dose over a period of 3 weeks. A second oral hypoglycemic agent may be initiated if needed. If blood glucose levels are still rising on maximum tolerated dose of metformin or if FPG is persistently >160mg/dl (>8.9 mmol/L) or RBG >200mg/dL (>11.1 mmol/L), add an SGLT2 inhibitor if available, e.g. empagliflozin up to 25 mg (max. dose). Alternatively, an insulin-sensitizer such as pioglitazone 30 mg (max. dose) can be used. Monitor blood glucose as clinically indicated and at least weekly until FPG resolves to ≤ 160 mg/dl or RBG ≤ 200 mg/dl. • If FPG does not resolve to ≤ 160 mg/dl (or RBG ≤ 200 mg/dl) within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level. • Continue with anti-diabetic treatment and check blood glucose at least weekly for 8 weeks, then continue checking at least every 2 weeks: alert treating physician if FPG > 250 mg/dl.
Grade 3 FPG or RBG > 250 - 500 mg/dL [> 13.9 - 27.8 mmol/L]	Omit alpelisib and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Regardless of fasting status, consider IV fluids if symptoms of hyperglycemia or signs of volume depletion are present. Exclude confounding factors such as urinary tract infection and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate. Start metformin and titrate as outlined for Grade 2, add insulin sensitizers (pioglitazone) or an SGLT2 inhibitor, if available, as outlined for Grade 2. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of cases of alpelisib-induced hyperglycemia given its short half-life. Monitor blood glucose as clinically indicated and at least twice weekly until FPG resolves to ≤ Grade 1. • If FPG resolves to ≤ 160 mg/dL (or RBG ≤ 200 mg/dL) within 3-5 days while off study treatment and on metformin, re-start alpelisib and reduce 1 dose level, continue with anti-diabetic treatment. A second and third oral hypoglycemic agent may be initiated concomitantly, if needed and in consultation with a diabetologist. Check blood glucose at least weekly for 8 weeks, then continue checking at least every 2 weeks. Alert treating physician if FPG > 250 mg/dl.

	• If FPG does not resolve to ≤ 160 mg/dl (or RBG ≤ 200 mg/dl) within 3-5 days while off study treatment and on metformin, consulting a diabetologist for management of diabetes is strongly recommended. • If FPG does not resolve to ≤ 160 mg/dL or RBG ≤ 200 mg/dL within 21 days after institution of appropriate anti-diabetic treatment in cooperation with diabetologist and exclusion of confounding factors, e.g. urinary tract infection, permanently discontinue patient from alpelisib treatment.
Grade 4 FPG or RBG > 500 mg/dL [≥ 27.8 mmol/L]	Omit alpelisib. Confirm fasting status of the assessment. If non-fasting, re-check within 24 hours. Regardless of fasting status, consider IV fluids. Exclude confounding factors such as urinary tract infection. Should consult with diabetologist, initiate or intensify medication with appropriate anti-diabetic treatment (see Grade 3), re-check within 24 hours. • If FPG or RBG improves to ≤ 500 mg/dl, then follow specific grade recommendations • If FPG or RBG is confirmed as > 500 mg/dl and confounding factors can be excluded, permanently discontinue patient from alpelisib.
A diabetologist consultation should always be considered. For all grades: instruct patient to follow dietary guidelines according to local and/or institutional standards for management of diabetes mellitus (such as those provided by the American Diabetes Association) during the study, e.g. controlled carbohydrate intake, high fiber, low processed food intake; three macronutrient balanced meals and 2 small snacks rather than one large meal. In cases of rapidly increasing serum glucose suspicious of severe clinical presentation and/or diabetic ketoacidosis) without obvious confounding factors and potential need of close observation and monitoring, a diabetologist should be consulted with consideration of potential hospitalization and close monitoring. *For specific recommendation please see section 6.3.2.1.3	
Investigations (Hematologic)	
Thrombocytopenia	
Grade 1 (platelets [PLT] < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	Maintain dose level

Grade 3 (PLT < 50-25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, decrease 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level
Investigations (renal)	
Serum creatinine	
< 2 x ULN	Maintain dose level
2 – 3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, maintain dose level • If resolved in > 7 days, decrease 1 dose level
Grade 3 (> 3.0 – 6.0 x ULN) Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from alpelisib
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (> ULN - 1.5 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (> 1.5 - 3.0 x ULN)	Interrupt dose until recovery to Grade ≤ 1 and resume at the same dose if resolved in ≤ 14 days or resume at the next lower dose level if resolved in > 14 days.
Grade 3 (> 3.0 - 10.0 x ULN)	Interrupt dose until recovery to grade ≤ 1, then resume at the next lower dose level.
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from alpelisib.
Isolated AST or ALT Elevation	
Grade 1 (> ULN – 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.

Grade 3 (> 5.0 - 20.0 x ULN)	Interrupt dose until recovery to grade ≤ 1, then resume at the next lower dose level.
Grade 4 (> 20.0 x ULN)	Permanently discontinue.
Combined elevations of AST or ALT and total Bilirubin	See Section 6.3.2.1.5
Gastrointestinal	
Diarrhea	
Grade 1	Maintain dose level but initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at same dose. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level. Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Grade 4	Discontinue subject from treatment. Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrheal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 (enzymatic elevation or radiologic findings only)	Omit dose until resolved to Grade ≤ 1, then resume treatment at dose reduced 1 level. If toxicity recurs, permanently discontinue patient from alpelisib.
Grade 3 For patients deriving clinical benefit upon investigator's judgement:	Omit dose until complete resolution of symptoms and lipase resolved to Grade ≤ 1, then resume treatment at ↓ 1 dose level. Only 1 dose reduction is allowed. If recovery to ≤ Grade 1 is longer than 28 days, the patient must be discontinued from the study. If toxicity reoccurs, permanently discontinue patient from alpelisib.

For other patients:	Permanently discontinue patient from alpelisib.
Grade 4	Permanently discontinue patient from alpelisib.
Stomatitis/Oral mucositis	
Grade 1/ Tolerable Grade 2	Maintain dose level Non-alcoholic or salt-water mouth wash
Intolerable Grade 2 or Grade 3	First occurrence: hold until ≤ Grade 1 and decrease 1 dose level (if stomatitis is readily manageable with optimal management, re-introduction at the same level might be considered at the discretion of the investigator). Second occurrence: hold until ≤ Grade 1 and decrease 1 dose level.
Grade 4	Permanently discontinue patient from alpelisib.
Skin and subcutaneous tissue disorders	
Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity. Dermatologist consultation is mandated for serious cutaneous reactions (i.e. fulfilling seriousness criteria for AE Reporting) and for severe cutaneous reactions like Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). See Section 6.3.2.1.2.	
Rash	
Grade 1 (< 10% body surface area (BSA) with active skin toxicity*)	Maintain dose level. Initiate topical corticosteroids 3-4 x daily: preferred compounds to use are triamcinolone and betamethasone as long as skin toxicity is active, for a maximum of 28 days. If active rash is not resolved within 28 days of appropriate treatment, add low dose systemic corticosteroid (20-40 mg/d) such as prednisone 10 mg 3x/day.

	For subjects with symptoms like burning and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 2 (10-30% BSA with active skin toxicity*)	Maintain dose level. Initiate or intensify topical corticosteroids 3-4x daily: preferred compounds to use are triamcinolone or betamethasone as long as skin toxicity is active, for a max. of 28 days Add systemic corticosteroids 20-40mg/d. If rash resolves to ≤ G1 within 10 days, systemic corticosteroid may be discontinued. For subjects with symptoms like burning, stinging and/or pruritus, add non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 3 (> 30% BSA with active skin toxicity*)	Omit alpelisib dose until rash/skin toxicity has improved to Grade 1 or resolved. Recommend documentation by photography and consider performing a skin biopsy. Initiate topical corticosteroids 3-4 x daily: preferred compounds to use are triamcinolone or betamethasone for at least 28 days. Add systemic corticosteroids 20-40mg/d. If rash resolves to ≤ G1 within 10 days, systemic corticosteroids may be discontinued. Re-start alpelisib dose once rash/skin toxicity is fading but no longer active (G1): • At a reduced dose in case of first occurrence. • If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with alpelisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued. For subjects with symptoms like burning, stinging and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with alpelisib.

Grade 4 (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• Permanently discontinue patient from alpelisib. • Consult a dermatologist, ensure documentation by photography and obtain a skin biopsy. • Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. • Additional measures may be taken as per local treatment guidance.
Any Grade of Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis / Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or other SJS/TEN/DRESS-like severe skin reactions	• Permanently discontinue patient from alpelisib treatment. • Consult dermatologist, ensure documentation by photography and obtain skin biopsy. • Follow local treatment guidelines for SJS/TEN/DRESS.
*"Active" skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered "active" any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	
Immune system disorders	
Hypersensitivity. See Section 6.3.2.1.6	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.3.2.1.1.	
Investigations (Metabolic)	
Asymptomatic amylase and/or lipase elevation (see also Section 6.3.2.1.4)	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥ 3 (> 2.0 x ULN)	Omit dose until resolved to baseline, then: • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then decrease 1 dose level

	Note: In cases of isolated amylase elevations only, dosing may be maintained provided amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. Monitor total amylase (and continue to assess fractionated amylase) as specified in Section 6.3.2.1.4.
Note: Withhold study treatment for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; and perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
Investigations (any other)	
Other adverse events	
Grade 1 or 2	Maintain dose level.
Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
Grade 4	Permanently discontinue from alpelisib. Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice).

For additional details on the safety profile of alpelisib, please refer to the alpelisib Investigator's Brochure.

6.3.2.1 Additional follow-up for selected toxicities

6.3.2.1.1 Management of pneumonitis / Interstitial lung disease

Alpelisib is associated with pneumonitis/interstitial lung disease. Closely monitor all subjects for signs and symptoms of pneumonitis.

All patients will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Patients suspected of having developed pneumonitis should interrupt alpelisib immediately (but may continue fulvestrant if clinically indicated) and undergo appropriate imaging (high resolution CT scan) and broncho-alveolar lavage. Biopsy should be considered if clinically appropriate. Infectious causes of interstitial lung disease should be ruled out.

Investigators should follow institutional practice for the management of pneumonitis, which generally includes treatment with high dose corticosteroids. Antibiotic therapy should be administered concurrently if infectious causes are suspected. Consultation with a pulmonologist is highly recommended for any case of pneumonitis during study treatment. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with alpelisib and promptly initiate appropriate treatment and supportive measures.

Table 6-11 Management of pneumonitis

Pneumonitis (any grade)	Immediately interrupt alpelisib for any case of suspected pneumonitis. Fulvestrant may be continued, if clinically indicated. Obtain appropriate imaging (high resolution CT scan) and consider BAL and biopsy if appropriate based on clinical judgment. See Section 6.3.2.1.1 for details of management of pneumonitis. Treatment for pneumonitis should be initiated based on institution guidelines and generally includes high dose corticosteroids; antibiotic therapy should be administered concurrently if infectious causes are suspected. Alpelisib should be permanently discontinued in all patients with confirmed pneumonitis.

6.3.2.1.2 Guidelines for the treatment of study drug induced skin toxicity

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi agents.

Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as an adverse event. The most frequent skin adverse events reported are maculopapular rash (only a minority present acneiform rash); pruritus and dry skin. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed. Skin reactions may improve over several weeks. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity at any grade and mandated if severe cutaneous reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or drug reaction with eosinophilia and systemic symptoms is suspected.

Workup for skin toxicity events includes skin photography, a complete blood count with differential and a full chemistry panel. A paired skin biopsy should be obtained (from both

affected and an unaffected skin area) for local histopathology assessment to further assess skin toxicity, especially to confirm suspected diagnosis of any severe cutaneous reactions.

Skin photographs must be taken, and a skin biopsy performed in case of Grade 4 skin toxicity or any Grade of suspected severe cutaneous reactions. In case of Grade 3 skin toxicity, Novartis recommends that photographs be taken, and a biopsy performed.

Skin biopsies will be sent to a Novartis designated laboratory, together with dermatologist and pathology reports, if available, for further research purpose on the pathology and mechanism of PI3K inhibitor treatment induced skin toxicity.

Antihistamines administered prior to rash onset may decrease incidence and severity of rash based on Study CBYL719C2301. Therefore, at the Investigator's discretion, non-sedating antihistamines (e.g. cetirizine [Zyrtec©] fexofenadine [Allegra], loratadine [Claritin]) may be used as prophylactic treatment to reduce severity of rash in all subjects and especially for subjects with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies.

For grade 4 skin events or any grade of severe cutaneous reactions (including SJS, TEN, EM and DRESS), alpelisib treatment must be permanently discontinued without any re-challenge.

Recommended therapies for skin toxicity events include:

- Mild to high potency topical steroids such as triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion or cream preparations for ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.
- GABA agonists: gabapentin 300 mg every 8 hours, pregabalin 50-75 mg every 8 hours (to adjust for renal impairment). Depending on the subject's clinical condition, be aware of potential and common side effects observed with GABA agonists such as somnolence, dizziness (both drugs) and peripheral edema (gabapentin) among others adverse events.

Dry skin has been reported. It is recommended that patients with dry skin use mild and fragrance-free soaps and detergents.

Although preclinical experiments demonstrated that alpelisib has no potential phototoxic effect, patients should avoid sun exposure during treatment with alpelisib, especially when they have already experienced rash or other skin toxicities as the increased blood flow to the skin may worsen skin symptoms. Patients should be advised to take measures to protect themselves from direct exposure to sunlight, including the wearing of sunglasses as well as the regular use of sunscreen, hats, long-sleeve shirts and long pants when outdoors.

6.3.2.1.3 Guidelines for the treatment of alpelisib induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis, which may result in increases of plasma glucose and insulin resistance (Busaidy 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Patients with pre-diabetes (i.e. FPG 100-125 mg/dl; 5.6 - 6.9 mmol/L) and those with an established diagnosis of type 2 diabetes mellitus should be monitored carefully, thus allowing early detection and prompt

management of increases in FPG or RBG while on alpelisib treatment. However, all patients, even those with FPG within normal limits at screening, may develop alpelisib induced hyperglycemia. Patients should always be instructed to follow dietary guidelines provided by the American Diabetes Association, e.g. small frequent meals, low carbohydrate content, high fiber, low processed food intake, three macronutrient balanced meals and 2 small snacks rather than one large meal and exercise as appropriate.

Detailed guidelines for the management of alpelisib induced hyperglycemia is provided in Table 6.10. This includes early administration of metformin. Metformin may be titrated to a daily dose of 1000 mg BID.

Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting plasma glucose testing may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance.

Special attention should be paid to the risk of hypoglycemia in patients interrupting alpelisib treatment and concomitantly receiving insulin and/or sulfonylureas. Due to the short half-life of alpelisib, all glucose lowering medications should be discontinued when alpelisib is stopped.

Consultation with a diabetologist is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

6.3.2.1.4 Follow-up on amylase or lipase elevation (≥ CTCAE Grade 3)

Patient with amylase or lipase elevation ≥ CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until ≤ Grade 1 (or baseline). After resumption of dosing, continue to test weekly for one additional cycle. If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle.

An exception to these follow-up guidelines will be made for cases of isolated amylase elevations in which amylase fractionation demonstrates that pancreatic amylase is ≤ Grade 1. In such cases, total amylase and fractionated amylase should be monitored weekly (or more frequently if clinically indicated) for 4 weeks. If pancreatic amylase remains ≤ Grade 1, subsequent monitoring must be performed at least every 4 weeks (or more frequently if clinically indicated).

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks).

If amylase and/or lipase elevations are accompanied by new or progressive unexplained abdominal symptoms such as severe pain or vomiting, withhold study treatment, then perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.

See also dose modification guidelines described in Table 6.10.

6.3.2.1.5 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI and should be considered as clinically important events.

In general, any increase of serum aminotransferases to > 3 x ULN should be followed by repeat testing within 48 to 72 hours. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required.

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], 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 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. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver 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.

Upon presentation:

- Perform comprehensive medical history including cardiac disease, blood transfusions, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc.
- History of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
- Exclude other causes of liver disease.

Subject monitoring:

- Repeat liver chemistry tests within 48-72 hours.
- Retest frequency can decrease to weekly or less if abnormalities stabilize, drug has been discontinued, and the subject is asymptomatic.

As drug-induced liver injury (DILI) is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed (see Table 6-12). Liver biopsy has limited value in the diagnosis of DILI as

histopathological findings in DILI can resemble many other liver conditions. However, biopsy can be useful to establish an alternative diagnosis especially if other tests are inconclusive.

If DILI is confirmed, permanently discontinue.

If DILI is unlikely, interrupt treatment. Treat identified cause according to institutional guidelines. If resolved, reduce by one dose level. Re-administration of study treatment should be considered only if the investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen should be discussed with the Novartis medical safety team.

Table 6-12 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, gammaGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Following appropriate causality assessments as outlined above, the causality of the drug is estimated as “probable” i.e. > 50% likely if it appears greater than all other causes combined. The term “drug-induced” indicates probably caused by the drug, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

6.3.2.1.6 Guidelines for hypersensitivity

Alpelisib and combination drug are associated with hypersensitivity reactions, including anaphylaxis. These are manifested by symptoms including, but not limited to dyspnea, flushing, rash, fever or tachycardia. Alpelisib and/or combination drug should be permanently discontinued and should not be re-introduced in subjects with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

6.3.3 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed at least once a week (or more frequently if required by institutional practices, or if clinically indicated) until resolution or stabilization of the event, whichever comes first. Clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

All patients will be followed up for adverse events and serious adverse events for 30 days following the last dose of study treatment. Patients stopping study treatment but still receiving ribociclib outside of this trial (e.g., commercial supply) will be followed up for safety up to 30 days independently of resolution/stabilization of AEs.

6.4 Concomitant medications (core phase)

6.4.1 Permitted concomitant medication

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, vitamins, herbal/natural medications and blood transfusions) administered within 30 days prior to the start of any study treatment and up to 30 days after the last dose of study treatment must be listed on the Prior and Concomitant Medications or the Surgical and Medical Procedures eCRF.

If patients take concomitant medications chronically, any change in the dose schedule of these medications should be clearly documented throughout the study period.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.4.1.1 Biphosphonates 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 bone metastases is permitted.
- Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.

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

6.4.1.2 Hematopoietic growth factor

Prophylactic use of WBC growth factors with ribociclib is not recommended.

6.4.1.3 Palliative radiotherapy

Palliative radiation is permitted and 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 must be ruled out.

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

Refer to the ribociclib Summary of Product Characteristics and letrozole drug package insert and Appendix 14.1 for information on possible interactions with other drugs.

6.4.1.4 Use of antiemetic medications

Ribociclib has low to minimal emetogenic potential as per 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 resulting from study treatment (NCCN Clinical Practice Guidelines in Oncology. Antiemesis, 2017; Roila F et al 2016).

Potential drug interaction between ribociclib/placebo 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 Section 6.4.3 and Appendix 14.1 for medications that are prohibited or allowed to be used with ribociclib/placebo.

6.4.2 Concomitant therapy requiring caution

Medications to be used with caution during treatment with combined ribociclib and letrozole are listed below (see Table 14.2 in Appendix 14.1). This list is not comprehensive and is only meant to be used as a guide. **Please contact the medical monitor with any questions**. These medications should be excluded from the 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 (may increase or decrease ribociclib exposure, respectively)
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index (ribociclib may increase exposure to these medications)
- Strong inhibitors of Bile Salt Export Pump (based on in vitro data coadministration with ribociclib may lead to intrahepatic cholestasis).
- Medications that carry a possible risk for QT prolongation (may precipitate QT prolongation and TdP).
- Sensitive substrates of the renal transporters, MATE1, and OCT2, BCRP (has a potential to increase exposure to substrates of these transporters, although no animal or clinical data are available to support these statements).
- 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).

- Substrates metabolized predominantly by CYP2C19 or CYP2A6 with a narrow therapeutic index (that could be affected by letrozole).

6.4.2.1 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 sub-therapeutic 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)

6.4.3 Prohibited concomitant therapy

The following medications are prohibited during study treatment (see Table 14.1 in Appendix 14.1). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions:

- Strong inhibitors or inducers of CYP3A4/5 (may significantly increase or decrease ribociclib exposure, respectively).
- Substrates of CYP3A4/5 with a narrow therapeutic index (ribociclib may increase exposure to these medications resulting in toxicity to these medications).
- Medications with a known risk for QT prolongation (may precipitate QT prolongation and TdP in combination with ribociclib).
- Other investigational and antineoplastic therapies.
- Herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5 or those with a known risk of QT prolongation. These include but are 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 all herbal medications at least 7 days prior to first dose of study treatment.

6.4.4 Drugs with QT prolongation

As far as possible, avoid co-administering medications with a "known", "possible" or "conditional" risk of TdP (www.crediblemeds.org) or any other medication with the potential to increase the risk of drug-related QT prolongation (e.g. via a potential DDI increasing the exposure of ribociclib or the exposure of the QT prolonging drug). If concomitant administration of drugs with a known risk of TdP is required and cannot be avoided, ribociclib must be interrupted (see Table 6.7). If during the study, concomitant administration of a drug with "Possible risk" or "Conditional risk" of TdP is required based on investigator assessment

and clinical need, study treatment may be resumed under close clinical and ECG monitoring to ensure patient safety. A list of drugs associated with QT prolongation and/or TdP is available online (www.crediblemeds.org). Medications with a known risk for QT prolongation are prohibited during study treatment.

6.5 Concomitant medications (extension phase- patients with a PIK3CA mutation)

6.5.1 Permitted concomitant therapy

Medications required to treat adverse events, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited (see Appendix 14.2.2).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including vitamins, physical therapy, and blood transfusions) administered within 30 days prior to the start of study treatment and up to 30 days after the last dose of study treatment must be listed on the Concomitant Medications or the Surgical and Medical Procedures eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.5.1.1 Oral anti-diabetics

Patients who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association) guidance (https://professional.diabetes.org/content-page/practice-guidelines-resources). It is recommended to start treatment with metformin. Patients receiving oral antidiabetics which are predominantly metabolized by CYP2C9 and CYP2C8, including but not limited to, repaglinide, rosiglitazone, glipizide and tolbutamide, should be monitored with respect to their effectiveness as alpelisib was found to be an inducer of CYP2C9 in vitro (refer to Appendix 14.2).

6.5.1.2 Gastric protection agents

Alpelisib is characterized by pH-dependent solubility but can be co-administered with acid reducing agents (ARAs, e.g. proton-pump inhibitors, H2-antagonists and antacids) as long as it is taken after food. In a joint food effect and acid reducing DDI study, food exhibited a more pronounced effect on the solubility of alpelisib than the effect of gastric pH value leading to a net decrease in AUC of an average of 21% when administered after a meal.

6.5.1.3 Corticosteroids

Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia (steroid-induced diabetes). Hyperglycemia is a common

adverse event for PI3K inhibitors like alpelisib and should therefore be used with caution and patients closely monitored.

6.5.1.4 Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy in order to rule out progression of disease. In case of progressive disease, patients should discontinue treatment. No dose modification of study treatment is needed during radiotherapy.

6.5.1.5 Hematopoietic growth factor

Hematopoietic growth factors may be used according to American Society of Clinical Oncology (ASCO) guidelines.

6.5.2 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib and fulvestrant treatment in this study are listed below (see also Table 14-3 in Appendix 14.2.1). This list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions.

These medications should be excluded from use if possible. If they must be given based on the investigator's judgment, then use with caution and consider an alpelisib drug interruption, as appropriate, if the concomitant medication is only needed for a short time.

Medications to be used with caution:

- Sensitive substrates for CYP3A4, CYP2C9 or CYP2B6 and/or which have a narrow therapeutic index (Table 14-3).
  - CYP2C9 substrates with narrow therapeutic index (NTI) (e.g. anticoagulants): In vitro evaluations indicated that pharmacological activity may be reduced by the CYP2C9 induction effects of alpelisib. In the absence of clinical data, caution is recommended with therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs. Alternatively, therapeutic anticoagulation may be accomplished using low-molecular-weight heparin or Direct Thrombin Inhibitors (DTIs) and Factor Xa inhibitors.
  - CYP2B6 sensitive substrates or CYP2B6 substrates with NTI: Based on a static mechanistic assessment with sensitive CYP2B6 substrates such as bupropion, a reduction of exposure by up to 3-fold can be expected when co-administered with alpelisib. In absence of clinical data, sensitive CYP2B6 substrates (e.g. bupropion, efavirenz) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib, as alpelisib may reduce the clinical activity of such drugs.
  - Selected CYP3A4 substrates: Alpelisib can be co-administered with sensitive CYP3A4 substrates (e.g. everolimus, midazolam) and CYP3A4 substrates with narrow

therapeutic window (e.g. fentanyl). Caution is recommended when alpelisib is used in combination with CYP3A4 substrates that also possess an additional time-dependent inhibition and induction potential on CYP3A4 that affects their own metabolism (e.g. ribociclib, encorafenib). Systemic exposures of such CYP3A4 auto-inhibitors and auto-inducers may be either decreased or increased, respectively, depending on the drug and nature of auto-perpetrator potential when alpelisib is co administered, based on PBPK simulations.

- Herbal Medications: The use of herbal preparations/medications and dietary supplements are permitted with caution unless explicitly prohibited (see Section 6.5.4) for being strong inducers of CYP3A4 such as St. John's wort (Hypericum perforatum) and avasimibe (see Table 14-4) or BCRP inhibitors such as curcumin (see Table 14-5). Medications such as Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, black cohosh and ginseng should be avoided if possible due to their potential for complex interactions. Since cannabinoids have been shown to inhibit BCRP in vitro, medical cannabis should be used with caution. The use/frequency of use should be documented as a concomitant medication. Subjects closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, subjects should stop using all herbal medications.

6.5.3 Use of biphosphonates

The use of bisphosphonates/denosumab regardless of indication is allowed provided subjects have been on stable doses for at least 2 weeks prior to enrollment. Stable dose should be maintained during the treatment period.

Bisphosphonates may be given according to local prescribing information and routine clinical practice, at the investigator's discretion.

Subjects requiring initiation of bisphosphonate/denosumab treatment during the course of the study should be assessed by appropriate image modalities to exclude disease progression; if disease progression is documented, the subject should discontinue study treatment. If bisphosphonate therapy/denosumab is to be started after the first dose of study treatment, the reason for its use must be clearly documented.

Osteonecrosis of the jaw (ONJ) is a known adverse reaction for bisphosphonates/denosumab. In the phase III Study C2301, ONJ was reported in 4.2% subjects (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% subjects (4/287) in the placebo plus fulvestrant arm. All subjects experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in subjects receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, prescribing information of bisphosphonates should be followed.

6.5.4 Prohibited concomitant therapy

The following medications are prohibited during treatment with alpelisib (see Table 14-4 and Table 14-5 in Appendix 14.2), this list is not comprehensive and is only meant to be used as a guide. Please contact the medical monitor with any questions:

- Strong inducers of CYP3A4: avoid co-administration of alpelisib with a strong CYP3A4 inducers as it could potentially reduce the effectiveness of alpelisib (see Table 14.4).
- Inhibitors of Breast Cancer Resistance Protein (BCRP) efflux transporter: avoid the use of BCRP inhibitors in subjects treated with alpelisib (see Table 14.5). If unable to use alternative drugs, closely monitor for increased adverse reactions.
- Other investigational and antineoplastic therapies

6.6 Patient numbering

Upon signing the informed consent form, the patient will be given a unique identification number.

6.6.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.) when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database.

Once a Subject No. is assigned, it must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened.

6.6.2 Treatment assignment

All patients will be treated with ribociclib + letrozole in first line (core phase). Following treatment discontinuation, patients with PIK3CA mutations will be treated with alpelisib + fulvestrant in second line (extension phase).

6.6.3 Treatment blinding

Not applicable; this is an open label study.

6.7 Study drug preparation and dispensation

Patients will be provided with an adequate supply of study drug for self-administration at home on an outpatient basis, including instructions for administration, until at least their next scheduled study visit. The investigator shall provide the patient with instructions for ribociclib and alpelisib administration according to the protocol.

Letrozole and fulvestrant should be dispensed and administered according to local prescribing information and practice.

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 eCRF(s).

6.7.1 Study treatment packaging and labeling

Ribociclib will be provided as local commercial supply (in the locally approved formulation and packaging configuration) and labeled for the study.

Letrozole will be provided as local commercial supply (in the locally approved formulation and packaging configuration) and labeled for the study.

Alpelisib will be supplied as 50 mg and 200 mg film coated tablets as individual patient supply, packaged in bottles labelled for the study. Fulvestrant will be provided as local commercial supply (in the locally approved formulation and packaging configuration) and labeled for the study.

Study treatment labels will comply with local legal requirements. If the label has 2 parts (base plus tear-off label), site personnel will detach the outer part of the label from the package and affix it to the patient's source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with local legal requirements.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments for the core phase 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 documentation.

Note:

- During screening visits, lab assessments are required to be collected within 14 days of C1D1 and ECG within 5 days of C1D1 for eligibility assessment.

  Electrolytes should be monitored at the beginning of each cycle before resuming ribociclib dose during the first 6 cycles and as clinically indicated thereafter. ECGs will be performed at screening (within 5 days of C1D1), C1D15, C2D1, then as clinically indicated, and at End of Treatment (EOT).
- If treatment is withheld at any time during the study, all study visits, safety assessments, and efficacy assessments should be adjusted accordingly to match the treatment cycles.
- For all visits, there is a +/- 3-day window on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise.

Table 7-1 Visit evaluation schedule – Core phase (ribociclib + letrozole)

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening -28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Screening														
Informed consent	11.3	X												
Inclusion/exclusion criteria	5.2, 5.3	X												
Patient history														
Demography	7.1.1.3	X												
Medical history including post menopausal status	7.1.1.3	X												
Diagnosis and extent of cancer	7.1.1.3	X												
Prior antineoplastic therapy-medication	7.1.1.3	X												
Prior antineoplastic therapy-radiotherapy	7.1.1.3	X												
Prior antineoplastic therapy-surgery	7.1.1.3	X												
Prior and concomitant medication	7.1.1.3	X	Continuous – up to 30 days after last dose											

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening -28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Surgical and medical procedures	7.1.1.3	X	Continuous – up to 30 days after last dose											
Physical examination														
Physical examination	7.2.3.1	X	X		X		X	X	X	X	X	X		
ECOG-PS	7.2.3.4	X	X		X		X	X	X	X	X	X		
Height	7.2.3.3	X												
Weight	7.2.3.3	X			X			X		X	X	X		
Vital signs	7.2.3.2	X	X		X		X	X	X	X	X	X		
Laboratory assessments														
Hematology (see Table 7.5)	7.2.3.5	(-14 days to day 1)		X	X	X	X	X	X	X	X	X		
Chemistry (see Table 7.5)	7.2.3.5	(-14 days to day 1		X	X	X	X	X	X	X	X	X		
Coagulation (INR)	7.2.3.5	X	As clinically indicated											
Biological assessments														
Blood for liquid biopsy[3] and serum[3]	7.2.1.2	X		X	X[4]	At first imaging evaluation.						X[5]		
[redacted]														
Tumor tissue sample	7.2.1.1	X[6]										X[7]		
Tumor assessments														
Tumor assessment	7.2.2	X	Recommendation: every 12 weeks from start of study treatment [8]									X[10]		
Cardiac assessment														
ECG (standard 12 lead)	7.2.3.6	-5 days to day 1		X	X		As clinically indicated					X[11]		
Safety														
Adverse events	8	Continuous for up to 30 days after last dose of study treatment												

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening -28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Treatment														
Ribociclib	6		Daily: Day 1-21											
Letrozole	6		Daily											
Discontinuation														
Antineoplastic therapies since discontinuation of study treatment												X	X	X

[1] End of study treatment (EOT) visit should be done within 7 days from the last dose of study treatment and prior to initiating subsequent therapy or to continue therapy as commercially available drug. Patients with PIK3CA mutations could proceed to the extension phase to be treated with alpelisib + fulvestrant or, after study termination by sponsor, could access PTA.
[2] Within 30 days of last dose of study treatment. Following treatment discontinuation, patients with PIK3CA mutations can be treated with alpelisib + fulvestrant.
[3] Liquid biopsy to analyze ctDNA and serum to analyze thymidine kinase 1 activity.
[4] It is recommended to collect C2D1 biological samples after 4 weeks from C1D1
[5] Blood for ctDNA and TK1 should be collected for all patients who discontinue treatment excluding those who discontinue due to study termination by sponsor.
[6] Newly obtained tissue biopsy or an archival tumor tissue derived by a recent biopsy of the locoregionally recurrent or metastatic disease (bone biopsy are acceptable). In cases this is not clinically feasible, the submission of an archival tumor tissue of the primary tumor is acceptable
[7] New tissue biopsy should be done only for patients who discontinue the treatment due to disease progression.
[8]. The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of First Imaging biological sample collection (whole blood for liquid biopsy and serum for TK1).
[9] Post treatment follow-up is not required for patients who discontinue due to study termination by sponsor.[10] Tumor assesment at end of study treatment is not required for patients who discontinue due to study termination by sponsor.
[11] ECG at end of study treatment is not required for patients who discontinue due to study termination by sponsor.

Table 7-2 lists all of the assessments for the extension phase 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 documentation.

Note: If treatment is withheld at any time during the study, all study visits, safety assessments, and efficacy assessments should be adjusted accordingly to match the treatment cycles.
Screening assessments must occur before 28 days-1 of the start of treatment as per Table 7-2 except for lab assessments and ECG that are required to be collected within 14 days to day -1 of C1D1.
For all visits within C2D1, a +/- 3-day window on assessments is allowed to take into account scheduling over public holidays.
From C3D1 a +/- 7-day window is allowed.

Table 7-2 Visit evaluation schedule – Extension phase (alpelisib + fulvestrant- patients with a PIK3CA mutation)

		Treatment phase_EXT							End of study treatment_ EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1]_ EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
Obtain extension informed consent	11.3	X									
Inclusion/exclusion criteria	5.2, 5.3	X									
Diagnosis and extent of cancer	7.1.1.3	X									
Prior and concomitant medication	7.1.1.3	Continuous – up to 30 days after last dose									
Surgical and medical procedures	7.1.1.3	Continuous – up to 30 days after last dose									
Physical examination											
Physical examination	7.2.3.1	X	X	X	X	X	X	As clinically indicated	X		
ECOG-PS	7.2.3.4	X				X		X	X		
Weight	7.2.3.3	X				X		X	X		

		Treatment phase_EXT							End of study treatment_ EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1]_ EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
Vital signs	7.2.3.2	X	X	X	X	X	X	X	X		
Laboratory assessments											
Hematology (see Table 7.7)	7.2.3.5	(-14 days to day -1)	X		X	X		X	X		
Chemistry (full) (see Table 7.7)	7.2.3.5	(-14 days to day -1)				X			X		
Chemistry (partial)			X		X			X			
Fasting plasma glucose		(-14 days to day -1)									
Fasting or random plasma glucose			X	X	X	X	X	X	X		
HbA1C		(-14 days to day -1)	C2D1 and then every 3 cycles (i.e. C5D1, C8D1...)								
Fasting lipid panel		(-14 days to day -1)							X		
Fasting lipase and amylase		(-14 days to day -1)						C3D1 and then as clinically indicated	X		
Coagulation	7.2.3.5	(-14 days to day -1)	As clinically indicated								
Urine analysis	7.2.3.5	(-14 days to day -1)	As clinically indicated						X		
Biological assessments											
Blood for liquid biopsy	7.2.1.2	X[3]				X[4]	At first imaging evaluation.		X[5]		
Tumor biopsy[6]									X		
Tumor assessments											
Tumor assessment	7.2.2	X[8]	Recommendation: every 12 weeks from start of study treatment[7]						X9		
Cardiac assessment											

		Treatment phase_EXT							End of study treatment_ EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1]_ EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
ECG (standard 12 lead)	7.2.3.6	(-14 days to day -1)	As clinically indicated						X[10]		
Cardiac Imaging (MUGA or Echo)		X	As clinically indicated						X[11]		
Safety											
Adverse events	8	Continuous for up to 30 days after last dose of study treatment									
Treatment											
Alpelisib	6		Daily								
Fulvestrant	6		X		X	X		X			
Discontinuation											
Antineoplastic therapies since discontinuation of study treatment									X	X	X
Survival follow-up											X

[1] End of study treatment (EOT) visit should be done within 28 days of last dose of study drug and prior to initiating alpelisib in PTA or a subsequent therapy.

[2] Within 30 days of last dose of study treatment.

[3] Liquid biopsy at screening is required only if not obtained at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent. form

[4] C2D1 biological samples should be collected 4 weeks from C1D1

[5] Blood for ctDNA should be collected for all patients who discontinue the treatment except those discontinuing due to study termination by sponsor.

[6] Newly obtained tissue biopsy should be done for patients who discontinue the treatment due to disease progression.

[7] The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of first imaging biological sample collection (whole blood for liquid biopsy).

[8] Any imaging assessments already completed during the core phase of the trial (i.e. last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

[9] Tumor assessment is not required for patients who discontinue due to study termination by sponsor

[10] ECG at end of study treatment is not required for patients who discontinue due to study termination by sponsor.

[11] Cardiac imaging at end of study treatment is not required for patients who discontinue due to study termination by sponsor.

7.1.1 Screening

Core phase

After signing the study Informed Consent Form (ICF), screening assessments will be done within 1 to 28 days prior to start of study treatment or within 5 days prior to start of study treatment for ECG and within 14 days prior to start of study treatment for laboratory assessments (see Table 7.1 for list of assessments to be performed). If the patient meets all inclusion and no exclusion criteria, the screening labs can be used for baseline if the patient is dosed within 14 days of the screening visit. If the patient cannot be dosed within 14 days of screening, then the labs should be repeated the day before patient starts treatment (see Table 7.1)

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before. In this case the Subject No. 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, a repeated evaluation within the screening window is permitted for screening results out of the defined range.

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

Extension phase

Extension phase is reserved to patient with a PIK3CA mutation as determined in tumor tissue and/or plasma by a Novartis designated laboratory (results of tissue samples obtained during the core phase, screening or EOT, are acceptable).

After signing the ICF specific for the extension phase, patients with a PIK3CA mutation will be newly screened (see Table 7.2 for list of assessments to be performed). The date of the EOT visit of the core phase could correspond to the date of the Informed Consent Signature for the extension phase.

Extension screening assessments will be done within 1 to 28 days prior to start of extension study treatment. ECG and laboratory assessments are required within 14 days prior to start study treatment extended phase (see Table 7.2 for list of assessments to be performed). Re-screening of patients is only allowed once per patient. For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range.

Extension C1D1 Visit has to be done at least 7 days after the discontinuation of ribociclib and letrozole assumed in the core phase.

Any imaging assessments already completed during the core phase of the trial (i.e. last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

7.1.1.1 Eligibility screening

Following registration for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the eCRF.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent form but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page.

The following information will be collected on screen failures:

- Demographic information (core phase only)
- Informed consent
- Inclusion/Exclusion
- Death
- Withdrawal of consent, if applicable, must also be completed. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event (SAE) during the Screening Phase (see Section 8 for SAE reporting details).

7.1.1.3 Patient demographics and other baseline characteristics

The data collected at screening for the core phase include:

- Demography (Date of birth, sex, race, ethnicity)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history/current medical conditions.
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications taken within 30 days before the first dose is administered must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there are any new changes to the medications.
- Surgeries and Medical Procedures prior to Informed Consent are recorded on the Medical History eCRF. The Surgical and Medical Procedures after signing Informed Consent are recorded on Surgical and Medical Procedures eCRF.

The following assessments will be performed at screening:

- Newly obtained tissue biopsies will be collected at screening for biological analyses. The baseline tumor sample should be obtained during the screening process prior to starting treatment. If fresh biopsy is not clinically feasible, archival tissue (preferably the most recent biopsy of the locoregionally recurrent or metastatic disease) will be acceptable.

[redacted]

- Blood samples to analyze ctDNA (liquid biopsy) and thymidine kinase 1 activity (serum) will be collected.
- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, INR, chemistry)
- ECG
- Tumor assessments

The data collected at screening for the extension phase include:

- Inclusion/exclusion criteria
- All medications taken within 30 days before the first dose is administered must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there are any new changes to the medications.

The following assessments will be performed at screening:

- Blood samples to analyze ctDNA (liquid biopsy) will be collected if not obtained at EOT of core phase
- Vital signs
- Weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations
- Urine analysis
- ECG
- Cardiac Imaging (MUGA or Echo)
- Tumor assessments

7.1.2 Treatment period

Core phase: patients will be treated with ribociclib + letrozole until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. For details of assessments, see Table 7.1.

Extension phase: following discontinuation of ribociclib + letrozole, patients with PIK3CA mutations will be treated in second line with alpelisib + fulvestrant until disease progression, death, unacceptable toxicity or discontinuation from the study treatment due to any other reason. For details of assessments, see Table 7.2.

7.1.3 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 a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. Patients 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 may 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 voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

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
- 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 due to toxicity that result in discontinuation. Please see Section 6.3.
- Use of prohibited medication. See Section 6.4.3 (core phase) and Section 6.5.4 (extension phase)
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30-day safety follow-up and by a 3 months post treatment follow up visit/phone call, except if EOT visit is performed for study termination by sponsor.

At EOT visit, all the assessments listed in Table 7.1 (ribociclib + letrozole) and Table 7.2 (alpelisib + fulvestrant) will be performed. If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the patient return for an additional visit.

7.1.4 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 any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. If a patient withdraws consent, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

7.1.5 Follow-up period

All patients will complete safety evaluations within 30 days after the last dose of study treatment. Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

All patients will complete also a 3 months post treatment visit/phone call in which the first antineoplastic therapy started since discontinuation of study treatment will be collected, except if EOT visit is performed for study termination by sponsor.

7.1.6 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 eCRF.

7.2 Assessment types

7.2.1 Biological assessments

Biomarker analyses of samples collected from patients enrolled in this study will be used to investigate the mechanisms of response and resistance to therapy with ribociclib in combination with letrozole and to therapy with alpelisib in combination with fulvestrant.

During the study, tumor, blood [redacted] samples will be collected to perform biological assessments. A summary of the biological sample collection plan is provided in Table 7.3 and

Table 7.4. All assessments will be performed by a Novartis designated laboratory. Instruction for collection, preparation and shipment of all samples can be found in the central laboratory manual. Required sample collection information must be entered on the appropriate eCRF pages and requisition forms.

There may be circumstances when a decision is made to not perform or discontinue an analysis due to either practical or feasibility reasons. For example, there may be inadequate sample number, issue related to the quality of the sample or issue related to the assay that preclude analysis. Alternatively, there may be insufficient data to allow correlative analyses. Therefore, depending on the results obtained during the study, analysis of some samples/timepoints may be omitted.

Table 7-3 Biological sample collection plan: ribociclib + letrozole

Sample type	Volume/quantity	Visit	Timepoint
Tumor samples			
Mandatory Fresh baseline tumor biopsy or archival formalin fixed –paraffin embedded tumor sample (preferred type: recent biopsy of locoregionally recurrent or metastatic disease).	FFPE tumor block or 20 unstained slides	Screening	Day -28 to day 1 (any time before of study treatment)
Mandatory (if medically feasible, i.e. no contraindications) Newly obtained tumor sample	FFPE tumor block or 20 unstained slides	EOT*	Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy.
Blood samples			
Mandatory Blood for ctDNA	10 mL	Screening	Day -28 to day 1 (any time before of study treatment)
	10 mL	C1D15	
	10 mL	C2D1	
	10 mL	First Imaging (12 weeks ± 7 days)	
	10 mL	EOT*	Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy.
Mandatory Serum samples for TK1 activity analysis	10 mL	Screening	Day -28 to day 1 (any time before of study treatment)
	10 mL	C1D15	
	10 mL	C2D1	
	10 mL	First Imaging (12 weeks ± 7 days)	
	10 mL	At the time of EOT due to disease progression	Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy.

[redacted]

In the event that blood samples are lost or damaged, patients may be asked to provide additional samples as reported in the informed consent form

[redacted]

* if EOT is performed due to study termination by sponsor, no biological samples are required.

Table 7-4 Biological sample collection plan: alpelisib + fulvestrant

Sample type	Volume	Visit	Timepoint
Tumor samples			
Mandatory (if medically feasible, i.e. no contraindications) Newly obtained tumor sample	FFPE tumor block or 20 unstained slides	EOT upon progression of disease	Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy
Blood samples			
Mandatory Blood for ctDNA	10 mL	Extension screening if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form	
	10 mL	C2D1	
	10 mL	First Imaging (12 weeks ± 7 days)	
	10 mL	EOT*	Possibly within 7 days from the last dose of study treatment but always prior to initiating any subsequent therapy.
In the event that blood samples are lost or damaged, patients may be asked to provide additional samples as reported in the informed consent form			

* if EOT is performed due to study termination by sponsor, no biological samples are required.

7.2.1.1 Assessments in tumor tissues

Tumor tissue samples acquired at core baseline and upon progression of disease in the core phase (if clinically feasible) and upon progression of disease in the extension phase (if clinically feasible) will be analyzed to assess mutational aberrations across different patient profiles and to assess [redacted] protein biomarkers.

Patient must have a core baseline tumor sample. It is recommended to collect a newly obtained tissue biopsy or to provide an archival tumor tissue derived by a recent biopsy of the locoregionally recurrent or metastatic disease (bone biopsies are acceptable). In cases this is not clinically feasible, the submission of an archival tumor tissue of the primary tumor is acceptable. Tumor blocks are preferred option but if not possible, 20 unstained slides should be made available.

An addition tumor biopsy collection (if clinically feasible) is requested at time of tumor progression and prior to subsequent therapy in the core phase and at time of tumor progression and prior to subsequent therapy in the extension phase.

Tumor tissues will be used to assess molecular alterations of several genes related to ER+ breast cancer and CDK4/6 pathway for identifying biomarkers that may be predictive of benefit from study treatment or lack of response/progression. The approach will use technologies such as Next Generation Sequencing platform and will be based on a customized gene panel that includes, but is not limited to, *RB1*, *ESR1*, *CCND1*, *CDKN2A, PIK3CA, TP53* and *PTEN*.

[redacted]

Moreover the expression of some proteins by IHC will be assessed, i.e. VEGFR, an angiogenesis biomarker.

Additional method and biomarkers may be utilized if indicated by new findings from the literature as well as from Novartis Internal data.

Instructions for the collection, preparation and shipment of samples can be found in the laboratory manual.

7.2.1.2 Assessments in blood

During the core phase (treatment with ribociclib + letrozole), blood samples (whole blood and serum) will be collected at baseline, and then at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, and at EOT. For patients with PIK3CA mutations treated with alpelisib + fulvestrant following discontinuation of treatment with ribociclib + letrozole (extension phase), blood samples for ctDNA will be collected at extension screening (if not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form), cycle 2-day 1, at first imaging evaluation and at EOT.

Blood samples will be used to perform multiple gene assessments of ctDNA. The use of ctDNA offers a unique opportunity for serially monitoring tumor mutations in a less invasive manner during the course of treatment, allowing for the detection of changes in tumor burden and monitoring response to treatment. Evaluation of tumor mutations at time of progression may provide information regarding potential mechanisms of resistance to hormone and/or CDK4/6 target therapy. The approach will use technologies such as Next Generation Sequencing platform and will be based on a customized gene panel that includes, but is not limited to, *RB1*, *ESR1*, *CCND1*, *CDKN2A, PIK3CA, TP53* and *PTEN*. The findings will then be compared to those obtained on tissue biopsy.

Serum samples will be used to measure TK1 activity (only core phase). TK1 Thymidine kinase 1 (TK1) is an enzyme involved in nucleic acid synthesis and therefore considered to be an important tumor proliferation marker. TK1 will be analyzed on serum by chemiluminescence immunoassay.

Additional method and serum biomarkers may be utilized if indicated by new findings from the literature as well as from Novartis Internal data. Instructions for the collection, preparation and shipment of samples can be found in the laboratory manual.

[redacted]

7.2.2 Efficacy assessments

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (Appendix 14.7) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 7.5. There will be no central review of imaging assessments.

Table 7-5 Imaging Assessment Collection Guidelines

Procedure	Screening (core and extension phase)	Treatment phase*	End of treatment*
CT or MRI (chest, abdomen, pelvis)	Mandated***	Recommended every 12 weeks	Mandated
Brain CT or MRI	Only if suspected brain metastasis***	As clinically indicated	As clinically indicated
Whole body bone scan**	Mandated***	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan (or skeletal survey) at screening that are not visible in the chest, abdomen, pelvis CT/MRI. ***	If bone lesion at screening, recommended every 12 weeks.	Mandated only if bone lesion at screening.
Skin visual inspection and measurement	Only if skin lesions at screening	Recommended every 12 weeks.	Mandated if skin lesions at screening.
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening***	If lesion identified at baseline, recommended 12 weeks.	Mandated if lesion at screening.

*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 12) and for patients whose previous tumor assessment did not demonstrate PD and was done more than 28 days prior to end of treatment visit. Tumor evaluation at EOT is not required for those patients exiting the trial due to sponsor termination.
The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of First Imaging biological sample collection (whole blood for liquid biopsy and serum for TK1).
** Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET).
*** Any imaging assessments already completed during the core phase of the trial (i.e. last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

Baseline/Screening imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

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

Any imaging assessments already completed during the core phase of the trial (i.e. last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

Any imaging assessments obtained after study treatment cannot be considered baseline images.

The following imaging assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI, if clinically indicated
- Whole body bone scan
- Localized bone CT, MRI or X-ray, for any lesions identified on the full body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- Visual inspection and measurement of skin lesions (only if skin lesions at screening)
- CT or MRI of other metastatic sites (e.g. neck), if clinically indicated

If a patient is known to have a contraindication to CT intravenous contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

If brain metastases are suspected at baseline, brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A full body bone scan should be performed per institutional standard of care [e.g., Tc-99 bone scan, whole body bone MRI, fluorodeoxyglucose positron emission tomography or sodium fluoride PET]. Localized CT, MRI or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease should be performed as appropriate.

If skin lesions are present at screening, lesion will be measured and visually monitored.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 7.5 should be performed at the timepoints specified using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 7.1 and Table 7.2). Imaging assessments for response evaluation will be performed in a recommended timeframe of every 12 weeks, until disease progression, death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the first dose date as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments are performed.

The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of first imaging and biological sample collection (whole blood for liquid biopsy [core and extension phase] and serum for TK1 [core phase]).

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by visual inspection and measurement and when possible, by the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease as per RECIST 1.1.

7.2.3 Safety and tolerability assessments

Safety will be monitored by assessing physical exams, ECOG performance status, ECGs, Cardiac Imaging (only extension phase), vital signs, hematological and chemistry labs (including glucose monitoring in the extension phase) as well as by collecting adverse events at every visit (Table 7.1 and Table 7.2). For details on AE collection and reporting, see Section 8.

7.2.3.1 Physical examination

A complete physical examination will include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological review. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examinations are to be performed according to the visit schedule as outlined in Table 7.1 and Table 7.2.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History 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.

7.2.3.2 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.3.3 Height and weight

Height will be measured at screening.

Body weight will be measured at screening and at subsequent time points as specified in Table 7.1 and Table 7.2.

7.2.3.4 Performance status

The ECOG Performance status scale will be used as described in Table 7.6.

Table 7-6 ECOG Performance Status

Grade	ECOG Performance 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

7.2.3.5 Laboratory evaluation

Local site laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring, as well as physical and chemical urine examination (see Table 7.7). All unscheduled blood testing and urine analyses will also be performed locally. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (see Section 7.1 and Table 7.2).

Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require dose adjustments of ribociclib treatment (see Section 8.1) constitute an adverse event (AE) and must be reported as an AE on the AE eCRF page.

Laboratory values obtained at the screening visit will be used to assess eligibility to meet Inclusion criteria. If a patient meets all inclusion and no exclusion criteria, the screening labs can be used for baseline if patient is dosed within 14 days of the screening visit. If patient cannot be dosed within 14 days of screening, then the labs should be repeated the day before patient starts dosing.

Table 7-7 Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	WBC, ANC, lymphocyte. Hemoglobin, platelets. Additional parameters for extension phase: Hematocrit, MCH, MCHC, MCV, Red Blood cells, Differential WBC (Basophils, Eosinophils, Lymphocytes, Neutrophils, Monocytes).
Chemistry	Alkaline Phosphatase, ALT (SGPT), AST (SGOT), calcium corrected for serum albumin, creatinine or creatinine clearance, potassium, sodium, magnesium, phosphorus, total bilirubin (or direct bilirubin if Gilbert's syndrome) Additional parameters for extension phase (chemistry full) treatment with alpelisib: C-peptide, direct bilirubin, indirect bilirubin, gamma-glutamyl-transferase (GGT), total protein, albumin, creatin-kinase (CK), blood urea nitrogen (BUN) or urea, uric acid, Lactate dehydrogenase (LDH). See Table 7.2 for time point reference
Pancreatic Enzymes	Amylase fasting, lipase fasting.

Fasting lipid panel during extension phase	Total cholesterol, LDL, HDL, triglyceride.
Chemistry (partial) during extension phase	Creatinine, creatine kinase, ALT, AST, total bilirubin
Glucose metabolism during extension phase	Fasting or random plasma glucose (Blood glucose levels measured from a blood sample taken at a random time, regardless of when the subject last ate) HbA1C
Coagulation	International normalized ratio (INR). Additional parameters for extension phase: activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT).
Urine analysis during extension phase	pH, WBC, blood, protein and glucose.
Hormones to confirm post-menopausal status*	FSH, estradiol

***** FSH and estradiol are needed only for patients < 60 years and in amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression). The FSH and estradiol values are acceptable if performed within the 28 days before C1D1. If older, FSH and estradiol should be performed as part of the screening procedure in order to confirm patient's eligibility.

7.2.3.6 Cardiac assessments

7.2.3.6.1 Electrocardiogram

Standard 12 lead ECG assessments will be performed locally at screening, C1D15, C2D1, and thereafter as clinically indicated, and EOT visit (see Table 7.1 and Table 7.2). There will be no central review of ECGs. QT interval corrected by Fridericia's formula (QTcF) will be used in this trial for trial eligibility and safety assessments.

If an abnormal ECG or QTcF value of ≥ 481 ms is obtained at any time after C1D1, study treatment must be interrupted, repeat ECG and follow management guidelines detailed in Table 6.7 for ribociclib.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. 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 abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

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

The left ventricular heart function will be evaluated by ECHO or MUGA at Screening and according to the schedule of assessments and collection plan outlined respectively in Table 7-2. Additional cardiac imaging during treatment is to be performed if indicated by clinical signs or symptoms. The same imaging modality should be used.

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 eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. 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 and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

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

2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
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. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met.
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event 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 eCRF 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 eCRF.

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 criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), 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 eCRF. 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.

8.1.3 Adverse Events of Special Interest (AESI)

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the SmPC and in the Investigator Brochure of Alpelisib.

AESIs for ribociclib: hematologic disorders (neutropenia including febrile neutropenia, neutropenic infection and neutropenic sepsis), QT prolongation, arrhythmia, hepatic dysfunction, liver toxicity, renal failure.

AESIs for alpelisib: GI toxicity (nausea, vomiting, diarrhea), hyperglycemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis, pneumonitis, severe cutaneous reactions.

8.2 Serious Adverse Events

8.2.1 Definition

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:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (i.e. to perform study related assessments)
    - 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
    - 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

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 additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes 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.

Any SAEs experienced after the 30-day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed 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 submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, 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, aNovartis Patient Safety 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 Pregnancies

This trial is planned for post-menopausal women, so no pregnancies are expected for study patients. However, in the rare cases when this occurs, to ensure patient 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 Chief Medical Office and Patient Safety (CMO&PS).

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. The Study Doctor will collect information such as progression of the pregnancy, the pregnancy outcome and the health of the baby. The collection of this information could last for up to 3 months following the birth of the child. The Study Doctor and Novartis may decide what pertinent information is collected as necessary or indicated based on the study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.4 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 SmPC or Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Data Monitoring Committee

Not applicable

8.6 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a Steering Committee 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 who 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 Contract Research Organization [CRO]) will review the protocol, eCRF and Central Laboratory Requisition Form (CLRF) 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 eCRFs and CLRFs, adherence to the protocol to Good Clinical Practice and progress of enrollment. 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, and the results of any other tests or assessments. All information recorded on the eCRFs and CLRFs 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 eCRFs and CLRFs. Novartis monitoring standards require full verification for the presence of informed consent, adherence to inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs and CLRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

This study will use Electronic Data Capture (EDC) and the designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs 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 eCRFs and allow modification or verification of the entered data by the investigator staff.

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

Blood and tissue samples for biological analysis will be collected from the Investigator sites and analyzed by a central laboratory. The results will be sent electronically to Novartis or designee vendor for the completion of the database. Designated investigational site staff will complete the information required by the protocol in the CLRFs. Field monitors will review the CLRFs for accuracy and completeness and instruct site personnel to make any required

corrections or additions. One copy of the requisition form will be forwarded to the centralized analytical laboratory.

10 Statistical methods and data analysis

This protocol seeks to explore the mechanisms of resistance to cancer treatment and predictive biomarkers of response through the analysis of data from tumor samples at baseline and after development of disease progression, as well as from ctDNA blood samples collected at baseline, and then at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, as well as upon progression of disease in the core phase, and collected at cycle 2-day 1, at first imaging evaluation, as well as upon progression of disease in the extension phase.

[redacted]

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting:

Ribociclib + letrozole

- Full Analysis Set (FAS): all patients who receive at least one dose of study medication defined as either ribociclib or letrozole.
- Biomarker Analysis Set (BAS): all subjects of the Full Analysis set who have an evaluable biomarker profile (at least baseline samples) and who do not have violations of the main inclusion-exclusion criteria.
- Safety Set (SAF): all patients who receive at least one dose of study medication defined as either ribociclib or letrozole. For this study, the definition of FAS is the same as that of the Safety set.

Alpelisib + fulvestrant

- Full Analysis Set – Extension (FAS-EXT): all patients entering the extension phase who receive at least one dose of study medication defined as either alpelisib or fulvestrant.
- Biomarker Analysis Set – Extension (BAS-EXT): all subjects of the FAS-EXT who have an evaluable biomarker profile (at least baseline samples) and who do not have violations of the main inclusion-exclusion criteria.
- Safety Set - – Extension (SAF-EXT): all patients entering the extension phase who receive at least one dose of study medication defined as either alpelisib or fulvestrant.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics and prior treatment will be summarized descriptively for the FAS, BAS, FAS-EXT and BAS-EXT.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

The following analyses will be performed on both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment.

Duration of study treatment exposure, cumulative dose, dose intensity and relative dose intensity will be summarized by treatment. In addition, the duration of exposure to study treatment will be categorized into time intervals; frequency counts and percentages will be presented for the number of patients in each interval.

The number of patients with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatments will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

10.4 Primary objective

The primary objective is to identify ctDNA alterations, how they evolve, and their possible association with clinical outcomes in both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment.

The proportions of patients with ctDNA alterations (i.e. such as but not limited to *RB1*, *ESR1*, *CCND1*, *CDKN2A, PIK3CA, TP53* and *PTEN*) will be provided over time to characterize the biological evolution of the disease in each patient. The association of these alterations with clinical outcomes will also be provided. In particular, the alterations will be analyzed at scheduled sample collections to define potential patterns of response, and at progression of disease to define potential mechanisms of resistance to CDK4/6 inhibitors and to alpelisib.

The analysis will be performed separately for ribociclib + letrozole and alpelisib + fulvestrant study phases.

Further details will be described in the statistical analysis plan.

10.5 Secondary objectives

The secondary objectives are the following:

- To evaluate serum thymidine kinase 1 (TK1) activity over time and its association with clinical outcome, as blood marker of proliferation.

Descriptive statistics of serum TK1 concentrations will be provided over time (i.e. as both absolute value and change from baseline value) for the BAS. The association/correlation of serum TK1 concentrations with clinical outcomes will also be provided.

• To identify patterns and evolution over time of ctDNA alterations associated specifically to long responders and to patients with early progression in both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment.

The proportions of patients with ctDNA alterations (i.e. such as but not limited to *RB1*, *ESR1*, *CCND1*, *CDKN2A, PIK3CA, TP53* and *PTEN*) will be provided separately for the two treatment phases over time, according to the scheduled sample collections, in the subsets of long responder patients (i.e. Time to Progression > 25 months) and those with early progression (i.e. patients progressed at first imaging evaluation) in the BAS and BAS-EXT.

[redacted]

• To assess mutational and gene aberrations across different patient profiles in both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment.

The proportions of patients with mutations as assessed at baseline by means of ctDNA sample, and tissue biopsy will be provided separately for the two treatment phases for the BAS and BAS-EXT and compared between the following patient profiles defined according to disease history (i.e. newly diagnosed vs. recurrent disease).

• To evaluate correlations between blood and tissue samples in both the ribociclib + letrozole and alpelisib + fulvestrant phases of treatment.

The proportions of patients with alterations detected at baseline and at disease progression will be compared between the two different procedures of detection (i.e. detection through liquid biopsy vs. tissue biopsy) for the BAS and BAS-EXT.

[redacted]

Further details will be described in the statistical analysis plan.

• To assess the clinical efficacy of ribociclib + letrozole and of alpelisib + fulvestrant.

The following endpoints as defined by RECIST1.1 will be described separately for the two treatment phases for the FAS and FAS-EXT:

- Time-to-Progression (TTP) based on investigators' assessment.

- Overall response rate (ORR) for patients with measurable disease.

- Clinical Benefit Rate (CBR) (including patients with CR, PR, SD/NCRNPD>24 weeks).

Time to progression (TTP) is defined as the time from date of start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication. When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

Overall response rate (ORR) is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1.

Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of complete response (CR), or partial response (PR) or an overall lesion response of stable disease (SD), lasting as per local review, for a duration of at least 24 weeks. CR, PR and SD are defined according to RECIST 1.1.

The distribution of TTP will be estimated using the Kaplan-Meier method. The median TTP along with 95% confidence intervals will be presented. Proportions of patients with ORR and CBR as assessed by investigator will be calculated and presented along with the approximate 95% confidence intervals using Clopper and Pearson (1934) exact method.

In addition, the Progression Free Survival on the second line treatment (PFS2), based on investigators' assessment and defined as the time from date of start of treatment to the date of first documented progression on second-line treatment or death from any cause, will also be assessed. PFS2 will be analyzed as described for TTP.

10.5.1 Safety objectives

10.5.1.1 Adverse events (AEs)

The number and percentages (%) of patients who experienced adverse events (AEs) will be calculated for the following AE categories:

- Any AEs

- Grade 3/4 AEs

- Serious Adverse Events (SAEs)

- AEs of Special Interest (Neutropenia (including febrile neutropenia), QT prolongation, hepatobiliary AEs)

- AEs leading to discontinuation

- AEs leading to dose reduction or dose interruption

- Deaths

AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). A summary of AEs by System Organ Class, Preferred Term and grade will be also provided.

All non-fatal SAEs, AEs of Special Interest, AEs leading to discontinuation and AEs with an outcome of death will be summarized by MedDRA SOC and PT and will be also listed.

Review of these safety data will be conducted on an on-going basis by members of the study team. The findings will be documented and will be made available upon request.

[redacted]

10.7 Interim analysis

Interim analyses may be performed periodically to fulfill safety updates, analysis of different endpoints or for publication purposes.

10.8 Sample size calculation

Sample size is aligned with other biomarker studies and is based on a feasibility analysis of the trial and relative timelines. The study is descriptive in nature and no formal statistical testing is necessary or applicable.

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 IEC

The protocol and the proposed informed consent form must be reviewed and approved by an Independent Ethics Committee (IEC) 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 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, IECs and regulatory authorities as required.

11.3 Informed consent procedures

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

Informed consent must be obtained before conducting any study-specific procedures (i.e. all the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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 IEC, and a copy of the approved version must be provided to the Novartis after IEC approval.

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 4.3.

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 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 eCRF and CLRF are the primary data collection instruments for this study. The investigator should ensure the accuracy, completeness, legibility, and

timeliness of the data reported in the eCRFs and CLRFs and all other required reports. Data reported on the eCRFs and CLRFs that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRFs and CLRFs must be recorded. Any missing data must be explained. Any change or correction should be dated, initialed, and explained (if necessary) and should not obscure the original entry. The investigator should retain records of the changes and corrections.

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.

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 IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (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, and the IEC. Only amendments that are required for patient safety may be implemented prior to IEC 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 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 Concomitant Medications with Ribociclib

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 not comprehensive and are only meant to be used as a guide. The lists are based on Oncology Clinical Pharmacology guidance, Drug-Drug Interaction and Co-Medication Considerations (v06, release date: 2017), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction 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://.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (http://.druginteractioninfo.org/). For current lists of medications that may cause QT prolongation and/or torsade de pointes (TdP), refer to the CredibleMeds® website//www.crediblemeds.org). Please contact the medical monitor with any questions.

Table 14-1 List of prohibited medications during treatment with ribociclib

Category	Drug Name
Strong CYP3A4/5 inhibitors	Atazanavir/ritonavirb, oceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (VIEKIRA PAK), posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin)3, St. John's wort (hypericum perforatum)[2],[3],
CYP3A4/5 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, papaverin HCL (intra-coronary, pentamidine, pimozide, probucol, procainamide, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, sulpiride, sultopride, terlipressin, teroldiline, 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.
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 including raloxifenel, 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, 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 that have <2-fold difference in the minimum toxic concentrations and minimum effective concentrations in blood.
[2] Herbal product
[3] P-gp inducer
[4] The list provided is as of January 2018. Check crediblemeds.org/healthcare-providers/drug-list for the most updated list.
[5] Drug has warning for risk of hepatotoxicity. 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 prolongation 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 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 treatment with ribociclib

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, lopinavir[5], modafinil, nafcillin, telotristat
Sensitive CYP3A4/5 substrates with NTI[1]	Alpha-dihydroergocryptine, apixaban, aprepitant, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatinib, ebastine, eletriptan, eplerenone, everolimus, felopidine, 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, clofazimine, dabigatran, dipyridamole, glyburide, grazoprevir, ledipasvir, mifepristone, pioglitazone, reserpine, rifamycin, simeprevir,telmisartan, timcodar, troglitazone, valinomycin, velpatasvir.
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 (cyanmepromazine), 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, olanzapine, osimertinib, oxytocin, paliperidone, palonosetron, panobinostat, pasireotide, pazopanib, perflutren lipid microspheres, perphenazine, pilsicainide, pimavanserin, pipamperone, promethazine, prothipendyl, quetiapine, ranolazine, rilpivirine, risperidone, romidespin, sertindole, sorafenib, sunitinib, tamoxifen, telavancin, tetrabenazine, tipiracil/trifluridine, tizanidine, tolterodine, toremifene, trimipramine, tropisetron, vardenafil, vemurafenib, venlafaxine,, ziprasidone
MATE 1/2 substartes[3]	Acyclovir, cephalexin, cimetidine, fexofenadine, ganciclovir, glycopyrronium, metformin, pindolol, plisicainide, ranitidine, topetecan, varencicline
OCT1/2 substartes[4]	Amantadine, Beta-hydroxycortisol, carboplastin, cisplatin, cephalexin, cephradine, ipratropium, lamivudine, linagliptin, metformin, oxyplatin, oxybutynin, phenformin, picoplatin, pilsicainide, pindolol, ranitidine, sorafenib, tropisetron, trospium, umeclidinium, zidovudine
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 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.

14.2 Concomitant medications with Alpelisib

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 BYL719 and/or fulvestrant. Please note that all lists in Appendix 14.2 are not comprehensive. Please refer to regular updated online sources and the label of a concomitant drug to decide whether a drug is permitted (with caution) or prohibited based on Section 6.5. In doubt please the contact medical monitor with any questions.

14.2.1 Permitted medications to be used with caution

This list of CYP substrates was compiled from the University of Washington's Drug Interaction Database (Updated April 2019) and is only meant to be used as a guide.

Table 14-3 List of CYP450 substrates to be used with caution

Category	Drug names
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin
Sensitive substrates of CYP2C9	Benzbromarone, Celecoxib, Glimepiride, Glipizide, (R)/(S)-Ibuprofen, Lornoxicam, Meloxicam, Piroxicam, Tolbutamide, (S)-Warfarin
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	Not Applicable
Sensitive substrates of CYP2B6	Bupropion, Efavirenz
Selected CYP3A4 substrates	
CYP3A4 substrates which are known or potential auto-perpetrators	Clarithromycin, Conivaptan, Encorafenib, Erythromycin, Diltiazem, Mifepriston, Ribociclib, Telthromycin, Troleandomycin, Verapamil

Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): 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, QT prolongation).

CYP3A4 substrates which are auto-perpetrators: Based on Novartis internal assessment

14.2.2 Prohibited medication

Strong inducers of CYP3A4

This list of CYP inducers was compiled from the University of Washington's Drug Interaction Database (Updated April 2019). This list only meant to be used as a guide.

Table 14-4 List of prohibited strong inducers of CYP3A

Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe1, Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifabutin, Rifapentine, Rifampin (Rifampicin), St. John's wort (hypericum perforatum)1

[1] Herbal product

Inhibitors of BCRP

The table encompasses only drugs and molecular entities for which inhibition of BCRP has been investigated and/or formally shown in vivo in a clinical DDI study. Please note that this is not an exhaustive list and only meant to be used as a guide. When in doubt, refer to the prescribing information of the drug to assess whether a potential for BCRP inhibition is described

Table 14-5 List of prohibited BCRP inhibitors

Category	Drug Name
BCRP inhibitors - Evidence for DDI potential shown in vivo	Protease Inhibitors: Atazanavir/ritonavir[1,2], Elvitegravir/cobicistat[1,2], Lopinavir/ritonavir[1,2], Tipranavir/ritonavir[1,2]Curcumin[1,2], Cyclosporine[1,2], Daclatasvir[1,2], Eltrombopag[1,2], Gefitinib[2], Lapatinib[1], Ledipasvir[2], Pantoprazole[1,2], Paritepravir[2], Tipranavir[2]

[1] Lee et al 2015

[2] Novartis PK Sciences DDI List (January 2018)

14.3 Guidelines for the treatment of alpelisib induced diarrhea

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent alpelisib. In order to effectively manage diarrhea and mitigate the escalation in severity or duration of diarrhea, patient education as well as proper management of diarrhea is mandatory. The following section outlines the recommended algorithm for management and treatment of alpelisib induced diarrhea (Benson et al 2004; Kornblau et al 2000; Wadler et al 1998).

The algorithm for treatment for diarrhea management is based on (Wadler et al 1998; Kornblau et al 2000).

Patient history of diarrhea

At screening, the patient's history of diarrhea should be reviewed, and the patient should be appropriately informed of potential study drug-induced diarrhea and its management:

- Review previous medical history of diarrhea within the last 12 months; laxative use, colon surgery, abdominal and pelvic irradiation, nocturnal diarrhea, pain, ulcerative colitis and other diarrhea-inducing diseases/conditions;
- Stop all diarrheogenic agents at screening if possible, otherwise exclude from trial;
- Instruct patients regarding risk of developing diarrhea;
- Perform baseline clinical/laboratory studies according to the trial protocol (e.g. one could rule out carrier state of Salmonella spp., Clostridium difficile, Campylobacter spp., Giardia, Entamoeba, Cryptosporidium which can lead to opportunistic infections in immunosuppressed patients);
- Explain the frequency of diarrhea and its relationship to NCI CTCAE grading (Table 14-7).

Table 14-6 NCI CTCAE version 4.03 grading of diarrhea for patients without colostomy

Toxicity	0	1	2	3	4
Diarrhea ADL	None	Increase of < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting selfcare	Life-threatening consequences; urgent intervention indicated
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements.					

First report of diarrhea

- Obtain history of onset and duration of diarrhea
- Description of number of stools and stool composition (e.g. watery, blood, mucus in stool)

- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (i.e., rule out risk for sepsis, bowel obstruction, dehydration)
- Obtain medication profile (i.e., to identify any diarrheogenic agents) and dietary profile (i.e., to identify diarrhea-enhancing foods)

Proactively look for occurrence of diarrhea. If no problems occur, instruct the patient to call when a problem does arise.

Management of diarrhea

General recommendations:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fiber (e.g. Metamucil®) and stool softeners (e.g. docusate sodium, Colace®)
- Stop high-osmolar food supplements such as Ensure Plus® and Jevity Plus® (with fiber)
- Drink 8 to 10 large glasses of clear liquids per day (e.g. water, Pedialyte®, Gatorade®, broth)
- Eat frequent small meals (e.g. bananas, rice, apple sauce, toast)

It is recommended that patients are provided with loperamide tablets at the start of each cycle. Patients should be instructed on the use of loperamide at Cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the site should ensure that the patient understands the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhea or diarrhea related symptoms. If symptoms were experienced, then the site should question the patient regarding the actions taken for these symptoms.

Intensive management of diarrhea must be instituted at the first sign of abdominal cramping, loose stools or overt diarrhea. Note that all concomitant therapies used for treatment of diarrhea must be recorded on the Concomitant Medications/Non-drug Therapies section of the patient record.

Loperamide is the first-line treatment of diarrhea (any Grade) in this recommended algorithm. Persistent symptoms may require the administration of high dose loperamide followed by treatment with second-line agents such as opium tincture and octreotide acetate, based on severity and duration of diarrhea and related signs/symptoms. Another first-line treatment for diarrhea is diphenoxylate hydrochloride/atropine sulfate. This medication may be used in place of loperamide however it is important to note that loperamide and diphenoxylate hydrochloride/atropine sulfate must not be used in conjunction with one another due to the risk of developing paralytic ileus. Upon treatment with any antidiarrheal agents, the patient's response to treatment should be observed and appropriately documented in the source document and within the patient record.

Treatment of diarrhea CTCAE grade 1 or 2

Diarrhea CTCAE grade 1 or 2 will be treated with standard loperamide (initial at first administration 4 mg, then 2 mg every 4 hrs (maximum of 16 mg/day) or after each unformed stool).

12-24 hrs later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12 hrs diarrhea-free interval

Diarrhea unresolved

Persisting diarrhea CTCAE grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections with monitoring of the patient's condition (to rule out dehydration, sepsis, ileus) medical check and selected workup if patient does not need hospitalization (see section Diarrhea workup and additional test in the particular trial protocol). Observe patient for response to antidiarrheal treatment.

Persisting diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs) and addition of opium tincture (DTO) or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12-24 hrs:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12 hrs diarrhea-free interval

Diarrhea unresolved

- If diarrhea still persisting (CTCAE grades 1 and 2), after 2x 24 hrs with high dose loperamide and opiates then admit to hospital and employ measures as for CTCAE grade 3 and 4 until diarrhea resolved.
- If diarrhea still persisting and progressed to CTCAE grades 3 and 4, employ measures described below.

Treatment of diarrhea CTCAE grade 3 or 4

Severe diarrhea CTCAE grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hrs and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (see section

Diarrhea workup and additional test in the particular trial protocol). Observe patient for response.

After 12-24 hrs:

- If diarrhea persisting administer s.c. Sandostatin/octreotide (100-500 μg tid)
- Continue IV fluids and antibiotics as needed
- If diarrhea CTCAE grade 3 or 4 still persists patients should receive opium tincture or dihydrocodeine tartrate injections s.c. or i.m.
- If diarrhea CTCAE grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 μg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine et al 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Fecal leukocytes (Wright's staining and microscopy) or
- Clostridium difficile toxin
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic E. coli - enterotoxigenic, enterohemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

Endoscopic examinations

Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis and thus great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid - re. bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis.

14.4 Guidelines for the treatment of alpelisib induced stomatitis/oral mucositis

General guidance and management include patient awareness and early intervention. Evaluation for herpes virus or fungal infection should be considered.

Patients should be informed about the possibility of developing mouth ulcers/oral mucositis and instructed to report promptly any signs or symptoms to their physician,

Patients should be educated about good oral hygiene, instructed to avoid spicy/acidic/salty foods, and should follow the following guidelines:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt-water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents should be avoided unless a fungal infection is diagnosed as they may interfere with alpelisib metabolism (see Section 6.4 and Appendix 3).

14.5 Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-7 Liver event and laboratory trigger definitions

	Definition/threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

	Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms. TBL: total bilirubin; ULN: upper limit of normal

Based on the investigator's discretion, investigation for contributing factors for the liver event can include serology tests, imaging and pathology assessments, hepatologist's consultancy, obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

14.6 Bone marrow reserve in adults

Table 14-8 Bone Marrow Reserve in Adults

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

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

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

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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

14.7.1 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 14.3.2 and the definition of best response in Section 14.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.3.18 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 14.3.29 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

14.7.2 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.

14.7.3 Definitions

14.7.4 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 14.3.26

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 non-cystic 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.

14.7.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). 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 14.3.26.

14.7.6 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 major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from

conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. 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 new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
    - 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.
- **Physical exams:** Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. 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.

14.7.7 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).

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 14.3.4.
- **Nodal target**: See Section 14.3.4.

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.

14.7.8 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 14.4) and non-target lesions (Table 14.5) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14.6) as well as the presence or absence of new lesions.

14.7.9 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.

14.7.10 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 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.

14.7.11 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.

14.7.12 Determination of target lesion response

Table 14-9 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. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 14.3.6).

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 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 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 14.4 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.
- 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.

- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances, an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

14.7.13 Determination of non-target lesion response

Table 14-10 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 lesion 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[2].
1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail. 2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)	

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.

- 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 there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- **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 14.3.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.7.14 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 14.3.15).
- 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 14.3.6.

14.7.15 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 14.6.

Table 14-11 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 14.3.8.			

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

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.

14.7.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.3.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.7.17 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
- 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)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6-week tumor assessment frequency. However, these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

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.

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. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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).

14.7.18 Time to event variables

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

14.7.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

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.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

14.7.20 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.

14.7.21 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.

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.

14.7.22 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this

endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

14.7.23 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.

14.7.24 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.

14.7.25 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 14.3.23. 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 and 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.

14.7.26 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.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

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 14.3.26).

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.

14.7.27 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.

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 non-measurable disease is derived slightly differently according to Table 14.7.

Table 14-12 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 14.3.8.

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.

14.7.28 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 14.3.25, 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:

Table 14-13 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) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
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 14.3.25.
[2.] =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.3.25.
[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.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

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 14.8 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.

14.7.29 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).

14.7.30 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).

14.7.31 End of treatment phase completion

Patients **may** voluntarily withdraw from each study treatment phase 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 7 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
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- 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)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

14.7.32 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
- Progressive disease
- Study terminated by the sponsor

14.7.33 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment 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). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) 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 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.

14.7.34 Programming rules

The following should be used for programming of efficacy results:

14.7.35 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.

14.7.36 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 14.3.25). 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.

14.7.37 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.

14.7.38 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)'.

14.7.39 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.7.40 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.

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 14.8)
- 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 14.3.25. 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.

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