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Clinical Trial Protocol

EPIK-O: A Phase III, multi-center, randomized (1:1), open-label, active-controlled study to assess the efficacy and safety of alpelisib (BYL719) in combination with olaparib as compared to single agent cytotoxic chemotherapy, in participants with no germline BRCA mutation detected, platinum-resistant or refractory, high-grade serous ovarian cancer

Synopsis/Clinical Trial Protocol Number: CBYL719K12301

Version Number: 04 (Amended Protocol) (Clean)

Compound: BYL719

Brief Title: Study to assess the efficacy and safety of alpelisib in combination with olaparib in participants with platinum-resistant or refractory gBRCAnm HGSOC

Study Phase: III

Study Acronym: EPIK-O

Regulatory Agency Identifier Number(s): 2019-004682-40 (EudraCT number) 2024-510782-42 (EU CT number)

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List of abbreviations

ADA	American Diabetes Association
ADL	Activities of Daily Living
ADP	Adenosine diphosphate
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKT	Protein Kinase B
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANA	Antinuclear antibody
ANC	Absolute Neutrophil Count
APTT	Activated Partial Thromboplastin Time
ARA	Acid Reducing Agent
ASCO	American Society of Clinical Oncology
ASMA	Antismooth muscle antibody
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATM	Ataxia-telangiectasia Mutation
AUC	Area Under the Curve
AV	Atrioventricular
BCRP	Breast Cancer Resistance Protein
BER	Base Excision Repair
bid/BID	Twice a day
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
CCI	[redacted]
BRCA	Breast Cancer gene
BRCAnm	BRCA non-mutated
BRCAwt	BRCA wild type
BSA	Body Surface Area
BSEP	Bile Salt Export Pump
BUN	Blood Urea Nitrogen
CA-125	Cancer Antigen 125
CABG	Coronary Artery Bypass Graft
CBR	Clinical Benefit Rate
CD-transferrin	Carbohydrate-deficient Transferrin
CDx	Companion Diagnostics
CFR	Code of Federal Regulation
CGIG	Gynecologic Cancer Intergroup
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatinine Kinase
Clast	Last Measureable Concentration
Cmax	Maximum Plasma Concentration
CMO	Chief Medical Officer
CMV	Cytomegalovirus

CNS	Central Nervous System
CO	Country Organization
CO_2	Carbon dioxide
COVID-19	Coronavirus Disease 2019 (SARS-CoV-2 virus)
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTRD	Clinical Trial Results Database
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DDI	Drug-Drug Interactions
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration Of Response
DRESS	Drug Reaction with Eosinophilia and Systemic Syndrome
DSBs	Double-Strand Breaks
DTI	Direct Thrombin Inhibitor
EBV	Epstein-Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EM	Erythema Multiforme
EMA	European Medicines Agency
EOC	Epithelial Ovarian cancer
EOT	End of Treatment
CCI	[redacted]
ER	Estrogen Receptor
ERCP	Endoscopic Retrograde Cholangiopancreatography
ERK	Extracellular Signal-regulated Kinase
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
ETS	Proto-oncogene 1, Transcription factor
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FACT-O TOI	Function Assessment of Cancer Therapy-Ovarian Trial Outcome Index
FAS	Full Analysis Set

FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIGO	International Federation of Gynecology and Obstetrics
FPFV	First Participant First Visit
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone
GABA	Gamma-aminobutyric acid
gBRCAm	Germline BRCA mutated
gBRCAnm	Germline BRCA non-mutated
GCIC	Gynecologic Cancer Intergroup criteria
GCP	Good Clinical Practice
GCS	Global Clinical Supply
G-CSF	Granulocyte Colony-stimulating Factor
GGT	Gamma-glutamyl transferase
GI	Gastro-intestinal
h	Hour
HAV	Hepatitis A virus
HbA1c	Glycosylated Hemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCP	Healthcare Professional
HCT	Haematocrit
HCV	Hepatitis C Virus
HER	Human Epidermal growth factor Receptor
HEV	Hepatitis E Virus
HGS	High-grade serous
HGSOC	High-grade serous ovarian cancer
HR	Hormone Receptor
HRD	Homologous recombination repair deficient
HRP	HRR-proficient
HRQoL	Health-Related Quality of Life
HRR	Homologous recombination repair
HSV	Herpes Simplex Virus
i.v.	Intravenous
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions For Use
IgM/G/E/A	Immunoglobulin M/G/E/A
IMMPACT	Initiative on Methods Measurement and Pain Assessment in Clinical Trials
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent To Treat
IUD	Intrauterine Device
IUS	Intrauterine System
K3-EDTA	Tripotassium Ethylenediaminetetraacetic Acid
kg	kilogram
LDH	Lactate dehydrogenase
LFT	Liver function test
LLN	Lower Limit of Normal
LLOQ	lower limit of quantitation
LPLV	Last Participant Last Visit
LVEF	Left Ventricular Ejection Fraction
MATE1	Multidrug and Toxin Extrusion 1
MCV	Mean Corpusal Volume
MDS	Myelodysplastic Syndrome
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
MRP2	Multidrug resistance associated protein 2
MTD	Maximum Tolerated Dose
mTOR	mammalian Target Of Rapamycin
MUGA	Multigated Acquisition Scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NOAC	Non-vitamin K Antagonist Oral Anticoagulants
NTI	Narrow Therapeutic Index
NVS	Novartis
OAT3	Organic Anion Transporter 3
OC	Ovarian Cancer
OCT2	Organic Cation Transporter 2
ONJ	Osteonecrosis of the Jaw
ORR	Overall Response Rate
OS	Overall Survival
pAKT	Phosphorylated AKT
PARP	Poly-ADP ribose polymerase
PARPi	poly-ADP ribose polymerase inhibitor
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PDX	Patient-Derived Xenograft
PFI	Platinum-Free Interval
PFS	Progression Free Survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphoinositide-3-kinase catalytic subunit alpha

PIKKs	Phospoinositol 3-kinase-related-kinases
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PLT	Platelets
PPT	Partial Thromboplastin Time
PR	Partial Response
PR-EOC	Platinum Resistant Epithelial Ovarian Cancer
PRO	Patient Reported Outcomes
PS	Patient Safety
PSA	Prostate Specific Antigen
PTA	Post- Trial Access
PTEN	Phosphatase and tensin homolog protein
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RDC	Remote Data Capture
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RI	Reticulocyte Index
RNA	Ribonucleic acid
RP2D	Recommended phase two dose
Rsqadj	Square of the correlation coefficient associated with lambda_z
RTKs	Receptor Tyrosine Kinases
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sBRCA	Somatic BRCA
sBRCAm	Somatic Mutations in BRCA 1/2
SC	Steering Committee
SD	Stable Disease
SGLT	Sodium-glucose Linked Transporter
SJS	Steven-Johnson Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SMT	Safety Management Team
SoC	Standard Of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	Elimination half-life
TBIL	Total bilirubin
TCGA	The Cancer Genome Atlas
TEN	Toxic Epidermal Necrolysis
Tlast	Last Measureable Concentration Sampling (time)
Tmax	Time to reach peak plasma concentration
TP53	Tumor Protein p53
TTR	Time To Response

ULN	Upper limit of normal
US	Ultrasound
CCI	[redacted]
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (IMP) (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from study participants
Cohort	A specific group of participants fulfilling certain criteria
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes.

Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial participants, regardless of randomization group, rescue medication, active drug run-ins etc.)
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
Randomization number	A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
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
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant not at the investigative site investigator will conduct the trial.

Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 04 (05-Dec-2024)

Amendment rationale

As of CCI there are a total of [redacted] participants on treatment ([redacted] in Olaparib + Alpelisib arm and [redacted] on Paclitaxel/PLD arm). The main purpose of this amendment is to align the protocol with the EU CTR requirements since the study has transitioned to EU CTR.

Efficacy follow-up was removed throughout the protocol since Overall Survival was removed previously.

Also, editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. The following sections have been revised in the amended protocol:



Minor editorial changes (e.g. typographical and grammatical corrections, rewording) were also implemented throughout the protocol to improve flow and consistency.

IRBs/IECs

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

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

Amendment 03 (09-Oct-2023)

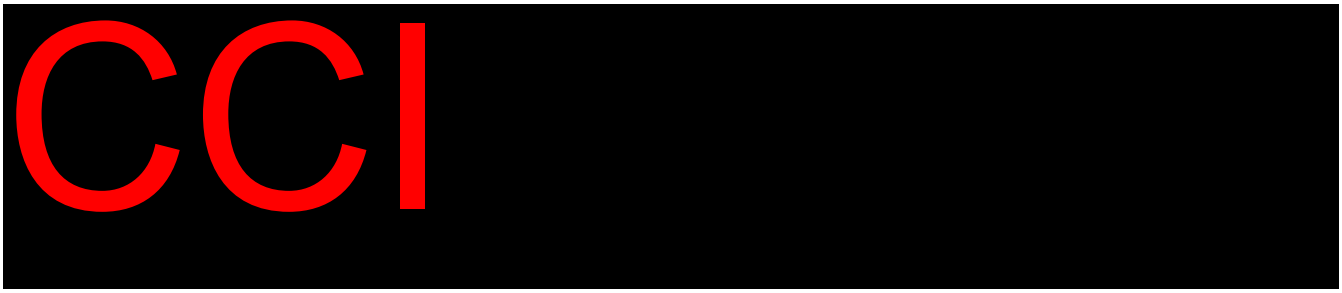
As of January 2023, enrollment was completed with a total of 358 participants (180 in alpelisib + olaparib arm and 178 in paclitaxel/pegylated liposomal doxorubicin (PLD) arm). At the time of the final progression-free survival (PFS) analysis conducted in July 2023, the study did not meet its primary endpoint based on PFS by blinded independent review committee (BIRC). In addition, an increased frequency of on-treatment deaths (up to 30 days after last dose of treatment) in the alpelisib + olaparib arm as compared to the paclitaxel/PLD arm was observed. Hence, Novartis released an CCI to notify investigators/HA/EC of these results. Participants benefitting from treatment with alpelisib + olaparib were permitted to continue treatment after discussion with the sponsor. As of CCI , there are a total of CCI participants (CCI in alpelisib + olaparib arm and CCI in paclitaxel/PLD arm). The main purpose of this amendment is to streamline safety and efficacy assessments based on the PFS analysis results and align them with the local standard of care. The major changes implemented following protocol amendment 03 are as follows:

- Central safety laboratory analyses were replaced with local safety laboratory analyses. There will be no survival follow-up for the participants and those who are already in the survival follow-up phase will end the study participation.
- Patient reported outcomes (PRO) questionnaires assessments, pharmacokinetic (PK) assessments were removed in addition to the other changes to the assessment schedule. Imaging assessments are to be performed locally and their frequency updated to be conducted as per local standard clinical practice.
- The language related to the timeframe of use of highly effective contraception was updated to reflect the PLD label update.

Changes to the protocol




CCI



The protocol summary was updated to reflect these changes.

Minor editorial changes (e.g. typographical and grammatical corrections, rewording) were also implemented throughout the protocol to improve flow and consistency.

Amendment 02 (01-Mar-2023)

As of 01-Mar-2023, 653 patients have been enrolled into the study and 358 patients have received study treatment.

In addition, the DMC met on January 18, 2023 and they noted that the futility boundary (1-sided p-value CCI , i.e., an approximate hazard ratio of CCI) was crossed. CCI

[redacted]

Amendment rationale

The main purpose of this amendment is to extend the contraception duration for patients randomized to treatment arm 1 based on the newly released Olaparib IB Edition 21.2.

In addition, the following changes are implemented:

- Addition of protocol language related to the newly released Alpelisib IB Edition 17 including the management of diabetes, hyperglycemia, colitis, skin and subcutaneous tissue disorders.
- Also, editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.

Changes to the protocol

[redacted]



The protocol summary has been updated to reflect the changes throughout the document.

Lastly, minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency, and correction of spelling errors or typographical errors, have been made throughout the protocol.

Amendment 01 (28-Apr-2021)

As of 28-April-2021, no patients have been enrolled into the study and therefore no patients have received study treatment.

Amendment rationale

The main purpose of this amendment is to update the language in Section 6.1 to clarify that paclitaxel and PLD will be procured locally where available generics are permitted, however generic products that were withdrawn from or rejected by either FDA or EMA should not be used.

In addition, the following changes are implemented:

- Addition of protocol language related to rationale for public health emergency mitigation procedures (when it limits or prevents on-site study visits during the pandemic)
- Wording changes to align with Novartis protocol language latest template version 4.0

Also, editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.

Changes to the protocol




CCI


CCI



The protocol summary has been updated to reflect the changes throughout the document as well as the glossary of terms.

Lastly, minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency, and correction of spelling errors or typographical errors, have been made throughout the protocol.

IRBs/IECs

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

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

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

Protocol summary

Protocol number	CBYL719K12301
Full Title	EPIK-O: A Phase III, multi-center, randomized (1:1), open-label, active-controlled study to assess the efficacy and safety of alpelisib (BYL719) in combination with olaparib as compared to single agent cytotoxic chemotherapy, in participants with no germline BRCA mutation detected, platinum-resistant or refractory, high-grade serous ovarian cancer
Brief title	Study to assess the efficacy and safety of alpelisib in combination with olaparib in participants with platinum-resistant or refractory gBRCAnm HGSOC
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this study is to evaluate the efficacy and safety of the combination of alpelisib with olaparib compared to standard-of-care chemotherapy in participants with platinum resistant or refractory HGSOC with no germline BRCA mutation detected (gBRCAnm) irrespective of PIK3CA mutation status, a population with poor outcomes and unmet medical needs.
Primary Objective(s)	To determine whether treatment with alpelisib in combination with olaparib prolongs PFS compared to single agent cytotoxic chemotherapy in participants with platinum resistant/refractory, gBRCAnm HGSOC The primary scientific question of interest is: what is the treatment effect based on PFS for alpelisib in combination with olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD) in participants with platinum-resistant or refractory, no germline BRCA mutation detected, high grade serous ovarian cancer, regardless of study treatment discontinuation or start of new anti-neoplastic therapy?
Secondary Objectives	● To assess safety and tolerability of alpelisib in combination with olaparib when administered to participants with platinum-resistant or refractory, gBRCA nm HGSOC ● To evaluate alpelisib in combination with olaparib compared to single agent cytotoxic chemotherapy in participants with platinum-resistant or refractory, gBRCAnm HGSOC with respect to time to deterioration of ECOG (Eastern Cooperative Oncology Group) performance status ● To assess additional efficacy parameters ● To characterize the PK alpelisib and olaparib when administered in combination in patients with platinum-resistant or refractory, gBRCAnm HGSOC. ● To evaluate patient reported-outcomes of alpelisib in combination with olaparib compared to single agent cytotoxic chemotherapy in adult participants with platinum-resistant or refractory, gBRCAnm HGSOC The key secondary scientific question of interest is: what is the treatment effect based on OS for alpelisib in combination with olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD) in participants with platinum-resistant or refractory, no germline BRCA mutation detected high grade serous ovarian cancer regardless of study treatment discontinuation or start of new anti-neoplastic therapy?
Study design	This study is a Phase III, multicenter, open-label, randomized (1:1), active-controlled study to assess the efficacy and safety of alpelisib in combination with olaparib compared with single agent cytotoxic chemotherapy, in patients with platinum-resistant or refractory, gBRCAnm HGSOC, irrespective of PIK3CA mutation status Randomization will be stratified by three stratification factors: ● Relapse within < 3 months from last platinum dose vs. within 3-6 months from last platinum dose ● Prior PARP inhibitor use (yes vs. no) ● Prior bevacizumab use (yes vs. no) The total number of participants with non-measurable disease will be limited to up to CCI of the overall study population.
Rationale	PR-EOC represents a disease area of significant unmet medical need with median OS in patients of 12-15 months. The ORR for patients with gBRCAm treated with a single

	agent PARP inhibitor is approximately 30%. However, for BRCAwt patients ORR is only around 5% with PARP inhibitor monotherapy. The standard treatment option for BRCAwt patients is cytotoxic chemotherapy, which has been shown to have an ORR ranging from 8 to 30% and median PFS ranging from 3.5 to 3.9 months with PLD or weekly paclitaxel. A defective homologous recombination repair (HRR) of DNA double strand breaks occurs in approximately 50% of EOC, rendering these tumors sensitive to PARP inhibitors via synthetic lethality. However, in PR-BRCAwt EOC such alterations are uncommon and these tumors are typically HRR proficient and, thus, relatively insensitive to PARP inhibitors. Preclinical evidence suggests that inhibition of the PI3K pathway can induce a functional homologous recombination repair deficient (HRD) state in HRR proficient tumors. Therefore, the addition of a PI3K inhibitor may sensitize and augment the effect of a PARP inhibitor in BRCAwt PR-EOC. To investigate this concept, the combination of olaparib and alpelisib was explored in a Phase Ib study with encouraging efficacy, ORR of 31% in participants with gBRCAwt PR-EOC, and a tolerable safety profile. No new or unexpected toxicities were observed (Konstantinopoulos et al 2019). These encouraging efficacy outcomes are supported by preclinical evidence that showed the potential of PI3K pathway inhibition to induce a functional HRD state and, therefore, sensitize or potentially re-sensitize tumors to PARP inhibitors. Therefore, in participants with platinum-resistant or refractory, gBRCAnm HGSOC, the combination of alpelisib and olaparib may offer improved efficacy as compared to single agent cytotoxic chemotherapy. The terminology BRCAnm is preferred to BRCAwt, since BRCAnm more accurately describes that a deleterious or suspected deleterious BRCAm has not been detected.
Key Inclusion criteria	● Participant has histologically confirmed diagnosis of high-grade serous or high-grade endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer ● Measurable disease, i.e., at least one measurable lesion per RECIST 1.1 criteria (a lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation) ● If no measurable disease is present, the disease should be assessable by Gynecologic Cancer Intergroup criteria (GCIC) for CA-125 ● Participant has no germline BRCA1/2 mutation as determined by an FDA-approved assay ● Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ● Participant has platinum-resistant (progression within one to six months after completing platinum-based therapy) or platinum refractory disease (progression during treatment or within 4 weeks after the last dose), where platinum-based therapy is not an option, according to the GCIG 5th Ovarian Cancer Consensus Conference definitions (Wilson et al 2016). The platinum-based chemotherapy regimen does not necessarily need to be the last regimen the participant received prior to study entry ● Participant must have received at least one but no more than three prior systemic treatment regimens and for whom single-agent chemotherapy is appropriate as the next line of treatment ● Participant has received prior bevacizumab or is not eligible to receive bevacizumab due to medical reasons.

Key Exclusion criteria	● Participant has received prior treatment with any PI3K, mTOR or AKT inhibitor ● Participant is concurrently using other anti-cancer therapy ● Participant is in a state of small or large bowel obstruction or has other impairment of gastrointestinal (GI) function or GI disease ● Participant has had surgery within 14 days prior to starting study drug or has not recovered from major adverse effects ● Participant has not recovered from all toxicities related to prior anticancer therapies to baseline or NCI CTCAE Version 4.03 Grade ≤1. Exception to this criterion: participants with any grade of alopecia are allowed to enter the study ● Participant has an established diagnosis of diabetes mellitus type I or uncontrolled type II based on fasting plasma glucose and HbA1c ● Participants with liver impairment and Child Pugh score B or C ● Participant has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to baseline, grade 1 or better from related adverse effects of such therapy (with the exception of alopecia) ● Participant has a known hypersensitivity to any of the study drugs or excipients ● Participant has a history of myelodysplastic syndrome or acute myeloid leukemia, or presents clinical and/ or laboratory features suggestive thereof.
Study treatment	Arm 1: Alpelisib 200 mg orally once daily + olaparib 200 mg orally twice daily Arm 2: Investigator's choice of one of two single agent chemotherapies: Paclitaxel 80 mg/m^2 intravenously weekly or Pegylated Liposomal Doxorubicin 40 - 50 mg/m^2 (physician's discretion) intravenously every 28 days
Efficacy assessments	● Radiological tumor assessments by a Blinded Independent Review Committee (BIRC) per RECIST 1.1 will be performed and used for the primary analysis of PFS: At screening within 28 days prior to Cycle 1 Day 1. Imaging assessments for response evaluation will be performed every 8 weeks (±7 days) after randomization during the first 18 months and every 12 weeks (±7 days) thereafter ● Survival follow-up assessments will be performed and used to assess the key secondary endpoint of overall survival ● Clinical disease progression as per GCIG criteria will be assessed and used for supplemental analysis of PFS
Pharmacokinetic assessments	Pharmacokinetic profile of alpelisib and olaparib
Key safety assessments	● Physical examination ● ECOG performance status ● Body weight and vital signs ● Laboratory assessments, including coagulation, hematology, biochemistry, liver function tests, renal function test and urinalysis ● Electrocardiogram (ECG) ● Cardiac imaging ● Adverse events (AEs), the severity, the relationship with the study treatment and the seriousness
Other assessments	CCI [redacted] Patient-reported outcomes: Patient questionnaires (FACT-O, CCI [redacted]) will be collected to assess health-related quality-of-life, health status, functioning, disease symptoms, side effects, and cancer-related pain.
Data analysis	● The primary objective is to determine whether treatment with alpelisib in combination with olaparib prolongs PFS compared to treatment with single agent cytotoxic chemotherapy (paclitaxel or pegylated liposomal doxorubicin) in participants with platinum-resistant or refractory, gBRCAnm high grade serous ovarian cancer ● The secondary objectives of this study are to compare the two treatment groups with respect to overall survival (OS), and to evaluate the overall response rate (ORR),

	clinical benefit rate (CBR), time to response (TTR), duration of response (DOR), time to definitive deterioration in quality of life, time to definitive deterioration in ECOG performance status, pharmacokinetics, and safety. OS is the key secondary endpoint (variable attribute of the key secondary estimand). A hierarchical testing strategy will be used to control the overall type I error rate, where OS will only be formally tested and interpreted if the primary analysis of PFS is statistically significant.
Key words	Alpelisib, olaparib, paclitaxel, pegylated liposomal doxorubicin, high grade serous ovarian, fallopian or peritoneal cancer, no germline BRCA mutation, BRCA wild type, platinum-resistant or refractory, prior PARP inhibitor exposure, EPIK-O

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

Globally, epithelial ovarian cancer (EOC) represents a common cancer in women, with approximately 295,000 cases and 185,000 deaths expected in 2018 (Bray et al 2018). It is the most common cause of death from gynecological cancer in developed countries; for example in the United States, 22,240 new diagnoses and 14,070 deaths were expected in 2018, making EOC the 5th most common cause of death from cancer in women (Siegel et al 2018).

The last decade has seen major developments in the understanding and classification of EOC. It is now generally recognized that the five major histological subtypes of EOC, namely high-grade serous (HGS), low-grade serous, endometrioid, clear-cell and mucinous, comprise different diseases with distinct pathogenic mechanisms and clinical course (Vaughan et al 2011, Matulonis et al 2016).

HGS ovarian cancer (HGSOC,) the most common histological subtype, presents as advanced disease in approximately 75% of patients and is responsible for up to 80% of deaths due to EOC (Bowtell et al 2015, Coburn et al 2017).

Controversy still exists as to the exact anatomical classification of extrauterine HGS cancer. However, it has become evident that the majority of these cancers arise in the distal fallopian tube and only secondarily spread to the ovaries and peritoneal cavity (Bowtell et al 2015, Labidi-Galy et al 2017). Regardless of their anatomical classification as fallopian tube, ovarian or primary peritoneal cancers, all HGS cancers are considered a single biological entity with uniform treatment recommendations (Colombo et al 2019) and, for the sake of simplicity, are referred to as HGSOC.

HGSOC is characterized by ubiquitous TP53 mutations (Ahmed et al 2010) and frequent copy-number alterations (Cancer Genome Atlas Research Network 2011). Approximately 10-15% of HGSOCs exhibit germline BRCA1 or BRCA2 mutations (gBRCAm) (Cancer Genome Atlas Research Network 2011, Konstantinopoulos et al 2015), impairing their ability to utilize homologous recombination repair (HRR) to repair DNA double-strand breaks (DSBs). A further 30-40% of tumors have either somatic mutations in BRCA1/2 (sBRCAm), hypermethylation of the BRCA1 promoter or inactivating mutations in other genes involved in HRR. Thus, up to 50% of HGSOC are considered HRR-deficient (HRD) (Konstantinopoulos et al 2015). Historically, endometrioid EOC has been sub-classified into either low or high-grade disease. However, it is now recognized that high grade endometrioid ovarian cancer (OC) more closely resembles HGSOC both molecularly and clinically (Kurman and Shih 2011).

HRD confers sensitivity to DNA-damaging agents such as platinum salts that cause inter-strand crosslinks (Bowtell et al 2015). It is also exploited in the treatment of HGSOC with poly adenosine diphospate (ADP) ribose polymerase (PARP) inhibitors, using the concept of synthetic lethality. This is the concept that tumors with a deficiency in one mode of DNA repair (HRR in this instance) will be uniquely susceptible to inhibition of a second pathway (base

excision repair [BER] in the case of PARP inhibitors), whereas normal cells will be unaffected (Ashworth A and Lord CJ 2018). This concept has found clinical application, with multiple PARP inhibitors now approved for the treatment of HGSOC (Mateo et al 2019).

HGSOC presents as advanced (stage III-IV) disease in the majority of patients. Initial treatment of HGSOC involves debulking surgery, with the goal of complete tumor resection and either adjuvant or neo-adjuvant chemotherapy. First line chemotherapy usually consists of a platinum-taxane doublet, most commonly carboplatin and paclitaxel for up to 6 cycles, either given as adjuvant treatment after surgery or split into pre- and post-operative courses (Lheureux et al 2019. Bevacizumab can be added to the chemotherapy backbone and continued as maintenance treatment; however, a clear impact on survival has not been demonstrated (Tewari et al 2019). More recently, olaparib has emerged as a maintenance treatment option for patients with germline or somatic BRCA mutations (BRCAm), based on the results of the double-blind, Phase III SOLO-1 study (Moore et al 2018). In SOLO-1, 391 patients with BRCAm HGS or endometrioid EOC and complete or partial response to initial chemotherapy were randomized 2:1 to maintenance olaparib or placebo. With a median duration of follow-up of 40.7 months, olaparib significantly prolonged progression-free survival (PFS) (HR=0.30, 95% CI: 0.23 to 0.41; median not reached for olaparib vs. 13.8 months for placebo) (Moore et al 2018). At the 2019 ESMO congress, the results of the PAOLA-1, PRIMA, and VELIA studies were presented:

- In the double-blind, Phase III PAOLA-1 study, 806 patients with advanced ovarian cancer who had complete or partial response after platinum-based chemotherapy and bevacizumab were randomized 2:1 to maintenance olaparib or placebo, in addition to bevacizumab. With a median duration of follow-up of approximately 24 months, olaparib significantly improved PFS compared to placebo, irrespective of BRCA status (HR=0.59, 95% CI: 0.49 to 0.72) (Ray-Coquard et al 2019). Patients with BRCAm appeared to benefit more (HR=0.31, 95% CI: 0.20 to 0.47, n =237) than patients with HRD but no BRCAm (HR=0.43, 95% CI: 0.28 to 0.66 n=152); patients with confirmed HRD-negative status did not appear to benefit (HR=1.00, 95% CI: 0.75 to 1.35, n=277) (Ray-Coquard et al 2019).
- Similarly, in the double-blind, placebo-controlled Phase III PRIMA study, 733 participants with advanced HGS or endometrioid tumors and complete or partial response after platinum-based chemotherapy were randomized 2:1 to maintenance niraparib or placebo. Similarly, PRIMA showed that maintenance niraparib significantly improved PFS in patients with high-grade serous or endometrioid EOC and response to initial chemotherapy, irrespective of BRCA status (HR=0.62, 95% CI: 0.5 to 0.76). The PFS benefit was more pronounced in patients with HRD and BRCAm (HR=0.40, 95% CI: 0.27 to 0.62, n=223) as well as those with HRD but no BRCAm (HR=0.50, 95% CI: 0.31 to 0.83, n=150) compared to HRR-proficient (HRP) patients (HR=0.68 to95% CI 0.49, 0.94, n=249) (González-Martín et al 2019)
- Finally, in the randomized, placebo-controlled Phase III VELIA study, 1140 participants with advanced HGSOC were randomly assigned in a 1:1:1 ratio to receive carboplatin and paclitaxel chemotherapy plus placebo followed by placebo maintenance (control), chemotherapy plus velaparib followed by placebo maintenance (velaparib combination only), or chemotherapy plus velaparib followed by velaparib

maintenance (velaparib throughout). The addition of velaparib concurrently with initial chemotherapy followed by maintenance treatment, again showed improvement in PFS, irrespective of BRCA status (HR=0.68, 95% CI: 0.56 to 0.83). As in PRIMA, the PFS benefit was more pronounced in patients with BRCAm (HR=0.44, 95% CI: 0.28 to 0.68, n=200) as well those with HRD (including BRCAm) (HR=0.57, 95% CI 0.44, 0.76, n=421) compared to patients with non-mutated BRCA (HR=0.80, 95% CI: 0.64 to 1.00, n=499) or HRP patients (HR=0.81, 95% CI: 0.6 to 1.09, n=249) (Coleman et al 2019).

Based on these studies, it is likely that PARP inhibitors will be incorporated in the initial treatment plan for HGSOC, irrespective of BRCA status in the near future, representing a new standard-of-care (Franzese et al 2019).

Despite good initial response to treatment, at least 75% of advanced HGSOC tumors will eventually relapse (Lheureux et al 2019). Subsequent treatment is mostly guided by the platinum-free interval (PFI), i.e. the time elapsed from completion of the last platinum-based chemotherapy regimen to progression of the disease. Generally, patients with a PFI of >12 months are considered platinum sensitive, and potentially platinum-sensitive if PFI is 6 - 12 months. These patients are usually retreated with platinum-based chemotherapy, frequently followed by PARP inhibitor treatment, irrespective of BRCA status (Bouberhan et al 2019). This treatment paradigm, however, is likely to evolve with the incorporation of PARP inhibitors in the initial treatment plan, as detailed above. As in the initial treatment setting, patients with relapsed HGSOC with documented HRD tend to show more sensitivity to platinum agents and can often receive multiple courses of platinum-based chemotherapy. Similarly, maintenance treatment with PARP inhibitors after response to platinum-based chemotherapy is more effective in patients with gBRCAm, followed by those with other alterations conferring HRD. However, even the 50% of HRP HGSOC patients seem to benefit, albeit to a lesser extent (Mirza et al 2016; Coleman et al 2017; Franzese et al 2019). Nevertheless, eventually almost all cancers will become platinum resistant or refractory (PR-EOC) (Bowtell et al 2015).

Platinum-refractory patients are defined as those whose tumors demonstrate disease progression while on treatment or within 1 month of completion of platinum-based chemotherapy (PFI< 1 month). Platinum-resistant patients are those whose tumors demonstrate progression after 1 to < 6 months from completion of last platinum cycle. A recent publication, using data from the AURELIA (Pujade-Lauraine et al 2014), CARTAXHY (Lotholary et al 2012) and PENELOPE (Kurzeder et al 2016 trials, found that a platinum-free interval of < 3 months vs. 3-6 months, was a significant prognostic factor in patients with platinum-resistant EOC (HR 1.43, p=0.008 per multivariate analysis) (Lee et al 2019).

Despite the available treatment options, the development of platinum resistance confers a dismal prognosis, with median survival of only 12-15 months (Pujade-Lauraine et al 2019).

The current standard of care for PR-EOC is cytotoxic chemotherapy, most commonly paclitaxel or pegylated liposomal doxorubicin (PLD), with gemcitabine and topotecan also considered as options (Pujade-Lauraine et al 2019). Based on the results of the open-label, Phase III AURELIA study, bevacizumab can be added to the chemotherapy backbone (Pujade-Lauraine et al 2014). In AURELIA, 361 patents with platinum-resistant (but not refractory) EOC were randomized 1:1 to bevacizumab plus physician's choice of chemotherapy

(paclitaxel, PLD or topotecan) or chemotherapy. With a median duration of follow-up of 13-13.9 months, bevacizumab in addition to chemotherapy significantly prolonged PFS (HR=0.48, 95% CI: 0.38 to 0.60; median of 6.7 months (95% CI: 5.7 to 7.9) vs 3.4 months (95% CI: 2.2 to 3.7) (Pujade-Lauraine et al 2014).

The role of bevacizumab in patients that have already been exposed to anti-angiogenic treatments earlier in their disease course is uncertain (Pujade-Lauraine et al 2019). Moreover, treatment with bevacizumab is associated with an increased risk of specific side effects including bowel perforation (especially in patients with bowel obstruction or bowel involvement), arterial thrombotic events, bleeding, hypertension, and proteinuria.

As bowel involvement with or without partial or total obstruction is a common clinical scenario in PR-EOC, careful patient selection is warranted; hence, for many patients with PR-EOC the addition of bevacizumab to chemotherapy is not appropriate.

1.1.2 The PI3K pathway in HGSOC

The phosphatidylinositol-3-kinase (PI3K) pathway is a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival and apoptosis. Constitutive activation of PI3K signaling is a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types, with PI3K as the oncogenic driver of the PI3K/Protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway (Liu et al 2009). Aberrant induction of PI3K pathway activity can occur through several events including upstream genetic alterations in receptor tyrosine kinases (RTKs), loss-of-function mutations in the tumor suppressor genes (such as PTEN) as well as mutations in PIK3CA, the gene encoding PI3Kα (Rodon et al 2013). PIK3CA encodes the p110α catalytic subunit of the class IA phosphatidylinositol 3-kinases (PI3Ks).

PI3K activity is stimulated by diverse oncogenes and growth factor receptors, and elevated PI3K signaling is considered a hallmark of cancer (Fruman et al 2017). It has been shown that PI3K inhibition leads to downregulation of BRCA1 or BRCA2 and abrogation of HRR, and subsequent sensitization to PARP inhibitors. Synergism between PI3K and PARP inhibitors has been observed both in vitro and in vivo, in HRR-proficient and HRR-deficient models of breast cancer (Ibrahim et al 2012, Juvekar et al 2012). PIK3CA mutations appear to be rare in HGSOC (~1-2%), but gene amplifications are common (~20%) (Cancer Genome Atlas Research Network 2011). Additionally, in ~7% of HGSOC tumors, the PI3K pathway is activated by homozygous PTEN loss (Cancer Genome Atlas Research Network 2011, Konstantinopoulos et al 2015). However, selection of patients according to PI3K pathway aberrations has not been shown to confer any advantage in terms of improved efficacy (Piha-Paul et al 2019). Preclinical evidence from breast cancer models suggests that inhibition of the PI3K pathway can downregulate the HRR pathway through extracellular signal regulated kinase (ERK)-dependent proto-oncogene 1, transcription factor (ETS1)-driven BRCA1/2 downregulation (Ibrahim et al 2012). Therefore, the addition of a PI3K pathway inhibitor to a PARP inhibitor may augment the latter's effect on HRP HGSOC (Konstantinopoulos et al 2015). Additionally, given that restoration of HRR is perhaps the most common mechanism of acquired PARP inhibitor resistance in HRD HGSOC (Mateo et al 2019), combination treatment with a PARP and PI3K pathway inhibitor could re-sensitize HRD HGSOC with acquired PARP-inhibitor resistance.

1.1.3 Overview of Alpelisib

Alpelisib is an oral, alpha-selective, 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.

1.1.3.1 Non-clinical experience

Alpelisib shows significant preclinical antitumor activity. In biochemical assays, alpelisib inhibits p110α (inhibitor concentration causing half maximal inhibition [IC50] = 4.6 nM) much more potently than the p110δ and γ isoforms and PIK4β and has weak or no activity against p110β, Vps34 and mTOR. Alpelisib is equipotent against the most common somatic mutations of p110α (H1047R, E545K) compared to wild type p110α, and is selective against a wide range of protein kinases with at least a 50-fold selectivity window compared to p110α. The potency and selectivity of alpelisib is confirmed at the cellular level in mechanistic and relevant tumor cell lines. Alpelisib potently inhibits p110α cellular activity (IC50=74 nM) and shows significant selectivity against the p110β and p110δ isoforms (above 15-fold). Alpelisib is not interfering with phosphoinositol 3-kinase-related- kinases (PIKKs) involved in DNA-damage repair processes (IC50> 30μM on S15P-p53 and IC50> 10μM on S1981P-ataxia-telangiectasia mutation [ATM]). In vitro, alpelisib inhibits the proliferation of various cancer cell lines, and showed increased activity in cell lines harboring gene alterations in PIK3CA. More detailed information on the pharmacology of alpelisib, single and multiple dose pharmacokinetic (PK) studies conducted in multiple species and nonclinical safety evaluations can be found in the Investigator Brochure.

1.1.3.2 Clinical experience

Clinical data

Alpelisib has been investigated both as a single agent and as combination therapy in 42 clinical studies and as of 23-May-2022, 25 studies have been completed and 17 studies are ongoing. The safety profile of alpelisib is well characterized and manageable with generally reversible AEs. More detailed preclinical and clinical information is provided in the [Alpelisib (BYL719) Investigator's Brochure].

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 receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. The approval was based on the results of CBYL719C2301 (SOLAR-1; Study C2301), a randomized, double-blind, placebo-controlled, multicenter, Phase III study that assessed alpelisib in combination with fulvestrant. SOLAR-1 met its primary endpoint in patients with a PIK3CA mutation with a statistically significant improvement in PFS by investigator assessment in favor of the alpelisib plus fulvestrant arm (HR=0.65, 95% CI: 0.50 to 0.85, p=0.00065). Median PFS was prolonged by 5.3 months, from 5.7 months (95% CI: 3.7 to 7.4) in the placebo plus fulvestrant arm to 11.0 months (95% CI: 7.5 to 14.5) in the alpelisib plus fulvestrant arm. The adverse events reported in the SOLAR-1 study were consistent with

the known safety profile of alpelisib. The most common adverse drug reactions for alpelisib plus fulvestrant (in more than 20% patients) were hyperglycemia, diarrhea, rash, nausea, fatigue and asthenia, decreased appetite, stomatitis, vomiting and weight decreased. Less commonly reported, but clinically important, adverse reactions were pneumonitis, severe hypersensitivity and severe cutaneous reactions.

Alpelisib has been investigated both as a single agent and as combination therapy in 42 clinical studies, including in combination with olaparib in a Phase Ib study in participants with recurrent EOC or breast cancer (see section "Alpelisib plus Olaparib") (Konstantinopoulos et al 2019). In this study, patients with gBRCAwt PR-EOC treated with a combination of alpelisib and olaparib had an ORR of 31% (95% CI: 11 to 59; n=16), which compares favorably to the ORR of 4% (n=26), previously reported for single agent olaparib in BRCAm negative or unknown PR-EOC patients (Gelmon et al 2011). However, in the Phase Ib dose escalation and expansion study of alpelisib (Study CBYL719X2101), responses among CCI patients with ovarian cancer treated with single agent alpelisib CCI ; all participants had either CCI as best overall response (BOR). The alpelisib safety profile is well characterized and manageable with generally reversible AEs. The alpelisib Investigator's Brochure (IB) provides a more detailed review of the preclinical and clinical information.

Clinical Pharmacology

The pharmacokinetics of alpelisib has been studied in healthy subjects and adult patients with solid tumors. Steady-state alpelisib maximum plasma concentration (Cmax) and Area Under the Curve (AUC) increased proportionally over the dose range of 30 mg to 450 mg (0.1 to 1.5 times the approved recommended dosage) under fed conditions. The mean accumulation of alpelisib is 1.3 to 1.5 and steady-state plasma concentrations are reached within 3 days following daily dosage. In adult patients who received alpelisib 300 mg once daily in the SOLAR-1 trial, mean steady-state alpelisib [coefficient of variation (CV%)] Cmax was 2480 (23%) ng/mL and AUC0-24hr was 33224 (21%) ng*h/mL based on a population PK approach. The median time to reach peak plasma concentration (Tmax) ranged between 2.0 to 4.0 hours. The half-life of alpelisib is predicted to be 8 to 9 hours. The mean (%CV) clearance of alpelisib is predicted to be 9.2 L/hr (21%) under fed conditions.

A high-fat high-calorie meal (985 calories with 58.1 g of fat) increased alpelisib AUC by 73% and Cmax by 84%, and a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased alpelisib AUC by 77% and Cmax by 145% following a single dose of alpelisib. 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. Following a single oral dose of 400 mg radiolabeled alpelisib under fasted condition, 81% of the administered dose was recovered in feces (36% unchanged, 32% BZG791) and 14% (2% unchanged, 7.1% BZG791) in urine. CYP3A4-mediated metabolites (12%) and glucuronides amounted to approximately 15% of the dose. Excretion of unchanged alpelisib occurs primarily via hepatobiliary export and/or

intestinal secretion of alpelisib. As alpelisib is a substrate of breast cancer resistance protein (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 pharmacokinetics of everolimus (a substrate of CYP3A4 and P-gp), however, were observed when co-administered with alpelisib. Alpelisib has a low potential to inhibit BCRP), MRP2, Bile Salt Export Pump (BSEP), organic anion transporter (OATP1B1, OATP1B3), organic cation transporter (OCT)1, OAT1, OAT3, OCT2, Multidrug and toxin extrusion 1 (MATE1), and MATE2K at clinically relevant concentrations.

1.1.4 Overview of olaparib

Olaparib is a PARP inhibitor, currently approved in multiple indications for the treatment of ovarian, pancreatic and breast cancer. It is approved by the US FDA for the treatment of ovarian cancer in the following settings:

i) maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy;

ii) in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability; and

iii) maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

Similarly, it is approved by EMA for:

i) maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy;

ii) maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy; and

iii) in combination with bevacizumab is indicated for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.

Notably, in the maintenance setting after chemotherapy for relapsed EOC, BRCA wild-type (BRCAwt) patients were only included in the double-blind Phase II Study 19. In Study 19, 265 patients with platinum-sensitive recurrent serous ovarian cancer who had received two or more courses of platinum-based chemotherapy and had responded to their latest regimen were randomly assigned (1:1) to receive oral maintenance olaparib (as capsules; 400 mg twice a day) or a matching placebo (Ledermann et al 2012). BRCA status was determined retrospectively. In the subgroup of patients reported as being BRCAwt (n=118), olaparib significantly prolonged PFS (HR 0.54, 95% CI 0.34 to 0.85) with a median PFS of 7.4 months (95% CI: 5.5 to 10.3) vs 5.5 months (95% CI: 3.7 to 5.6) (Ledermann et al 2014). However, in BRCAwt patients, maintenance therapy with olaparib failed to demonstrate a statistically significant improvement in overall survival (OS) observed (HR 0.83, 95% CI 0.55-1.24), with a median OS of 24.5 months in the olaparib arm (95% CI: 19.8 to 35.0) vs 26.6 months in the placebo arm (95% CI: 23.1 to 32.5) (Ledermann et al 2016).

Olaparib has shown single agent activity in relapsed ovarian cancer, but this is more pronounced in gBRCAm and/or platinum-sensitive disease (Mateo et al 2019). In an open-label, single-arm Phase II study, 3 of 12 (ORR = 25%) patients with platinum-resistant BRCAm tumors responded to olaparib whereas only 1 of 26 (ORR = 4%) patients with BRCAm negative or unknown tumors responded (Gelmon et al 2011).

Although earlier olaparib studies used the olaparib capsule formulation (recommended dose, 400 mg twice daily), olaparib is currently available as 150 mg or 100 mg tablets (recommended dose, 300 mg twice daily). The rationale for changing from the 50 mg capsule to the tablet was to reduce pill burden as the 400 mg twice daily capsule dose corresponded to 16 capsules a day. The two dosing schemes were shown to be equivalent in a bridging population PK analysis (Zhou et al 2019) and the tablet formulation was used in SOLO-1.

The most common adverse reactions (≥20%) in olaparib clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, neutropenia, leukopenia, nasopharyngitis / upper respiratory tract infection / influenza, respiratory tract infection, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation and stomatitis. The most common laboratory abnormalities (≥25%) were decrease in hemoglobin, increase in mean corpuscular volume, decrease in lymphocytes, decrease in leukocytes, decrease in absolute neutrophil count, increase in serum creatinine and decrease in platelets.

For additional details, please refer to Lynparza Summary of Product Characteristics (SmPC) and US Prescribing Information.

1.1.5 Alpelisib and olaparib combination in HGSOC

1.1.5.1 Preclinical development

Konstantinopoulos et al (Konstantinopoulos et al 2019) assessed the tolerability and efficacy of the olaparib plus alpelisib combination in ovarian cancer patient-derived xenograft (PDX) models. Initial tolerability studies in mice indicated that doses of olaparib of 100 mg/kg by oral gavage daily for 5 weeks along with alpelisib 50 mg/kg by oral gavage daily for 5 weeks were well tolerated without weight loss. Efficacy studies with this dosing schedule revealed that the combination of alpelisib and olaparib induced inhibition of tumor growth in a variety of ovarian PDX models including: (a) *BRCA1/2*wt, poly-ADP ribose polymerase inhibitor (PARPi) and

platinum resistant, HRP models (DF216, DF106, DF118), (b) the *BRCA1/2*wt, PARPi and platinum sensitive, HRD DF83 model, (c) and the *BRCA1* mutated, PARPi and platinum resistant DF101 model with acquired HRR proficiency. Furthermore, as a proof of mechanism, alpelisib inhibited HRR in the HRP DF216 model as evidenced by the decrease in the RAD51 foci positive cells after treatment with olaparib plus alpelisib compared to treatment with olaparib alone. RAD51 protein is involved in repair of DNA double strand breaks and has a central role in HRR (Konstantinopoulos et al 2015). Target engagement studies also demonstrated down regulation of phosphorylated AKT (pAKT), a downstream effector target of PI3K, after treatment with alpelisib and olaparib plus alpelisib (Konstantinopoulos et al 2019).

1.1.5.2 Clinical Development

The combination of alpelisib and olaparib was evaluated in a dose escalation and expansion Phase Ib study in recurrent ovarian and breast cancer. Twenty-eight patients were enrolled in the dose escalation cohort and the Recommended Phase II dose (RP2D) of alpelisib was 200 mg orally once daily with olaparib 200 mg orally twice daily. Among patients with gBRCAm PR-EOC, the overall response rate (ORR) was 33% (95% CI: 7 to 70; n=9), a proportion that is similar to prior reports with single agent olaparib in this setting (Audeh et al 2010, Gelmon et al 2011). However, the ORR of 31% (95% CI: 11 to 59; n=16) in PR-EOC gBRCAwt patients (Konstantinopoulos et al 2019), is encouraging compared with previous reports of an ORR with of 4% (n=26) with single agent olaparib in BRCAm negative or unknown PR-EOC patients (Gelmon et al 2011). ORR for single agent olaparib in patients who were BRCAm (germline and somatic) was 33% (4 out of 12 patients); all these patients had platinum resistant/refractory tumors.

In comparison, the ORR with chemotherapy in platinum-resistant (but not refractory) EOC, irrespective of BRCA status in AURELIA was 30% with paclitaxel (n=115), 8% with PLD (n=126) and 0% with topotecan (n=120) (Poveda et al 2015). The inclusion of any EOC histological subtype except borderline tumors, the exclusion of platinum-refractory patients, and an unknown proportion of patients with BRCAm in AURELIA, make any cross-trial comparison of the ORR with alpelisib plus olaparib vs chemotherapy difficult to interpret. Furthermore, AURELIA involved a significantly less heavily pretreated patient population, as it allowed patients with only up to two prior lines of anticancer therapy and more than 55% of patients had received only one prior line of anticancer therapy. In contrast, the Phase Ib olaparib plus alpelisib study included a patient population with a median of three prior lines of cytotoxic therapy (without counting prior hormonal therapy and radiation therapy as separate lines) and included patients with as many as eight prior lines of therapy. Hence, despite the more heavily pre-treated nature of the olaparib plus alpelisib study population, clinical activity was demonstrated.

Considering all dose levels, the most common (>10%) treatment-related adverse events in the Phase Ib study with alpelisib plus olaparib were: hyperglycaemia, fatigue, diarrhoea, vomiting, anorexia, headache, anaemia, constipation, increased creatinine, thrombocytopenia, acneiform rash, maculopapular rash, increased serum amylase, abdominal pain, increased alanine aminotransferase, dry skin, dysgeusia, dyspnoea, increased lipase, and mucositis oral. The most common grade 3–4 treatment-related adverse events were hyperglycaemia (16%), nausea (9%),

and increased alanine aminotransferase (9%). Three patients discontinued therapy for drug-related toxicity, one each for grade 3 and grade 4 hyperglycaemia and one for grade 2 nausea and vomiting. Serious adverse events included grade 4 hyperglycaemia (n=2), grade 4 febrile neutropenia (n=1), grade 2 hypothyroidism (n=1), and grade 2 small bowel fistula (n=1). There were no treatment-related deaths.

Based on this preliminary safety data, the safety profile of the combination is consistent with the individual components and no new or increased risk was observed.

Anticipated overlapping toxicities for alpelisib plus olaparib are gastrointestinal toxicity, pneumonitis, skin toxicity, hypersensitivity, decreased appetite, stomatitis, hematological toxicity, laboratory abnormalities (i.e, liver enzymes, pancreatic enzymes, and blood creatinine increased). Reproductive toxicity is also a potential risk in the participants with ovarian cancer. However, it is anticipated that the vast majority of patients treated with this combination will have had prior hysterectomy and bilateral salpingo-oophorectomy as part of the initial treatment of their cancer.

Based on the known clinical pharmacology of both alpelisib and olaparib no drug-drug interaction is anticipated. Additionally, no pharmacokinetic interactions were observed when alpelisib and olaparib were co-administered in participants with recurrent EOC or breast cancer (Konstantinopoulos et al 2019). However, more information on the PK in the combination will be acquired in this study (Section 8.5.2).

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of the combination of alpelisib with olaparib compared to standard-of-care chemotherapy in participants with platinum resistant or refractory HGSOC with no germline BRCA mutation detected (gBRCAnm) irrespective of PIK3CA mutation status, a population with poor outcomes and unmet medical needs.

2 Objectives and estimands

Table 2-1 Objectives and Endpoints

	Objective	Endpoint(s)
Primary	To determine whether treatment with alpelisib in combination with olaparib prolongs PFS compared to single agent cytotoxic chemotherapy in participants with platinum-resistant or refractory, gBRCAnm HGSOC	PFS based on BIRC assessment using RECIST 1.1 criteria
Key Secondary	To determine whether treatment with alpelisib in combination with olaparib prolongs OS compared to single agent cytotoxic chemotherapy in participants with platinum-resistant or refractory, gBRCAnm HGSOC	OS
Other Secondary	To assess safety and tolerability of alpelisib in combination with olaparib when	**Safety**: Incidence, type and severity of adverse events per CTCAE v4.03 criteria including changes in laboratory

	Objective	Endpoint(s)
	administered to participants with platinum-resistant or refractory, gBRCAnm HGSOC	values, vital signs, hepatic, renal and cardiac assessments. **Tolerability:** dose interruptions, reductions, dose intensity and duration of exposure for all drug components.
	To evaluate alpelisib in combination with olaparib compared to single agent cytotoxic chemotherapy in participants with platinum-resistant or refractory, gBRCAnm HGSOC with respect to time to deterioration of ECOG (Eastern Cooperative Oncology Group) performance status	Time to definitive deterioration of the ECOG performance status from baseline
	To assess additional efficacy parameters	Overall Response Rate (ORR) with confirmed response, Clinical Benefit Rate (CBR) with confirmed response, Duration Of Response (DOR) with confirmed response and Time To Response (TTR) (based on BIRC assessment using RECIST 1.1 criteria)
	To characterize the PK of alpelisib and olaparib when administered in combination in patients with platinum-resistant or refractory, gBRCAnm HGSOC.	Summary of statistics of PK parameters (including but not limited to AUCtau, AUClast, Cmax, Tmax) of alpelisib and olaparib (full PK subset only), Summary of statistics of plasma alpelisib and olaparib concentrations by time point.
	To evaluate patient reported-outcomes of alpelisib in combination with olaparib compared to single agent cytotoxic chemotherapy in adult participants with platinum-resistant or refractory, gBRCAnm HGSOC	Change from baseline in Function Assessment of Cancer Therapy-Ovarian Trial Outcome Index (FACT-O)
Exploratory		

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g premature discontinuation of treatment).The primary scientific question of interest of this study is: what is the treatment effect based on PFS for alpelisib in combination with olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD) in participants with gBRCAnm, platinum-resistant or refractory high grade serous ovarian cancer, regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The justification for targeting this treatment effect to assess the treatment effect not only during the on-treatment period but also after the discontinuation of study treatment, i.e., during the entire course of the study; and compare not just alpelisib + olaparib vs. SoC, but alpelisib + olaparib followed by any new anti-neoplastic therapy vs. SoC followed by any new anti-neoplastic therapy.

The primary estimand is characterized by the following attributes:

1. Population: all participants randomized with gBRCAnm, platinum-resistant or refractory high-grade serous or high-grade endometrioid ovarian cancer. Further details on the population are provided in Section 5.
2. Treatment: the investigational treatment is alpelisib in combination with olaparib plus any subsequent anti-neoplastic therapy as needed. The control treatment is single agent cytotoxic chemotherapy (paclitaxel or PLD) plus any subsequent anti-neoplastic therapy as needed. Further details about the investigational treatment and control treatment are provided in Section 6.
3. Variable: PFS based on BIRC assessment using RECIST 1.1 criteria. Further details on PFS are provided in Section 12.4.1.
4. Intercurrent events:
   - discontinuation of study treatment for any reason

   Details on how to handle intercurrent events are provided in Section 12.4.3.
5. Summary measure: PFS hazard ratio (alpelisib + olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD)) along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.4.2.

2.2 Secondary estimands

The key secondary scientific question of interest is: what is the treatment effect based on OS for alpelisib in combination with olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD) in participants with gBRCAnm, platinum-resistant or refractory high-grade serous or high-grade endometrioid ovarian cancer regardless of study treatment discontinuation or start of new anti-neoplastic therapy?

The justification for targeting this treatment effect is to assess the treatment effect based on OS and compare not just alpelisib + olaparib vs. SoC, but alpelisib + olaparib followed by any new anti-neoplastic therapy vs. SoC followed by any new anti-neoplastic therapy.

The key secondary estimand is characterized by the following attributes:

1. Population: all participants randomized with gBRCAnm, platinum-resistant or refractory high grade serous ovarian cancer. Further details on the population are provided in Section 5.
2. Treatment: the investigational treatment is alpelisib in combination with olaparib plus any subsequent anti-neoplastic therapy as needed. The control treatment is single agent cytotoxic chemotherapy (paclitaxel or PLD) plus any subsequent anti-neoplastic therapy as needed. Further details about the investigational treatment and control treatment are provided in Section 6.
3. Variable: OS. Further details on OS are provided in Section 12.5.1.1 .
4. Intercurrent events:
   - discontinuation of study treatment for any reason

   Details on how to handle intercurrent events are provided in Section 12.5.1.1.
5. Summary measure: OS hazard ratio (alpelisib + olaparib versus single agent cytotoxic chemotherapy (paclitaxel or PLD)) along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. Further details on how the summary measure will be tested are provided in Section 12.5.1.1.

3 Study design

Study CBYL719K12301 is a Phase III, multicenter, open-label, randomized (1:1), active-controlled study to assess the efficacy and safety of alpelisib in combination with olaparib in approximately 358 participants with platinum-resistant or refractory, gBRCAnm HGSOC. The purpose of the study is to evaluate the efficacy and safety profile of alpelisib in combination with olaparib compared to single agent cytotoxic chemotherapy in participants with platinum resistant or refractory HGSOC with no germline BRCA mutation detected.

During the Pre-Screening period, all participants will enter into Molecular Screening where testing for BRCAnm status is completed. Once BRCAnm status is confirmed (Refer to Section 8.1), participants will enter into Screening. Screening is up to 28 days in duration and will be used to assess eligibility of the participants to enter the Treatment period and to collect baseline values for some variables. Participants will be eligible regardless of their tumor PIK3CA mutation status.

Eligible participants will be randomized to receive:

- Experimental Arm (Arm 1): alpelisib 200 mg orally once daily with olaparib 200 mg orally twice daily starting on Cycle 1 Day 1 in a 28-day cycle.
- Control Arm (Arm 2): Investigator's choice of paclitaxel 80 mg/m^2 intravenously weekly in a 28 day treatment cycle, starting on Cycle 1 Day 1

OR

- pegylated liposomal doxorubicin (PLD) 40-50 mg/m^2 (physician discretion) intravenously every 28 days in a 28 day treatment cycle, starting on Cycle 1 Day 1.

Further details about the investigational and control treatments are provided in Section 6.1

Approximately 358 participants will be randomly assigned to either alpelisib plus olaparib or single agent cytotoxic chemotherapy (paclitaxel or PLD). Randomization to treatment will follow a 1:1 ratio and will be stratified by the factors listed below. If a participant is randomized to the chemotherapy arm, then the investigator will choose if paclitaxel or PLD will be administered based on the individual participant.

Randomization will be stratified by three stratification factors:

- Relapse within < 3 months from last platinum dose vs. within 3-6 months from last platinum dose
- Prior PARP inhibitor use (yes vs. no)
- Prior bevacizumab use (yes vs. no)

The total number of participants with non-measurable disease will be limited to up to CCI of the overall study population.

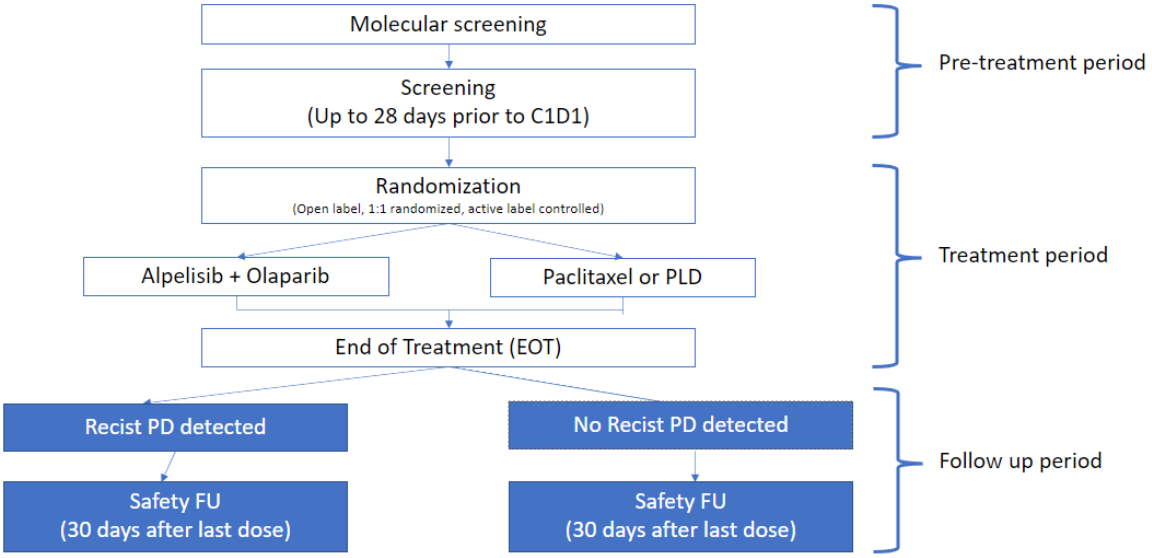
Treatment cross-over from one arm to another arm will not be permitted in this study; no switching between chemotherapy agents is allowed within Arm 2 once the first dose of chemotherapy is administered.

Prior to amendment 03, all participants who discontinue due to disease progression per RECIST 1.1. as assessed by BIRC will enter in the post-treatment follow-up period, which consists of a safety follow-up visit and an 8-week post-progression visit. Participants who discontinued for reasons other than disease progression per RECIST 1.1 as assessed by BIRC, death, lost to follow-up, or withdrawal of consent will enter in a post-treatment efficacy follow-up. Participants will then enter survival follow-up. The study Flow before the implementation of protocol amendment 03 is described in Figure 3-3

As per amendment 03, all participants who discontinue due to disease progression per RECIST 1.1. as assessed by local investigator will enter in the safety follow-up. Participants who discontinued for reasons other than disease progression per RECIST 1.1 as assessed by local investigator, death, lost to follow-up, or withdrawal of consent will enter in a post-treatment efficacy follow-up. Participants will no longer enter survival follow-up after protocol amendment 03. The Study Flow after implementation of protocol amendment 3 is described in Figure 3-2.

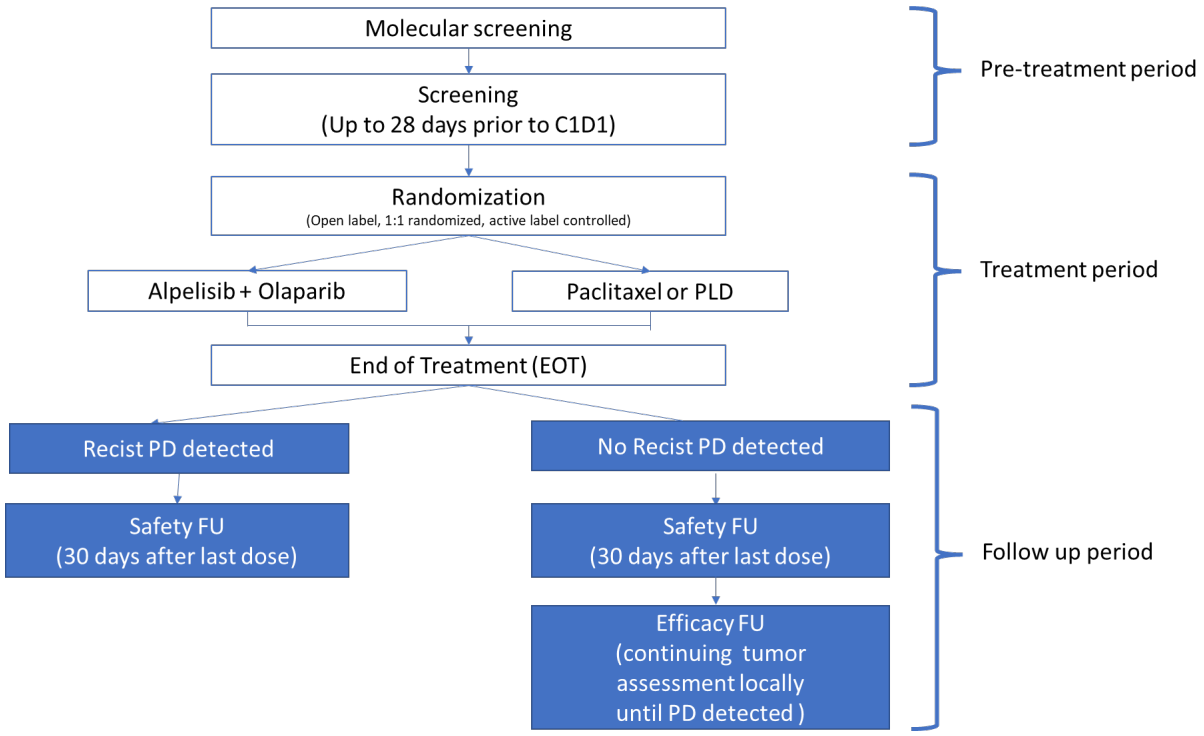
As per amendment 04, all participants who discontinue the treatment for reason other than disease progression per RECIST 1.1. as assessed by local investigator will enter the safety follow-up. Participants will no longer enter efficacy follow-up after protocol amendment 04. Participants already in efficacy follow-up will end study participation. The Study Flow after implementation of protocol amendment 04 is described in Figure 3-3.

Figure 3-1 Study flow



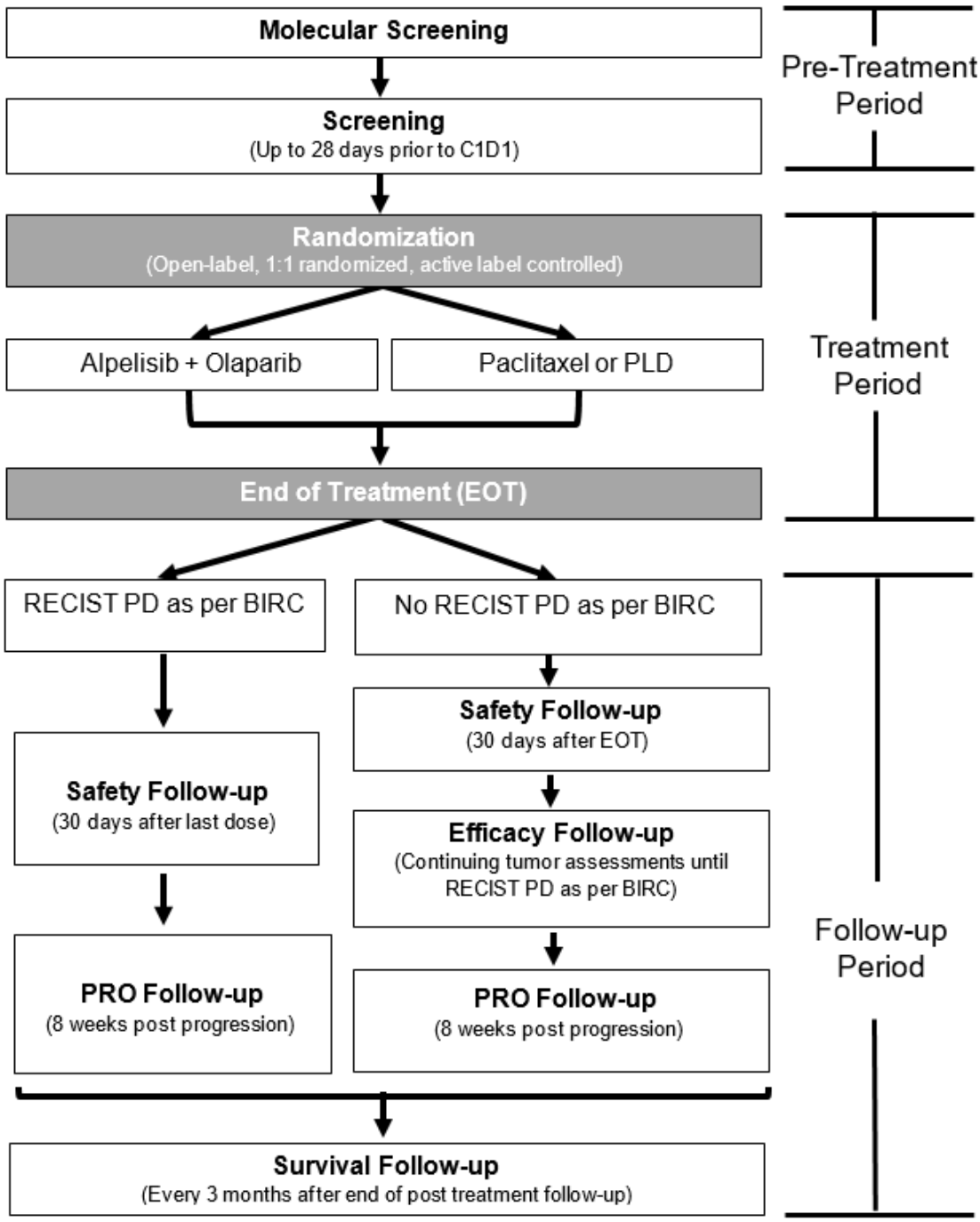
Note: Following protocol amendment 04 no further participants will enter efficacy follow up. Participants already in efficacy follow-up phase will end study participation.

Figure 3-2 Study flow (before implementation of protocol amendment 04)



Note: Following protocol amendment 03, no further participants will enter survival follow up. Participants already in efficacy follow-up phase will end study participation.

Figure 3-3 Study Flow (before implementation of protocol amendment 03)



This study will use an Interactive Response Technology (IRT) system for participant molecular screening, screening, enrollment, discontinuation, and study medication management.

4 Rationale

4.1 Rationale for study design

This is a multicenter, randomized, open-label Phase III trial to assess the efficacy of alpelisib when administered in combination with olaparib as compared to single agent cytotoxic chemotherapy. Approximately 358 participants will be randomized to receive alpelisib in combination with olaparib or investigator's choice of single agent cytotoxic chemotherapy with paclitaxel or PLD. Participants must have platinum resistant/ refractory, gBRCAnm HGSOC.

Trying to achieve double-blinding of treatment for participants and investigators, when the experimental arm consists of two oral agents and the control arm is a choice of two single intravenous agents, would significantly increase the burden and complexity of treatment, as it would necessitate multiple mock intravenous infusions and medically unnecessary premedication with steroids and/or antihistamines for participants randomized to the experimental arm. Additionally, drug-specific toxicities such as hyperglycemia with alpelisib or peripheral neuropathy and infusion reactions with paclitaxel make it unlikely that investigator blinding can be effectively maintained. Therefore, an open-label study design is preferred.

Stratification of randomization based on time from last platinum dose to relapse, prior PARP inhibitor use, and prior bevacizumab use in the current study will prevent imbalance between the two treatment arms.

PR-EOC represents a disease area of significant unmet medical need with median OS in patients of 12-15 months. The ORR for BRCA non-mutated (BRCAnm) patients is only around 5% with PARP inhibitor monotherapy (Konstantinopoulos et al 2019). The standard treatment option for these patients is cytotoxic chemotherapy with an ORR ranging from 8 to 30% and a median PFS ranging from 3.5 to 3.9 months with PLD or weekly paclitaxel (Pujade-Lauraine et al 2014, Poveda et al 2015).

4.2 Rationale for dose/regimen and duration of treatment

The selected study doses for alpelisib and olaparib are based on the Phase Ib study in participants with relapsed ovarian and breast cancers (Konstantinopoulos et al 2019).

Four dose levels were planned: the starting dose level of alpelisib 250 mg once a day plus olaparib 100 mg twice a day (dose level 0); alpelisib 250 mg once a day plus olaparib 200 mg twice a day (dose level 1); alpelisib 300 mg once a day plus olaparib 200 mg twice a day (dose level 2); and alpelisib 200 mg once a day plus olaparib 200 mg twice a day (dose level 3). Both drugs were administered orally, in tablet formulation. For olaparib, the recommended dose in the ovarian cancer label is 300 mg twice a day. However, in the Phase Ib study, this dose was not explored in combination with alpelisib, since stopping criteria for dose-escalation (Grade 4 neutropenia and fever, Grade 3 and 4 hyperglycemia, and inability to take more than 75% of study drug dose) was reached at prior dose levels. Thus, the maximum tolerated dose and recommended phase 2 dose were identified as alpelisib 200 mg once a day plus olaparib 200 mg twice a day (dose level 3) (Konstantinopoulos et al 2019). The recommended doses when used in combination are different than the doses specified in their respective labels. Additional information is in Section 1.1.5.2.

The selected doses for the comparison single agent cytotoxic chemotherapy agents are based on recommendations from clinical practice guidelines (Armstrong et al 2019) and have been commonly utilized in studies in platinum resistant or refractory HGSOC (See "Background on drugs used in the trial" section.)

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The combination of olaparib and alpelisib in a Phase Ib study demonstrated an ORR of 31% in participants with gBRCAwt PR-EOC with a tolerable safety profile (Konstantinopoulos et al 2019). These encouraging efficacy outcomes are supported by preclinical evidence that showed the potential of PI3K pathway inhibition to induce a functional HRD state and, therefore, sensitize or potentially re-sensitize tumors to PARP inhibitors.

Therefore, the combination of alpelisib and olaparib may offer improved efficacy as compared to cytotoxic chemotherapy in patients with platinum-resistant or refractory, gBRCAnm HGSOC. The terminology BRCAnm is preferred to BRCAwt, since BRCAnm more accurately describes that a deleterious or suspected deleterious BRCAm has not been detected.

In this study, a comparator arm of single agent olaparib was considered inappropriate since the ORR in platinum-resistant or refractory participants with negative or unknown BRCAm status is very low (4%, n=26) (Gelmon et al 2011). A similar low ORR for a single agent PARP inhibitor was also demonstrated with niraparib in the QUADRA study, with ORR of 3% in platinum-resistant or refractory HRD-negative or unknown participants (n=169) (Moore et al 2019). Additionally, in the Phase Ib dose escalation and expansion study of alpelisib (Study CBYL719X2101), CCI was observed with single agent alpelisib in participants with ovarian cancer. CCI participants with ovarian cancer were treated with alpelisib monotherapy at alpelisib once daily doses of CCI ; all participants had CCI as their best overall response. Therefore, a single agent alpelisib arm would not be clinically appropriate.

Hence, the comparator arm in this study consists of established single agent cytotoxic chemotherapy agents (paclitaxel or PLD) with known efficacy in the targeted population. Investigators may choose between one of two possible intravenous chemotherapy agents permitted in the control arm of the study.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis that allows the study to stop for lack of efficacy (futility) is planned after approximately 90 of the 224 targeted PFS events (i.e., at approximately 40% information fraction) have been documented (expected around 13.9 months from the date of first participant randomized in the study). There is no intention to stop for superiority at this interim analysis.

Only if final PFS analysis is statistically significant, interim analyses for OS will be conducted as detailed in Section 12.7.

The final PFS analysis was conducted in July 2023. The study did not meet its primary objective.

4.5 Risks and benefits

4.5.1 Potential benefits to clinical trial subjects

Treatment with alpelisib in combination with olaparib may provide a clinical benefit versus single agent cytotoxic chemotherapy (paclitaxel or PLD) in adult women with platinum-resistant or refractory, gBRCAnm high grade serous ovarian cancer.

For further details on clinical safety, please refer to the latest version of [Alpelisib (BYL719) Investigators Brochure] as well as local prescribing information for olaparib, paclitaxel, or PLD.

4.5.2 Potential risks to clinical trial participants

In light of the final PFS results, there are updated risks to participants on the alpelisib + olaparib arm as the final PFS analysis did not cross the pre-specified boundary for statistical significance (one sided $p \leq 0.025$). PFS hazard ratio was 1.14, (95% CI: (0.88, 1.48), p=0.84). The key secondary endpoint in this study is OS. The OS analysis result was not formally tested since the study did not meet its primary objective. The OS hazard ratio was 1.22 (95% CI: 0.87, 1.71) and descriptive one-sided p-value = 0.87.

A higher number of deaths were recorded in the alpelisib + olaparib arm: a total of 75 (41.7%) and 63 (38.4%) participants died during the study in the alpelisib + olaparib and paclitaxel/PLD arms respectively, with 26 (14.4%) and 7 (4.3%) on-treatment deaths (i.e. on treatment and up to 30 days after end of treatment). The main cause of all deaths during the study on alpelisib + olaparib and paclitaxel/PLD arms, respectively, was study indication (platinum refractory/resistant (PRR) ovarian cancer) (36.7% vs. 32.9% of participants). The main cause of on-treatment death was study indication in 19 (10.6%) participants in the alpelisib + olaparib arm and 4 (2.4%) participants in the paclitaxel/PLD arm.

No specific pattern of AEs was identified that would explain the increased number of on-treatment deaths. No new or unexpected adverse events were reported compared to the established safety profiles of the study drugs in their respective approved indications.

Participants in this study will be carefully monitored for key toxicities that have been observed with these study treatments (see Section 1.1.3.2), including periodic laboratory and cardiac assessments (ECGs). Cardiac function evaluation by Magnetic Resonance Imaging (MRI)/Echocardiography (ECHO)/Multigated Acquisition (MUGA) scan for key toxicities should be evaluated for participants only on PLD. Participants randomized to the control arm with chemotherapy may require additional monitoring specific to the agent administered based on the local label language and local standard of care.

Risks will be further minimized by adherence to inclusion/exclusion selection criteria (see Section 5), avoidance of prohibited medication (see Section 6.2.2), close safety monitoring (see Section 10), adherence to dose adjustment guidelines (see Section 6.6.1), and training of site personnel.

The independent data monitoring committee (DMC) will monitor critical safety and efficacy variables at defined intervals as outlined in the charter (see Section 10.2.2). The Study Steering Committee (SC), comprising of investigators participating in the study, a patient advocate, and Novartis personnel will ensure transparent management of the trial according to the protocol.

In addition, a Novartis Safety Management Team (SMT) will regularly review and evaluate all emerging data in this study and across the alpelisib program for potential safety signal assessments in a timely manner.

Women of child bearing potential must be informed that taking this study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

4.5.3 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

This study includes adult women with platinum-resistant or refractory, gBRCAnm HGSOC.

The investigator or designee must ensure that only patients who met all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent(s) must be obtained prior to participation in the study.
2. Participant is an adult woman ≥ 18 years old at the time of informed consent(s) and has signed informed consent(s) before any trial related activities and according to local guidelines.
3. Participant has histologically confirmed diagnosis of high-grade serous or high-grade endometrioid ovarian cancer, fallopian tube cancer or primary peritoneal cancer.
4. Participant has either:
    - Measurable disease, i.e., at least one measurable lesion per RECIST 1.1 criteria (a lesion at a previously irradiated site may only be counted as a target lesion if there is clear sign of progression since the irradiation) **OR**
    - If no measurable disease is present, the disease is assessable by Gynecologic Cancer Intergroup criteria (GCIC) for CA-125.
5. Participant has no germline BRCA1/2 mutation.

Note (for all countries except China): If a negative germline BRCA mutation result with the FDA-approved Myriad BRACAnalysis CDx test is provided by a local laboratory, this data can serve as confirmation of no BRCA mutation. If the FDA-approved Myriad BRACAnalysis CDx test is not available locally, a negative germline BRCA mutation result needs to be confirmed

by the Novartis (NVS) designated laboratory. For China, central testing for germline BRCA mutation (gBRCAnm) will be required at the NVS designated laboratory.

6. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Participant has received prior bevacizumab or is not eligible to receive bevacizumab due to medical reasons as per investigator's discretion (e.g., risk of bowel perforation, risk of bleeding, concurrent cardiovascular comorbidity, hypertension etc.).
8. Participant has platinum-resistant (progression within one to six months after completing a platinum-based therapy) or platinum refractory disease (progression during treatment or within 4 weeks after the last dose), where platinum-based therapy is not an option, according to the GCIG 5th Ovarian Cancer Consensus Conference definitions (Wilson et al 2016). The platinum-based chemotherapy regimen does not necessarily need to be the last regimen the participant received prior to study entry.
    - Exception: Participants with primary platinum refractory disease (i.e. never responded to platinum and progressed during initial platinum-based chemotherapy) are not eligible.
9. Participant must have received at least one but no more than three prior systemic treatment regimens and for whom single-agent chemotherapy is appropriate as the next line of treatment.
10. Participant can receive either paclitaxel weekly or PLD (physician's choice) if randomized to the control arm.
11. Participant has adequate bone marrow and organ function as defined by the following laboratory values (assessed by central laboratory for eligibility):
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L
    - Hemoglobin ≥ 10.0 g/dL
    - Calcium (corrected for serum albumin) and magnesium within normal limits or $\leq$ grade 1 according to Common Terminology Criteria for Adverse (CTCAE) Version 4.03 if judged clinically not significant by the investigator
    - Potassium within normal limits, or corrected with supplements and confirmed with central testing
    - INR ≤ 1.5
    - Creatinine Clearance (CrCl) ≥ 51 mL/min using Cockcroft-Gault formula
    - Total bilirubin < 2 ULN (any elevated bilirubin should be asymptomatic at enrollment) except for participants with Gilbert's syndrome who may only be included if the total bilirubin is $\leq 3.0 \times$ ULN or direct bilirubin $\leq 1.5 \times$ ULN
    - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $< 3 \times$ ULN. If the participant has liver metastases, ALT and AST $\leq 5 \times$ ULN (elevated ALT or AST values must be for 2 weeks, without evidence of biliary obstruction by imaging)
    - Fasting plasma glucose (FPG) ≤ 140 mg/dL (7.7 mmol/L) and Glycosylated Hemoglobin (HbA1c) $\leq 6.4\%$ (both criteria have to be met)

- Fasting serum amylase ≤ 2 × ULN
- Fasting serum lipase ≤ ULN

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Participant has received prior treatment with any PI3K, mTOR or AKT inhibitor.
2. Participant has a known hypersensitivity to alpelisib, olaparib, or BOTH paclitaxel and PLD.
3. Participant is concurrently using other anti-cancer therapy.
4. Participant has had surgery within 14 days prior to starting study drug or has not recovered from major adverse effects.
5. Participant has not recovered from all toxicities related to prior anticancer therapies to baseline or NCI CTCAE Version 4.03 Grade ≤1. Exception to this criterion: participants with any grade of alopecia are allowed to enter the study.
6. Participant has had prior exposure to murine antibodies or had a therapeutic paracentesis or pleurocentesis within 28 days prior to starting study drug (only applicable to participants with non-measurable disease by RECIST 1.1)
7. Participant has a known somatic BRCA mutation (sBRCAm); testing is not a mandatory requirement for eligibility.
8. Participant with liver impairment and Child Pugh score B or C.
9. Participant has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to baseline, grade 1 or better from related adverse effects of such therapy (with the exception of alopecia).
10. Participant has a concurrent malignancy or malignancy within 3 years of start of study treatment, with the exception of adequately treated basal or squamous cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
11. Participant has central nervous system (CNS) involvement. If participant is fulfilling the following 3 criteria she is eligible for the trial:
    - completed prior therapy (including radiation and/or surgery) for CNS metastases ≥ 28 days prior to the start of study, and
    - CNS tumor is clinically stable at the time of screening, and
    - participant is not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
12. Participant has an established diagnosis of diabetes mellitus type I or uncontrolled type II based on Fasting Plasma Glucose and HbA1c (see inclusion criteria 11).
13. Participant is in a state of small or large bowel obstruction or has other 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. Participant has radiologic evidence of bowel obstruction with impaired GI function.
15. Participant has a known history of acute pancreatitis within 1 year of screening or past medical history of chronic pancreatitis.

16. Participant has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate participation in the clinical study (e.g., chronic active hepatitis, severe hepatic impairment, etc.).
17. Participant has currently documented pneumonitis/interstitial lung disease (the chest CT scan performed prior to study entry for the purpose of tumor assessment should be reviewed to confirm that there are no relevant pulmonary complications present).
18. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
19. Participant has clinically significant, uncontrolled heart disease and/or recent cardiac events including any of the following:
    - History of angina pectoris, coronary artery bypass graft (CABG), symptomatic pericarditis, or myocardial infarction within 6 months prior to the start of study treatment
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Left Ventricular Ejection Fraction (LVEF) < 50% at screening as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
        - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
        - History of familial long QT syndrome or known family history of Torsades de Pointe
        - Resting heart rate (physical exam or 12 lead ECG) <60 bpm
    - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome, or resting QTcF ≥450 msec (male) or ≥460 msec (female) at pre-treatment screening (mean of triplicate ECGs).
    - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study
20. Participant has a history of severe cutaneous reaction, such as Steven-Johnson Syndrome (SJS), erythema multiforme (EM) or Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Syndrome (DRESS).
21. Participant has a history of myelodysplastic syndrome or acute myeloid leukemia, or presents clinical and/ or laboratory features suggestive thereof.
22. Participant has unresolved osteonecrosis of the jaw.
23. Participant is currently receiving any of the following medications and cannot be discontinued at least 7 days (or five half-lives whatever is longer) prior to the start of the treatment:

- Strong and moderate CYP3A4 inhibitors (including certain fruits and juices such as grapefruit or grapefruit juice)
- Strong and moderate CYP3A4 inducers
- Inhibitors of BCRP.

24. Participant 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 airways diseases), eye drops or local injections (e.g., intra-articular).

25. Participant participated in a prior investigational drug or device study within 30 days prior to the start of study treatment or within 5 half-lives of the investigational product, whichever is longer.
26. Participant is a woman of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and for 6 months after stopping alpelisib in combination with olaparib or paclitaxel, or for 8 months after stopping PLD.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) without hormonal component.

Women are considered postmenopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are postmenopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), or total hysterectomy at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

27. Participant is nursing (lactating) or pregnant confirmed by a positive serum (hCG) test prior to initiating study treatment.
28. Participant is not able to understand and to comply with study instructions and requirements, including taking oral medications.

6 Treatment

6.1 Study treatment

In this study, the term "study treatment" refers to the combination of alpelisib and olaparib or either paclitaxel or PLD. The term "investigational drug" refers to the Novartis study drug, alpelisib (BYL719) and olaparib (supplied by Global Clinical Supply (GCS) globally).

The other drugs to be used as comparator in this study are paclitaxel and PLD, which will be procured locally. Generic paclitaxel and PLD that were rejected by or withdrawn from either FDA or EMA should not be used.

This is an open-label study. Investigators, patients, and Sponsor will have full knowledge of the treatment allocation. In order to minimize the potential impact of treatment knowledge, until the primary analysis is conducted, no aggregate statistical analyses (efficacy or safety across the study) shall be performed by treatment (other than analyses as specified in the protocol).

The storage conditions for alpelisib and olaparib will be described on the prescribing information.

The storage conditions for paclitaxel and PLD should follow the locally approved prescribing information and local practices.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the appropriate electronic Case Report Form (eCRF).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
BYL719 (alpelisib) 200mg	Tablet	Oral use	Open label	Sponsor
BYL719 (alpelisib) 50mg	Tablet	Oral use	Open label	Sponsor
Olaparib 100mg	Tablet	Oral use	Open label	Sponsor)
Olaparib 150mg	Tablet	Oral use	Open label	Sponsor
Paclitaxel	Concentrate solution	IV	Open label; vial	Local
Pegylated Liposomal Doxorubicin	Concentrate solution	IV	Open label; vial	Local

6.1.1.1 Dose and treatment schedule

Arm 1:

- Alpelisib will be administered at 200 mg orally once daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.

AND

- Olaparib will be administered at 200 mg orally twice daily on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle. The morning dose of olaparib will be administered concomitantly with alpelisib after food. The evening dose of olaparib can be administered irrespective of food as per olabarib prescribing information.

Prophylactic use of metformin has been observed to decrease the incidence and severity of hyperglycemia when metformin is initiated 7 days prior to the initiation of alpelisib treatment as follows: metformin 500 mg twice daily from Day 1 to Day 3. Thereafter, based on tolerability, metformin may be continued and the dose may be increased to 1000 mg twice daily (METALLICA study (NCT04300790) (Llombart-Cussac A 2022).

Metformin XR was developed to allow a slower release of drug into the upper gastrointestinal tract to reduce toxicities such as diarrhea. The use of metformin XR can be considered as a suitable alternative to metformin IR due to its better tolerability and once daily dosing, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator (Jabbour and Ziring 2011).

A non-sedating antihistamine, such as cetirizine orally once daily on a continuous basis, is recommended starting on Cycle 1 Day 1 for approximately 8 weeks for the prevention of rash associated with PI3K inhibition. For participants benefiting from the antihistamine, treatment can be continued beyond the first 8 weeks, if clinically indicated at the investigator's discretion (Wang 2020). Refer to Table 6-4 and Section 6.6.2 for additional information on antihistamine treatment and incidence/severity of rash based on alpelisib clinical trial experience.

Arm 2:

- Paclitaxel will be administered at 80 mg/m^2 as an intravenous infusion weekly during a 28-day treatment cycle, starting on Cycle 1 Day 1, and on Day 8, Day 15 and Day 22 of every cycle thereafter (+/- 3 days allowed between cycles (C1, C2, ...); +/- 1 day allowed between cycle days (D1, D8, D15, and D22).

OR

- Pegylated liposomal doxorubicin (PLD) will be administered at 40-50 mg/m^2 (physician discretion) as an intravenous infusion once every 28-days in a 28 day treatment cycle, starting on Cycle 1 Day 1.

Further details about the investigational treatment and control treatment are provided in Section 6.1.

Additional study treatments

No auxiliary medicinal products (AxMP) or other treatments beyond alpelisib, olaparib, paclitaxel and pegylated liposomal doxorubicin (PLD) described in Table 6-1 are included in this trial.

Refer to Section 6.2.1.1 for permitted concomitant medications requiring caution and/or action.

6.1.2 Treatment arms/group

In this study, participants will be randomly assigned to one of the following two treatment arms in a ratio of 1:1:

- **Arm 1**: alpelisib orally once daily + olaparib orally twice daily
- **Arm 2**: Investigator's choice of one of 2 single agent cytotoxic chemotherapies: paclitaxel intravenously weekly or pegylated liposomal doxorubicin intravenously every 28 days.

Treatment cross-over from one Arm to another Arm or switching between chemotherapies within Arm 2 will not be permitted in this study.

6.1.3 Treatment duration

Participants will continue to receive study treatment until disease progression, unacceptable toxicity that precludes further treatment, or until discontinuation of study treatment due to any other reason (see Section 9.1.1).

If one of the two study drugs (alpelisib or olaparib) is permanently discontinued for any reason, the second study drug must also be discontinued, leading to end of study treatment.

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator’s evaluation may receive post-trial access. Post-Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, treatment is discontinued at the discretion of the investigator or the participant, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant’s country, or the clinical program is discontinued for any other reason.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition participants onto locally available treatment, or standard of care.

6.1.3.1 Treatment beyond disease progression

Study treatment beyond radiologically confirmed disease progression per RECIST 1.1 as assessed by BIRC, or as assessed locally with approval of protocol amendment 03, is not permitted in this study.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The use of any concomitant medications/non-drug therapies or procedures deemed necessary for pre-medication before chemotherapy administration, treatment of adverse events, management of cancer symptoms, treatment of concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed, except if specifically prohibited (see Section 6.2.2).

The investigator should instruct the participant to notify the study site about any new medications and/or non-drug therapies/procedures they take after signing the informed consent. All medications, procedures, and significant non-drug therapies (including vitamins, physical therapy, herbal/natural medications 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 recorded on the appropriate CRF.

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 randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Oral anti-diabetics

Participants who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association) guidance and/or European Association for the Study of Diabetes (EASD).

Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. It is recommended to start treatment with metformin, however sodium-glucose cotransporter 2 (SGLT2) inhibitors, as per standard practices/standard of care, may be a suitable alternative or add-on therapy to metformin. SGLT2 inhibitors are a class of diabetic medications that improve hyperglycemia primarily by promoting urinary glucose excretion.

In the SOLAR-1 study, among the 284 participants who were randomized to receive alpelisib plus fulvestrant, 190 participants (67%) developed hyperglycemia, with 18 patients (6%) discontinuing alpelisib treatment due to hyperglycemia, as of 30-Sep-2019.

Among those with hyperglycemia, 166 participants received concomitant anti-diabetic medications, primarily consisting of metformin (87%). However, in addition to metformin, 6 participants also received an SGLT2 inhibitor, consisting of empagliflozin, ipragliflozin, or dapagliflozin. All 6 participants had ≥ 1 risk factor at baseline for developing hyperglycemia, defined as prediabetes (n = 4; 1 of whom had documented history of type 2 diabetes), diabetes (n = 2), and obesity (n = 2). The most severe hyperglycemia in these participants was grade (G) 3 (n = 5). After initiating an SGLT2 inhibitor, all subsequent hyperglycemia events were G 1/2, except one G 3 event with steroids as a confounding factor. The duration of alpelisib ranged from 9.5 to 27.7 months in 4 patients who discontinued alpelisib; and notably, 2 patients were

continuing to receive alpelisib after 37.0 and 40.0 months, respectively. None of the 6 participants discontinued alpelisib due to hyperglycemia.

Participants with at least one risk factor for the development of severe hyperglycemia defined as prediabetes/diabetes, and/or obesity (BMI ≥ 30), and/or age ≥ 75 years, may benefit from the initiation of an SGLT2 inhibitor with metformin, which is available as a single oral combination pill or as two separate medications. The decision to initiate an SGLT2 inhibitor alone in combination with metformin prophylactically or at the onset of hyperglycemia (first fasting glucose level above the normal range) is at the discretion of the investigator.

Gastric protection agents

Alpelisib is characterized by a 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 immediately after food. In a joint food effect and acid reducing drug-drug interactions (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 on average by 21% when administered after a meal.

Palliative radiotherapy

Local radiotherapy for analgesic purposes or for lytic bone lesions at risk of fracture may be carried out if required. Participants requiring initiation of palliative radiotherapy during the course of the study should be assessed by the appropriate imaging modalities to exclude disease progression and the reason for its use must be clearly documented. In case of Progressive Disease (PD) is documented, participants should discontinue treatment.

Olaparib should be discontinued for a minimum of 3 days before a patient undergoes therapeutic or palliative radiation therapy. Post radiation therapy, olaparib should be restarted within 4 weeks as long as any bone marrow toxicity has recovered. No dose modification of alpelisib is needed.

Hematopoietic growth factors

Hematopoietic growth factors may be used according to American Society of Clinical Oncology (ASCO) guidelines (Smith et al 2015).

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 AE for PI3K inhibitors like alpelisib, so corticosteroids should therefore be used with caution and participants should be closely monitored.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during combined alpelisib and olaparib treatment in this study are described below and examples listed in Section 16.4. These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

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

Medications to be used with caution:

CYP3A4 sensitive substrates or CYP3A4 substrates with NTI: Based on limited in vitro data, olaparib may increase the exposure of drugs which are sensitive substrates of CYP3A4. For additional details, please refer to Lynparza Summary of Product Characteristics (SmPC) and US Prescribing Information. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic index.

CYP2C9 substrates with narrow therapeutic index (NTI) : 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 CYP2C9 substrates with an NIT such as therapeutic doses of warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants as alpelisib may reduce the clinical activity of such drugs.

Anticoagulants: Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable (See Section 8.4.1). Non-vitamin K antagonist oral anticoagulants (NOACs), Direct Thrombin Inhibitors (DTIs), subcutaneous heparin and low molecular weight heparin may be given concomitantly and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g apixaban and rivaroxaban) if possible.

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. Based on limited in vitro data, olaparib may also reduce the exposure of these substrates. Therefore, sensitive CYP2B6 substrates (e.g. bupropion) or CYP2B6 substrates with a narrow therapeutic window should be used with caution in combination with alpelisib and/or olaparib, as each drug may reduce the clinical activity of such drugs.

Substrates of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K: Based on limited in vitro data, olaparib may increase the exposure of drugs, which are substrates of the transporters BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. For additional details, please refer to Lynparza Summary of Product Characteristics (SmPC) and US Prescribing Information.

Herbal Medications: The use of herbal preparations/medications and dietary supplements are permitted with caution unless explicitly prohibited (see Section 6.2.2) for being strong inducers of CYP3A such as St. John's Wort (Hypericum perforatum) and Avasimibe (see Table 16-10) or BCRP inhibitors such as Curcumin (see Table 16-12). 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 should be documented as a concomitant medication. Participants

closely monitored for increased adverse reactions (as the relevance of this interaction in vivo is currently unknown). In case of unexpected toxicities, participants should stop using all herbal medications.

6.2.1.2 Use of bone modifying agents (BMA)

The use of bone modifying agents (BMA), e.g. bisphosphonates or denosumab) regardless of indication is allowed, provided participants have been on stable doses for at least 2 weeks prior to randomization. A stable dose should be maintained during the treatment period.

BMA may be given according to the local product license and routine clinical practice, at the investigator's discretion.

Participants taking BMA prior to entering the study should continue with the same bisphosphonate treatment, given as per local medical practice.

Participants requiring initiation of BMA treatment during the course of the study should be assessed by appropriate imaging modalities to exclude disease progression; if disease progression is documented, the participant should discontinue study treatment. If BMA therapy 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 BMA. In the SOLAR-1 Phase III clinical study, ONJ was reported in 4.2% participants (12/284) in the alpelisib plus fulvestrant arm compared to 1.4% participants (4/287) in the placebo plus fulvestrant arm. All participants experiencing ONJ were also exposed to prior or concomitant bisphosphonates (e.g. zoledronic acid). Therefore, in participants receiving alpelisib and bisphosphonates, an increased risk of development of ONJ cannot be excluded. For prevention and clinical management of ONJ, the prescribing information of the bisphosphonates/receptor activator of nuclear factor kappa-B (RANK)-ligand inhibitors (e.g. denosumab) should be followed.

6.2.2 Prohibited medication

The following medications are prohibited during combined alpelisib and olaparib treatment in this study (Section 16.4.1).

- **Moderate and strong inducers of CYP3A4:** Avoid co-administration of alpelisib and olaparib with moderate (only olaparib) and strong (both olaparib and alpelisib) CYP3A4 inducers as it could potentially reduce the effectiveness of either drug. Refer to
  Table 16-10.
- **Moderate and strong inhibitors of CYP3A4:** Avoid concomitant use of strong or moderate CYP3A4 inhibitors (including certain fruits and juices such as grapefruit or grapefruit juice) with olaparib. If the inhibitor cannot be avoided, reduce olaparib dose to 100 mg twice daily when used with a moderate CYP3A inhibitor or to150 mg once daily when used with a strong CYP3A inhibitor. Refer to Table 16-11.
- **Inhibitors of BCRP:** Avoid the use of BCRP inhibitors in participants treated with alpelisib. If unable to use alternative drugs, closely monitor for increased adverse reactions. Refer to Table 16-12.

- **Live virus vaccines and live bacterial vaccines:** Live virus vaccines and live bacterial vaccines are not permitted while the patient is receiving study medication and during the 30 day follow-up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.
- **Other investigational and antineoplastic therapies**

This list is not comprehensive and is only meant to be used as a guide. Refer to the local olaparib label for further information. Please contact the medical monitor with any questions.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (for more details, please refer to Section 6.1). Participants will be provided with an adequate supply of study drug (alpelisib and olaparib) for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Participants will receive alpelisib and olaparib on an outpatient basis. Only qualified and trained personnel to the preparation procedure will handle, prepare and dispense paclitaxel and pegylated liposomal doxorubicin (PLD) as described in the local Prescribing Information.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits (alpelisib and olaparib) to dispense to the participant by contacting the IRT and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in the IRT system.

As per Section 4.5.3, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant’s home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of a 1month supply. In this case, regular phone calls or virtual contacts (every 3 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and additional treatment

6.3.1.1 Handling of study treatment

Study treatment (alpelisib and olaparib) must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator’s Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis/CO Quality Assurance.

Prescribing information will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of each cycle or at the time of discontinuation of study treatment.

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

6.3.2 Instruction for prescribing and taking study treatment

Dosing and treatment schedule will be performed according to Section 6.1.1.1

All kits of study treatment assigned by the IRT will be recorded in the IRT system. For study treatment not assigned by the IRT (Arm 2), day 1 of each treatment cycle administered should be recorded in IRT.

6.3.2.1 Alpelisib and Olaparib administration

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

Alpelisib and olaparib are dosed on a flat scale of mg/day and not by weight or BSA. There will be no breaks between dosing cycles. Participants should be instructed to take the dose of alpelisib and the first dose of olaparib once daily at approximately the same time each day immediately after food (preferably in the morning), except on the days blood collection is scheduled at the clinic, at which time the participants should take their doses at the clinic when instructed by trial staff. The second dose of olaparib should be taken 12 hours after the first dose of olaparib. Olaparib can be taken without regard to meals.

Alpelisib and olaparib tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

Participants assigned to the alpelisib + olaparib arm (Arm 1) must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos, star fruits and cranberry juice from 7 days prior to the first dose of study drug and during the entire study

treatment period due to potential CYP3A interaction. Regular orange (Citrus X sinensis) juice is allowed.

Should any participant enrolled on the study miss a scheduled dose of alpelisib, the participant will be allowed to take the scheduled dose, immediately after food, up to a maximum of 9 hours after the scheduled dose time. If greater than 9 hours after the scheduled dose time, the missed dose should not be taken, and the participant should take their allotted dose at the next scheduled time. Should any participant enrolled on the study miss a scheduled dose of olaparib, the participant should be instructed to take the next dose at its scheduled time. Do not make up for the missed dose of olaparib.

If the participant vomits after taking the alpelisib and/or olaparib dose, the participant should not take an additional dose on that day, and should resume the usual dosing schedule the next day, at the usual time.

6.3.2.2 Paclitaxel and pegylated liposomal doxorubicin (PLD) administration

The administration and infusion durations of the study drugs paclitaxel and pegylated liposomal doxorubicin (PLD) should follow the local prescribing information and local practice.

6.3.2.3 Additional dosing guidelines for scheduled visits days

On days when pre-dose fasting safety samples are collected as described in Table 8-4, participants should be instructed to arrive at the site in fasted state. The following additional guidelines should be followed:

- The participants must be fasting overnight for at least 8-12 hours prior to the blood collection for fasting glucose, lipid profile, amylase/lipase samples. Water, coffee/tea (unsweetened and without milk) is allowed during all fasting periods; however juice is not permitted during the fasting period
- On scheduled visit days, participants must take study treatment in the clinic under the supervision of the Investigator or designee. On all other days participants will take alpelisib and olaparib at home
- The participants must take alpelisib immediately after food
- PRO assessments (if applicable) must be collected prior to any clinical assessments, drug dosing or diagnostic testing
- If a pre-dose ECG measurement should be collected, then the ECG measurement should occur before dosing of alpelisib, olaparib, paclitaxel, or PLD.
- If a pre-dose PK sample should be obtained, then the sample should be collected after the ECG and before dosing of alpelisib and olaparib.
- Pre-dose PK samples should be drawn prior to dosing. The sampling time of the PK samples and the dosing time must be captured in source documents and precisely recorded in the eCRF. Furthermore, the date and time of alpelisib and olaparib dose on the day before the PK assessment must be captured in source documents and precisely recorded in the eCRF
- Post-dose PK samples should be collected after dosing of alpelisib and olaparib.

ECG and PK sample collection will be performed according to Section 8.4.2 and Section 8.5.2.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a participant Number (participant No.), that is assigned when the participant is enrolled for molecular screening and is retained as the primary identifier for the participant throughout their entire participation in the trial. The participant No. consists of the center Number (center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it. A new participant No. will be assigned at every subsequent enrollment if the participant is re-screened for anything other than laboratory test results outside of the 28 day screening period that do not satisfy the eligibility criteria.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information to register the participant into the IRT. Once assigned, the participant No. must not be reused for any other participant and the participant No. for that individual must not be changed (except if case of re-screening, see Section 8.1). If the participant fails to be enrolled or to start treatment for any reason, the reason will be entered into the appropriate CRF page.

IRT should be notified within 2 days if the participant did not start treatment or is not randomized.

6.4.2 Treatment assignment, randomization

Prior to dosing, for all participants who fulfill all inclusion/exclusion criteria, the investigator or his/her delegate will log on to the IRT system and confirm that the participant fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system.

Note: Cycle 1 Day 1 visit and dosing should occur no later than 3 days after randomization in IRT.

All eligible participants will be randomized via IRT to one of the treatment groups at Cycle 1 Day 1. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment group and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

In addition, the IRT will limit the total number of participants with non-measurable disease to up to CCI of the overall study population.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

In this open-label randomized, active-controlled study, participants will be randomized in a 1:1 ratio to one of the 2 treatments groups (see Section 6.1.1.1). A participant can only be randomized once and randomization will be stratified (see Section 3). The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.5 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments and the and the Novartis clinical trial team (CTT). However, in order to minimize the potential impact of knowledge of treatments, the randomization list will be kept strictly confidential. No aggregate statistical analyses (efficacy or safety across the study) by treatment shall be performed prior to the database lock/interim analysis.

6.6 Dose escalation and dose modification

There is no dose escalation arm on this study.

6.6.1 Starting dose

The starting doses for alpelisib and olaparib will be approximately 50% and 50% of the single agent MTD. The doses are alpelisib – 200 mg/day and olaparib – 200 mg BID Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are permitted to allow participants to continue the study treatment.

Dose modifications of paclitaxel or PLD are at investigator's discretion and in accordance with institutional practice and local labeling.

Dose modifications for alpelisib are summarized in Table 6-2. Deviations to the stepwise recommended dose reductions are not allowed.

Dose modifications of olaparib must be performed as detailed in Table 6-3 however clinical judgement of the treating physician should guide the management plan of adverse reactions of each participant.

These dose changes must be recorded on the appropriate CRF.

Permanent discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-4 or listed in Section 9.

Recommendations for reduction or dose interruption of alpelisib and/or olaparib in the management of adverse reactions are summarized in Table 6-4. Clinical judgment of the treating physician, including confirmation of laboratory values if deemed necessary, should guide the management plan of each participant based on individual benefit/risk assessment.

Alpelisib dose modifications

One alpelisib dose reduction to 150 mg will be permitted. For subsequent toxicity mandating dose reduction, alpelisib may be interrupted and resumed at the 150mg dose once. If the alpelisib dose has been reduced, no re-escalation is allowed, even upon resolution of AE. If

further dose reductions are indicated (after the initial dose reduction to 150mg and then the interruption and resumption at the 150mg dose), the participant will permanently discontinue alpelisib.

If a participant requires an interruption of alpelisib, all scheduled assessments will continue to be performed as per protocol.

If a participant requires a permanent discontinuation of alpelisib, olaparib must also be discontinued, leading to end of study treatment. The end of treatment visit should be scheduled ≤ 14 days after last dose. Participants who discontinue study treatment due to adverse events should continue planned tumor assessments until disease progression per RECIST 1.1 as assessed by BIRC is reported, death, lost to follow-up or withdrawal of consent for efficacy follow-up.

Table 6-2 Stepwise dose reduction for alpelisib

Alpelisib dose level	Dose and schedule	Number of tablets & strength
Starting dose	200 mg/day continuously	1 x 200 mg tablet
Dose level -1*	150 mg/day continuously	3 x 50 mg tablet

* For subsequent toxicity mandating dose reduction, alpelisib may be interrupted and resumed at the 150mg dose once daily.

Olaparib dose modifications

Olaparib dose reductions will be permitted to 150 mg twice daily, and subsequently to 100 mg twice daily (Table 6-3) based on the local approved olaparib prescribing information. If the olaparib dose has been reduced, no re-escalation is allowed, even upon resolution of AE. Any planned variance from these guidelines in the view of the patient safety must be previously discussed with Novartis unless there is an urgent need for action. If the lowest dose of 100 mg twice daily is not tolerated, the participant must permanently discontinue olaparib.

If a participant requires an interruption of olaparib, per investigator discretion all scheduled assessments will continue to be performed as per protocol.

Olaparib should be discontinued for a minimum of [redacted] before a patient undergoes therapeutic or palliative radiation therapy. Post radiation therapy, olaparib should be restarted within [redacted] as long as any bone marrow toxicity has recovered.

If a participant requires permanent discontinuation of olaparib, alpelisib will be discontinued, the end of treatment visit should be scheduled ≤ 14 days after last dose. Participants who discontinue study treatment due to adverse events should continue planned tumor assessments until disease progression per RECIST 1.1 as assessed by BIRC is reported, death, lost to follow-up or withdrawal of consent for efficacy follow up.

Of note, all AEs not related to study drugs have to be managed according to local standard of care treatment.

Table 6-3 Stepwise dose reduction for olaparib

Olaparib dose level	Dose and schedule	Number of tablets & strength
Starting dose	200 mg BID continuously	2 x 100 mg tablet BID
Dose level -1	150 mg BID continuously	1 x 150 mg tablet BID
Dose level -2	100 mg BID continuously	1 x 100 mg tablet BID

Table 6-4 Criteria for dose reduction / interruption and re-initiation of alpelisib and olaparib treatment for adverse drug reactions.

Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib and olaparib treatment
Investigations (Fasting Glucose)	
Hyperglycemia (see also Section 6.6.2.4) Consultation with a diabetologist or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia. Always recommend/reinforce on lifestyle changes as per American Diabetes Association (ADA) and/or European Association for the study of Diabetes (EASD), i.e. exercise and dietary advice (e.g. controlled carbohydrate intake, high fiber, low process food intake. Three macronutrient balance meals and 2 optional small snacks rather than one large meal). **Note:** This table provides dose management recommendations. Local standard clinical practice may be followed for monitoring and managing hyperglycemia. Fasting glucose testing may be performed both locally and/or centrally for rapid availability for safety evaluation and management guidance. However, dose reductions should only be based on FPG. Metformin administration may be considered prophylactically starting 1 week before initiation of treatment with alpelisib. SGLT2 inhibitors, as per standard practices/standard of care, are acceptable as well and may be administered alone or in combination with metformin. The use of metformin XR can be considered as a suitable alternative to metformin IR, alone or in combination with an SGLT2 inhibitor, particularly for participants with at least one risk factor for the development of severe hyperglycemia, at the discretion of the Investigator. Refer to Section 6.2.1 for additional details regarding the use of metformin XR and/or SGLT2 inhibitors. In case of intolerance to or unavailability of metformin, investigator's judgment should be exercised and other oral anti-diabetic agents such as thiazolidinediones or dipeptidyl peptidase-4 Inhibitors can be used. SGLT2i may increase the risk of euglycemic diabetic ketoacidosis and therefore, monitoring with serum / urine ketones and consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist should be considered (please refer to the metformin label or standard of care).	
Grade 1 (FG > ULN - 160 mg/dL) [> ULN - 8.9 mmol/L] For participants with baseline values between >ULN – 140 mg/dL (ULN – 7.7 mmol/L) this apply only for values > 140 mg/dL (7.7 mmol/L)	• **Maintain dose level**, and remind participant of lifestyle changes*. • Start/intensify metformin as per guidance below or in cooperation with a healthcare expert experienced in hyperglycemia management or a diabetologist. Metformin 500 mg orally 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. Alternatively, metformin XR once daily dosing may be considered instead of metformin IR. Titrate to the MTD over a period of 3 weeks. • Alternatively, consider starting an SGLT2 inhibitor alone or in combination with metformin, especially in participants at risk for developing severe hyperglycemia (See Section 6.2.1). Starting dose and titration should be in accordance with the local prescribing information and consistent with local practice. Monitor fasting blood glucose levels as clinically indicated and at least twice weekly for 8 weeks, then continue checking at least weekly until FG is within baseline values.

Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib and olaparib treatment
Grade 2 (FG >160 - 250 mg/dL) [> 8.9 - 13.9 mmol/L]	• **Maintain dose level** and remind participant on lifestyle changes*, exclude confounding factors like e.g. urinary tract infection, and consider consultation with a healthcare expert experienced in hyperglycemia management or a diabetologist. • Start/intensify oral-antidiabetic treatment with metformin or alternatively start an SGLT2 inhibitor alone or in combination with metformin • Additional oral anti-diabetic agents may be initiated, if needed. If fasting blood glucose levels are still rising on maximum tolerated dose of metformin or persistently >160 mg/dl (>8.9 mmol/L), add an SGLT2 inhibitor if not already started, e.g. empagliflozin up to 25 mg (max. dose). Alternatively an insulin-sensitizer, e.g. pioglitazone 30 mg (max. dose) can be added. • Monitor fasting blood glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. • If FG does not resolve to ≤ Grade 1 within 21 days after institution of appropriate anti-diabetic treatment, reduce alpelisib by 1 dose level. • Continue with anti-diabetic treatment and check fasting blood glucose levels at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG > 250 mg/dL.
Grade 3 FG > 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. Exclude confounding factors like e.g. urinary tract infection and consider consultation with a diabetologist. Administer intravenous hydration and intervention for electrolyte / ketoacidosis / hyperosmolar disturbances as clinically appropriate. Insulin may be used for 1-2 days until hyperglycemia resolves, however this may not be necessary in the majority of alpelisib-induced hyperglycemia given the short half-life of alpelisib. Start oral-antidiabetic treatment and titrate as outlined for Grade 2. Monitor fasting blood glucose levels as clinically indicated and at least twice weekly until FG resolves to ≤ Grade 1. • If FG resolves to ≤ 160 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 anti-diabetic agent may be initiated concomitantly, if needed, in consultation with a diabetologist. Check FG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FG>250mg/dl. • If FG does not resolve to ≤ 160 mg/dL within 3-5 days while off study treatment and on metformin, consultation of a diabetologist for management of diabetes is strongly recommended. If FG does not resolve to ≤ 160 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 participant from alpelisib
Grade 4 FG > 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 like e.g. urinary tract infection. • Should consult with physician with experience in treating hyperglycemia, initiate or intensify appropriate anti-diabetic treatment (see Grade 3), administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances), re-check within 24 hours.

Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib and olaparib treatment**
	• If grade improves then follow specific grade recommendations. • If fasting glucose is confirmed as > 500 mg/dL in the absence of confounding factors, **permanently discontinue participant from alpelisib.**
* For specific recommendations please see Section 6.6.2.4	
Investigations (Nausea and vomiting)	
Grade 1 and Grade 2	**At first occurrence:** • Introduce appropriate antiemetics as clinically indicated. • If antiemetics are not sufficient to control nausea, **omit olaparib.** • When nausea has subsided, **resume olaparib at the same dose.** **Subsequent occurrence:** • If participant still complains of significant nausea despite antiemetics and previous olaparib interruption, **omit olaparib again**. • When nausea has subsided, **resume olaparib and reduce one dose level.** Note: nausea may be relieved in some participants when olaparib is taken with food.
Grade 3	• **Omit alpelisib and olaparib** until resolved to ≤ Grade 1, then reduce olaparib one dose level. If olaparib dose has previous been reduced, then reduce alpelisib one dose level. • **Omit alpelisib and olaparib** for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic as per local standard of care.
Grade 4	• **Permanently discontinue participant from alpelisib and olaparib.**
Investigations (Hematologic)	
Anemia	
Grade 1 (Hb ≥ 10g/dL)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated. Investigate causality.
Grade 2 (Hemoglobin (Hb > 8 g/dl and < 10 g/dL)	**At first occurrence"** • Start appropriate supportive treatment and investigate causality. **Continue or omit alpelisib and olaparib** at investigator's discretion for a maximum of 28 days. **At second occurrence:** • **Omit alpelisib and olaparib** until recovery to ≤ Grade 1, then resume alpelisib and olaparib at the same dose levels. Initiate appropriate medical therapy and monitor as clinically indicated Note: If anemia does not resolve to ≤ Grade 1 within 28 days, consult a hematologist for further investigations.
Grade ≥ 3 (Hb < 8 g/dl)	**At first occurrence:** • **Omit olaparib and alpelisib** until recovery to ≤ Grade 1 for up to a maximum of 28 days, then resume olaparib at the same and reduce alpelisib one dose level. **At second occurrence:** • **Permanently discontinue participant from alpelisib and olaparib. Note:** If anemia does not resolve to baseline or ≤ grade 1 within 28 days, consult a hematologist for further investigation.
Neutropenia or leukopenia	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)Grade 2 (ANC < 1.5 - 1.0 x 10^9/L)	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.
Grade ≥ 3 (ANC < 1.0 - 0.5 x 10^9/L)	**At first occurrence:**

Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib and olaparib treatment**
	• **Omit alpelisib and olaparib** until resolved to ≤ Grade 1, then reduce alpelisib one dose level and resume olaparib at the same dose. Initiate appropriate medical therapy and monitor as clinically indicated until resolved including granulocyte colony-stimulating factor (G-CSF) according to local hospital guidelines. **At second occurrence** • **Omit alpelisib and olaparib** until resolved to ≤ Grade 1, then resume alpelisib at the same dose and reduce olaparib one dose level. Initiate appropriate medical therapy and monitor as clinically indicated until resolved including G-CSF according to local hospital guidelines. **Note**: If neutropenia does not return to ≤ grade 1 within 28 days, consult a hematologist for further investigation. G-CSF should not be used within at least 24 h of the last dose of olaparib. Growth factor support should be stopped at least 24 h before restarting study drug (7 days for pegylated G-CSF.)
Febrile neutropenia	**Omit alpelisib and olaparib** for up to a maximum of 28 days. Initiate appropriate medical therapy and monitor as clinically indicated until resolved including G-CSF according to local hospital guidelines. When recovered to Grade ≤ 1, resume alpelisib at the same dose and reduce olaparib one dose level. If olaparib was previously reduced one level, then restart olaparib at the same dose and reduce alpelisib one dose level. **Note:** If resolution needs more than 28 days, consult a hematologist for further investigation. G-CSF should not be used within at least 24 h of the last dose of study treatment. Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated GCSF.)
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 - 50 x 10^9/L)	• **Maintain alpelisib and olaparib dose levels.** • Initiate appropriate medical therapy and monitor as clinically indicated.
Grade 3 (PLT < 50-25 x 10^9/L)	• **Omit alpelisib and olaparib** until resolved to ≤ Grade 1, then resume alpelisib at the same dose and decrease olaparib one dose level. If olaparib was previously reduced one level, then restart olaparib at the same dose and reduce alpelisib one dose level. If thrombocytopenia does not return to ≤ Grade 1 within 28 days, consult a hematologist for further investigation.
Grade 4 (PLT < 25 x 10^9/L)	• **Permanently discontinue participant from alpelisib and olaparib.**If thrombocytopenia does not return to ≤ Grade 1 within 28 days, consult a hematologist for further investigation.
Investigations (Renal)	
Serum creatinine	
< 2 x ULN	• **Maintain alpelisib and olaparib dose levels.**
2 – 3 x ULN	• **Omit alpelisib** dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then **maintain alpelisib dose level.** • If resolved in > 7 days, then **reduce alpelisib dose level.**
Grade 3 (> 3.0 – 6.0 x ULN)	• **Permanently discontinue participant from alpelisib and olaparib treatment.**
Grade 4 (> 6.0 x ULN)	• **Permanently discontinue participant from alpelisib and olaparib treatment.**
Investigations (Hepatic)	
Isolated total Bilirubin elevation	

Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib and olaparib treatment**
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)	• **Omit alpelisib** dose until recovery to ≤ Grade 1, then reduce alpelisib dose level.
Grade 4 (>10.0 x ULN)	• **Permanently discontinue participant from alpelisib and olaparib.**
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)	• **Omit alpelisib dose** until recovery to ≤ Grade 1, then reduce alpelisib dose level.
Grade 4 (> 20.0 x ULN)	• **Permanently discontinue participant from alpelisib and olaparib.**
Combined ALT/AST and TBIL elevation	• Please see specific instructions in Section 6.6.2.1
Investigations (Gastrointestinal)	
Diarrhea is defined as: A disorder characterized by frequent and watery bowel movements. (see also Section 16.2) **Colitis** is defined as a disorder characterized by inflammation of the colon	
Grade 1 (Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Asymptomatic colitis; clinical or diagnostic observations only; intervention not indicated	• **Maintain alpelisib and olaparib dose levels** but initiate appropriate medical therapy and monitor as clinically indicated.
Grade 2 (Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental Activities of Daily Living (ADL) OR Abdominal pain; mucus or blood in stool	• **Omit alpelisib 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 reduce dose level. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • For Grade 2 colitis consider additional treatment, such as steroids.
Grade 3 (Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL) OR	• **Omit alpelisib dose** until resolved to ≤ Grade 1, then reduce dose level. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated • "Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated. • For Grade 3 colitis consider additional treatment, such as steroids.

Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib and olaparib treatment**
Severe abdominal pain; peritoneal signs	
Grade 4 (Life-threatening consequences; urgent intervention indicated)	• **Permanently discontinue participant from alpelisib and olaparib.** • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • Manage according to local standard of care medical management, including electrolyte monitoring, administration of antiemetics and antidiarrhoeal medicinal products and/or fluid replacement and electrolyte supplements, as clinically indicated.
Investigations (Pancreatic)	
Pancreatitis	
Grade 2 or Grade 3	• Omit dose until resolved to Grade ≤ 1, then resume treatment at reduced dose level. If toxicity recurs, permanently discontinue participant from alpelisib
Intolerable Grade 2 or Grade 3	**At first occurrence**: • **Omit alpelisib** until ≤ Grade 1 and reduce 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). **At second occurrence:** • **Omit alpelisib** until ≤ Grade 1 and reintroduce at the same level at the discretion of the investigator.
Grade 4	• **Permanently discontinue participant from alpelisib and olaparib.**
Skin and subcutaneous tissue disorders	
Oral antihistamine administration may be considered prophylactically, at the time of initiation of treatment with alpelisib. Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity (see also Section 6.6.2.3). 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.	
Rash	
Grade 1 (< 10% body surface area (BSA) with active skin toxicity*)	• **Maintain alpelisib and olaparib dose levels.** • Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are triamcinolone and betamethasone for up to 28 days, as long as skin toxicity is active. • 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 daily. For participants with symptoms like burning and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating antihistamine such as diphenhydramine once daily at night
Grade 2 (10-30% BSA with active skin toxicity*)	• **Maintain alpelisib and olaparib dose level.** • Initiate or intensify high potency topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for up to 28 days, as long as skin toxicity is active • Add systemic corticosteroids 20-40 mg/d. • If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. For participants 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.
Grade 3	• **Omit alpelisib** dose until rash /skin toxicity has improved to ≤ Grade 1 or resolved

Worst toxicity - CTCAE Grade (value)	Dose Modifications for alpelisib and olaparib treatment
(> 30% BSA with active skin toxicity*)	• Strongly recommend documentation by photography and consider performing a skin biopsy. • Initiate high potency topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days. • Add systemic corticosteroids 20-40mg/d. • If rash improves to ≤ Grade 1 within 10 days systemic corticosteroid may be discontinued. • Re-start alpelisib dose once rash /skin toxicity is fading, but no longer active (Grade 1): • At 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. • Pruritus, add a non-sedating antihistamine such as cetirizine once daily during daytime and a sedating antihistamine 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 (e.g: severe bullous, blistering or exfoliating skin conditions). (any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	• **Permanently discontinue participant from alpelisib.** • Consult a dermatologist. Strongly recommend documentation by photography and obtain a skin biopsy**. Refer to Table 8-16. • 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 or other SJS/TEN/DRESS like severe skin reactions	• **Permanently discontinue participant from alpelisib and olaparib**. • Consult a dermatologist, ensure documentation by photography, and obtain a 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. ** Not applicable to participants enrolled in China unless accepted by the relevant health authorities.	
Immune system disorders	
Hypersensitivity	
Please see specific instructions in Section 6.6.2.6.	
Investigations (Pulmonary disorders)	
Pneumonitis	
Please see specific instructions in Section 6.6.2.2.	
Investigations (Metabolic)	

Worst toxicity - CTCAE Grade (value)	**Dose Modifications for alpelisib and olaparib treatment**
Asymptomatic amylase and/or lipase elevation (see also Section 6.6.2.5).	
Grade 1 (> ULN - 1.5 x ULN)	• **Maintain alpelisib and olaparib dose levels.**
Grade 2 (> 1.5 - 2.0 x ULN)	• **Maintain alpelisib and olaparib dose levels.**
Grade ≥ 3 (> 2.0 x ULN)	• **Omit alpelisib dose** until resolved to baseline, then • If resolved in ≤ 14 days, maintain dose level. • If resolved in > 14 days, then reduce 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 6.6.2.5.
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 alpelisib and olaparib dose levels.**
Grade 3	• **Omit alpelisib dose** until resolved to ≤ Grade 1**, then reduce alpelisib dose level.**
Grade 4	• **Permanently discontinue participant from alpelisib and olaparib.**

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

Renal Impairment:

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥ 51 mL/min) accompanied by a change in blood urea nitrogen (BUN) and/or proteinuria, retesting should be performed promptly. A CCI is recommended for patients who develop moderate renal impairment (calculated CrCl by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 mL/min) for any reason during the course of the study: the total daily dose of olaparib CCI . Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, CCI .

Olaparib and alpelisib have not been studied in patients with severe renal impairment (CrCl ≤ 30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease while on study is it recommended that olaparib and alpelisib CCI .

Management of prolonged hematological toxicities

On study treatment

If patient develops prolonged hematological toxicity such as:

- ≥ 2 weeks interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence.
- ≥ 2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L).
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L).

CCI [redacted] If any blood parameters remain clinically abnormal after CCI of dose interruption, the patient should be CCI [redacted] should be considered at this stage according to standard hematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to Novartis. Study treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

* CCI [redacted]

On post-treatment follow up

If prolonged unexpected hematological toxicity develops, the participant CCI [redacted] should be considered at this stage according to standard hematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE at any time during the follow up and full reports must be provided by the investigator to Novartis.

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

6.6.2 Follow-up for toxicities

All participants must be followed up for safety (adverse events and serious adverse events) for 30 days following the last dose of study treatment (alpelisib/olaparib or paclitaxel or PLD).

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or a clinically significant laboratory value must be followed until resolution or stabilization of the event, whichever comes first. Further guidelines and recommendations for the management of specific study treatment combination-induced toxicities are provided below.

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

Participants with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI. These events should be considered as clinically important and followed until resolution.

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 participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants 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 participants 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 participants without bone metastasis, or elevation of ALP liver fraction in participants 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 participants should be immediately discontinued from study treatment, and repeat Liver function test (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

- Obtain PK sample to determine exposure to study drug and metabolites
- 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.

Participant monitoring:

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

As 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 6-5). 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, CCI [redacted].

If DILI is unlikely - CCI . Treat identified cause according to institutional guidelines. If resolved, CCI Any decision regarding CCI should be discussed with the Novartis medical team.

Table 6-5 Alternative causes of liver disease

Disease	Assessment
Hepatitis A, B, C, E	Immunoglobulin (Ig) M; anti-Hepatitis A virus (HAV); Hepatitis B surface antigen (HBsAg), IgM anti-HBc, Hepatitis B virus (HBV) DNA; anti-Hepatitis C virus (HCV), HCV RNA, IgM & IgG anti-Hepatitis E virus (HEV), HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr virus (EBV) infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear antibody (ANA) & Antismooth muscle antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, mean corpuscular volume (MCV), carbohydrate-deficient transferrin (CD-transferrin)
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure (CHF), hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, endoscopic retrograde cholangiopancreatography (ERCP) as appropriate.
Wilson disease	Ceruloplasmin
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 a Serious Adverse Event (SAE).

6.6.2.2 Management of pneumonitis

Alpelisib and olaparib may be associated with pneumonitis/interstitial lung disease. Closely monitor all participants for signs and symptoms of pneumonitis.

All participants will be routinely asked about and observed for the occurrence of adverse events including new or changed pulmonary symptoms (consistent with lung abnormalities). Participants who are suspected to have developed pneumonitis should suspend the study treatment immediately 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 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 pneumonitis case during study treatment.

After ruling out infectious etiology and upon making a diagnosis of pneumonitis, CCI and promptly initiate appropriate treatment and supportive measures.

6.6.2.3 Guidelines for the treatment of alpelisib induced skin toxicity

Skin toxicity is a class-effect adverse reaction observed with PI3K inhibitors.

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 starting treatment and is reversible with adequate concomitant medications and alpelisib treatment interruption/reduction, 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 a severe cutaneous reaction, like Stevens-Johnson-Syndrome, Toxic Epidermal Necrolysis, Erythema multiforme or DRESS (Drug reaction with eosinophilia and systemic symptoms), is suspected.

Workup for skin toxicities 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 the skin toxicity, especially to confirm suspected diagnosis of any severe cutaneous reactions.

Skin photographs must be taken and skin biopsy must be performed in case of Grade 4 skin toxicity and any grade of suspected severe cutaneous reactions and stored at site as source document. In case of Grade 3 skin toxicity, Novartis strongly recommends that photographs are taken and a skin biopsy is performed and stored at site as source document. Skin biopsy will be sent to a Novartis designated laboratory, together with dermatologist and pathologist reports, if available, for further research purpose on the pathology and mechanism of PI3K inhibitor treatment induced skin toxicity. Following protocol amendment 03, **s**kin biopsy is performed and assessed locally at the investigator's discretion if clinically indicated.

In Study BYL719C2301 (SOLAR-1), among the 86 participants from the alpelisib group who received prophylaxis prior to rash onset, 73% did not develop a rash, while among the 198 participants from the alpelisib group who did not receive prophylaxis, 36% did not develop a rash. Similar trends were observed in the BYLieve study, where 70% of participants who received prophylaxis (n=10) did not develop a rash compared with 53% of patients who did not receive prophylaxis (n=117) did not develop a rash (C). Additionally, in a single center retrospective analysis of 102 patients receiving alpelisib, prophylaxis with non-sedating antihistamines (n=43) was correlated with a reduction in grade 1/2 rash events (OR 0.39, p=0.09) (Wang 2020). Based on these data, prophylactic treatment with non-sedating antihistamines (e.g. cetirizine (Zyrtec©), fexofenadine (Allegra), loratadine (Claritin) can be started on Cycle 1 Day 1 and continued for approximately 8 weeks in all participants, especially in those with a history of atopy such as allergic rhinitis, asthma, atopic dermatitis, or drug allergies, at the discretion of the investigator. Preventive strategies, including the administration of non-sedating, oral antihistamines before starting alpelisib and prior to rash onset, may decrease incidence and severity of rash based on alpelisib clinical trial experience.

Recommended therapies for skin toxicity events of all grades and as clinically indicated include:

- Mid to high potency topical steroids: triamcinolone 0.01% or fluocinonide 0.05% twice daily for at least 28 days. Recommend spray, lotion, or cream preparation for

ease of application on trunk. For scalp involvement, recommend a foam or solution preparation.

- Gamma-aminobutyric acid (GABA) Agonists: gabapentin 300 mg every 8 hours, pregabalin 50-75 mg every 8 hours (adjust as tolerated). Depending on participant'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.

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

If dry skin is reported, it is recommended that participants use mild and fragrance free soaps and detergents.

Although preclinical experiments demonstrated that alpelisib has no potential phototoxic effect, participants should avoid sun exposure during treatment with alpelisib, especially when they already have experienced rash or other skin toxicities as the increased blood flow of the skin may worsen skin symptoms. Participants 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.

6.6.2.4 Guidelines for the treatment of alpelisib-induced hyperglycemia

Alpelisib, like other PI3K inhibitors, may affect glucose homeostasis which could result in increases of plasma glucose and insulin resistance (Busaidy et al 2012). Alpelisib induced hyperglycemia is generally manageable with adequate antidiabetic treatment. Alpelisib induced hyperglycemia typically occurs within the first month of treatment. Participants with pre-diabetes (-i.e. fasting glucose 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 an early detection and prompt management of increases in fasting glucose while on alpelisib. However even participants, with fasting glucose within normal limits at screening, may develop alpelisib-induced hyperglycemia. Participants should always be instructed to follow dietary guidelines provided by the American Diabetes Association (ADA) and/or European Association for the Study of Diabetes (EASD), e.g. small frequent meals, low carbohydrate content, high fiber, balancing carbohydrates over the course of the day; three small meals and 2 small snacks rather than one large meal, and exercise, as appropriate.

Detailed guidelines for the management of alpelisib-induced hyperglycemia are provided in Table 6-4. This includes early administration of metformin; metformin may be titrated to a daily dose of 1000 mg orally (twice daily).

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 participants 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 or healthcare provider experienced in the management of hyperglycemia is highly recommended for better assessment and management of alpelisib-induced hyperglycemia.

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

Participants with amylase or lipase elevation ≥ CTCAE Grade 3 must be tested weekly (or more frequently if clinically indicated) until values return to ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle. If no re-occurrence 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).

Participants 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 6-4.

6.6.2.6 Guidelines for hypersensitivity

Alpelisib and olaparib, are associated with hypersensitivity reactions, including anaphylaxis and angioedema. These are manifested by symptoms including, but not limited to, dyspnea, flushing, rash, fever, hypotension, dizziness, tachycardia and facial or laryngeal oedema. Alpelisib and/or olaparib should be permanently discontinued and should not be re-introduced in participants with serious hypersensitivity reactions. Appropriate treatment should be promptly initiated.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote study treatment compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts for alpelisib and olaparib (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Alpelisib concentrations will be determined in all participants in study as detailed in pharmacokinetics Section 8.5.2. On PK sampling days, compliance will be assured by administrations of alpelisib and olaparib after food under the supervision of investigator or his/her designee.

6.7.2 Emergency breaking of assigned treatment code

This is an open label study; therefore, emergency breaking of assigned treatment code is not applicable.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given her level of understanding. If the participant is capable of doing so, she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents. The participant will first sign a separate molecular screening ICF prior to screening, then if eligible, they will sign the main ICF. For the optional full PK analysis sub-study, an additional signature in the main ICF is required for participation in this subgroup.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) and/or prescribing information for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Molecular Screening Consent
- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study

- A subsection that requires a separate signature for participation in the full PK subset at selected sites
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

The study includes an optional consent for additional research on personal data/DNA component. This will require a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments will in no way affect the participant's ability to join in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.5.3, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The updated assessment schedule under protocol amendment 04 is presented in Table 8-4; this should be followed until participants reach end of treatment, end of study or accepted a post-trial access option. The assessment schedule indicates with an "X", the visits when they are performed and with an "S", the visits when they are to be documented in the participant source medical record only. All data obtained from these assessments must be supported in the participant's source documentation.

Treatment cycles are intended to be 28 days, but the treatment can be delayed in order to manage toxicities according to the alpelisib and olaparib dose modification criteria in Section 6.6.1 and the locally approved label and local practice for Paclitaxel and Pegylated liposomal doxorubicin (PLD). Further details about the investigational treatment and control treatment are provided in Section 6.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-4) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from the study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visit as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Additional visits may be needed based on the investigator's discretion and are permitted at any time throughout the study.

At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF. Following protocol amendment 03, no PRO and survival follow-up visits will be conducted. All participants already in survival follow-up will exit the study. Following protocol amendment 04, no efficacy follow-up visits will be conducted.

During the course of the study visits, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1. The allowed visit windows before implementation of protocol amendment 04 are presented in Table 8-2. The allowed visit windows before implementation of protocol amendment 03 are presented in Table 8-3.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.5.3, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Allowable visit windows

Visit name	Window
All assessments during the treatment period (except tumor assessments)	+/-3 days
Paclitaxel infusion	+/-3 days allowed between cycles (C1, C2, ...); +/- 1 day allowed between cycle days (D1, D8, D15, and D22)
Pegylated liposomal doxorubicin (PLD) infusion	+/-3 days
Tumor assessments, including CA-125	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected
End of Treatment (EOT)	≤ 14 days from last dose
30 days safety follow-up visit	+/-3 days

Note: Following implementation of protocol amendment 04, no efficacy follow-up visits will be conducted.

Table 8-2 Allowable visit windows (before implementation of protocol amendment 04)

Visit name	Window
All assessments during the treatment period (except tumor assessments)	+/-3 days
Paclitaxel infusion	+/-3 days allowed between cycles (C1, C2, ...); +/- 1 day allowed between cycle days (D1, D8, D15, and D22)
Pegylated liposomal doxorubicin (PLD) infusion	+/-3 days
Tumor assessments, including CA-125	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected
End of Treatment (EOT)	≤ 14 days from last dose
30 days safety follow-up visit	+/-3 days
Efficacy follow-up visit as clinically indicated	+/-7 days

Note: Following implementation of protocol amendment 03, no survival follow-up visits will be conducted.

Table 8-3 Allowable visit windows (before implementation of protocol amendment 03)

Visit name	Window
Molecular Screening	Refer to Section 8.1
Screening	- 28 days
All assessments including C1D1, during the treatment period (except tumor assessments)	+/-3 days
Collection of Patient Reported Outcome (PRO) measures	+/-7 days
Paclitaxel infusion	+/-3 days allowed between cycles (C1, C2, ...); +/- 1 day allowed between cycle days (D1, D8, D15, and D22)
Pegylated liposomal doxorubicin (PLD) infusion	+/-3 days
PK sampling	Refer to Tables in Section 8.5.2
Tumor assessments, including CA-125	+/-7 days
End of Treatment (EOT)	≤ 14 days after last dose
30 days safety follow-up visit	+/-3 days
56 days (8 weeks post progression) follow-up visit after disease progression	+/- 7 days
Efficacy follow-up visit (if applicable)	+/-7 days
Survival follow-up visit	+/- 7 days

Note: If any drug of the study treatment is temporarily interrupted or permanently discontinued at any time during the study, efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Table 8-4 Assessment schedule

Period	**Treatment**	**End of Treatment**	**Post Treatment Follow-Up**
Visit Name	**Subsequent Cycles**	**End of Treatment**	
Days	**Day 1**	**14 Days from last dose**	
Informed consent	X[1]		
Concomitant Medications	Continuous up to 30 days after last dose of study treatment		
Performance status (ECOG)	X	X	
Body Weight	X	X	
Disposition		Completed upon end of study treatment or when a participant exits the study for any reason	
Vital Signs[2]	X	X	
Physical Examination	S	S	
Hematology	X	X	
Fasting Chemistry (full)	X	X	
Antineoplastic therapies since discontinuation of study treatment		X	
HbA1C	Every 4 cycles	X	
Pregnancy Test (serum)[3]	S[4]	S	S
CA-125	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
Urinalysis (macroscopic)	As per local standards of care, as clinically indicated		
CT or MRI (chest, abdomen, and pelvis)	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
CT or MRI of other metastatic sites	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
Body fluid/tissue collection results	As clinically indicated		
Skin biopsies	As clinically indicated[5]		

Period	**Treatment**	**End of Treatment**	**Post Treatment Follow-Up**
Visit Name	**Subsequent Cycles**	**End of Treatment**	
Days	**Day 1**	**14 Days from last dose**	
Electrocardiogram (ECG), performed locally	Every 12 weeks	X	
Cardiac Imaging (MRI or MUGA or ECHO)	As clinically indicated	X	
Adverse Events	Continuous, up to 30 days after the last dose of study treatment		
IRT IMP Dispensation	X		
IRT Dose Reduction(s)	X		
IRT Dosing Confirmation	X		
Alpelisib dosing[6]	X		
Olaparib dosing[7]	X		
Paclitaxel Infusion	X		
Pegylated liposomal doxorubicin (PLD) infusion	X		
Safety Follow-up visit			30 days after last dose

[1] Informed Consent when reconsent is required (not at every subsequent cycle)

[2]Body temperature, blood pressure and pulse

[3] All women of childbearing potential as defined in the inclusion/exclusion criteria who are not surgically sterile will have serum pregnancy testing

[4] During study treatment, local serum pregnancy test to be performed on Day 1 of each cycle and source documented

[5] Skin biopsy to be done and assessed locally at the investigator's discretion[6] Alpelisib will be administered at 200 mg orally once daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.

[7] Olaparib will be administered at 200 mg orally twice daily irrespective of meals on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessment to be recorded in the source documentation only

Table 8-5 Assessment schedule (before implementation of protocol amendment 04)

Period	**Treatment**	**End of Treatment**	**Post Treatment Follow-Up**
Visit Name	**Subsequent Cycles**	**End of Treatment**	
Days	**Day 1**	**14 Days from last dose**	
Informed consent	X[1]		
Concomitant Medications	Continuous up to 30 days after last dose of study treatment		
Performance status (ECOG)	X	X	
Body Weight	X	X	
Disposition		Completed upon end of study treatment or when a participant exits the study for any reason	
Vital Signs[2]	X	X	
Physical Examination	S	S	
Hematology	X	X	
Fasting Chemistry (full)	X	X	
Antineoplastic therapies since discontinuation of study treatment		X	
HbA1C	Every 4 cycles	X	
Pregnancy Test (serum)[3]	S[4]	S	S
CA-125	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
Urinalysis (macroscopic)	As per local standards of care, as clinically indicated		
CT or MRI (chest, abdomen, and pelvis)	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
CT or MRI of other metastatic sites	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected		
Body fluid/tissue collection results	As clinically indicated		
Skin biopsies	As clinically indicated[5]		

Period	**Treatment**	**End of Treatment**	**Post Treatment Follow-Up**
Visit Name	**Subsequent Cycles**	**End of Treatment**	
Days	**Day 1**	**14 Days from last dose**	
Electrocardiogram (ECG), performed locally	Every 12 weeks	X	
Cardiac Imaging (MRI or MUGA or ECHO)	As clinically indicated	X	
Adverse Events	Continuous, up to 30 days after the last dose of study treatment		
IRT IMP Dispensation	X		
IRT Dose Reduction(s)	X		
IRT Dosing Confirmation	X		
Alpelisib dosing[6]	X		
Olaparib dosing[7]	X		
Paclitaxel Infusion	X		
Pegylated liposomal doxorubicin (PLD) infusion	X		
Safety Follow-up visit			30 days after last dose
Efficacy Follow-up visit			As clinically indicated

[1] Informed Consent when reconsent is required (not at every subsequent cycle)

[2]Body temperature, blood pressure and pulse

[3] All women of childbearing potential as defined in the inclusion/exclusion criteria who are not surgically sterile will have serum pregnancy testing

[4] During study treatment, local serum pregnancy test to be performed on Day 1 of each cycle and source documented

[5] Skin biopsy to be done and assessed locally at the investigator's discretion[6] Alpelisib will be administered at 200 mg orally once daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.

[7] Olaparib will be administered at 200 mg orally twice daily irrespective of meals on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessment to be recorded in the source documentation only

Table 8-6 Assessment Schedule (before implementation of protocol amendment 03)

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
Molecular Screening Informed Consent	X																				
Blood germline BRCA 1/2 mutation[1]	X																				
Tumor tissue: New/recent biopsy or archival tumor block/slides[2]		X																			

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Informed Consent		X																			
IRT Registration (after ICF signature)		X																			
Demography		X																			
Inclusion / Exclusion criteria		X																			
Medical history/current medical conditions		X																			

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Diagnosis and Extent of Cancer		X																			
Eligibility checklist (within IRT)		X																			
Prior antineoplastic therapies		X																			
Prior or concomitant non-drug therapies/procedures		X																			
Concomitant medications		X		Continuous up to 30 days after last dose of study treatment																	

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Antineoplastic therapies since discontinuation of study treatment																	X	X	X		X
Performance status (ECOG)			X					X				X					X				
Physical Examination[3]			S	S	S	S		S				C3D1, and thereafter monthly					S		S[4]		

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
												until disease progression, withdrawal of consent, lost to follow-up,								

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
												participant/guardian decision at EOT									
Body Height		X																			
Body Weight			X	X				X				X					X				
Vital Signs[5]			X	X		X		X				X					X				
Disposition		X															Completed upon end of study		X		

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**													**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
																	treatment or when a subject exists the study for any reason				
CA-125			X	Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, lost to follow-up, participant/guardian decision, and at EOT															X[4]		
Hematology			X	X	X	X		X				After C3D1, ever					X				

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
												y 8 weeks for the first 18 months and every 12 weeks thereafter until								

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
												disease progression for participants in Treatment Arm 2. Participants								

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
												in Treatment Arm 1 should have hematology testing performed									

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks
												every 4 weeks for the first 12 months and then follow the same sch								

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
												edule as Arm 2 patients..									
Fasting Chemistry (Full)			X	X	X	X		X				X					X				
Fasting Chemistry (Partial)									X[16]	X[16]											
Fasting Lipase, Fasting Amylase			X	X		X		X				X									

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Fasting lipid panel			X	X				X				X									
Fasting glucose			X	X	X	X		X				X									
HbA1C			X					X				Every 3 cycles from C3D1 onwards					X				
Coagulation Panel			X	X		X		X				X									

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1 D1**	**C1 D8**	**C1D 15**	**C1 D22**	**C2D 1**	**C2 D8**	**C2D 15**	**C2 D22**	**C3D 1**	**C3 D8**	**C3D 15**	**C3D 22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Pregnancy Test (serum)[6]			X	S[7]				S[7]				S[7]					X	S[7]			
Urinalysis (Macroscopic)[8]			X	As clinically indicated													X				
CT or MRI (Chest, Abdomen, Pelvis)		X		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, lost to follow up, participant/guardian decision, and at EOT (If PR/CR is reported, confirmation of response is required) [14]															X[15]		
CT or MRI of other metastatic site(s)		If suspected lesion at screening		If lesion at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, lost to follow-up, participant/guardian decision, and at EOT (if PR/CR is reported, confirmation of response is required) [14]															X[15]		
Body Fluid/Tissue			As clinically indicated until clinical disease progression, death, withdrawal of consent, lost to follow-up, participant/guardian decision, and at EOT																X		

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
Collection Results																					
Electrocardiogram (ECG)		X		C1D1 and every 12 weeks thereafter													X				
Cardiac Imaging (MRI or MUGA or ECHO)[9]		X		As clinically indicated													X				
Adverse Events	Suspected SAEs only	X		Continuous, up to 30 days after the last dose of study treatment																	
Blood for circulating DNA[2]				X				X								Every 4 cycles from	X				

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
																C4D1 onwards					
Skin biopsies[2]				Anytime at the appearance of G3/4 skin toxicity, or any suspected severe cutaneous reactions. Refer to Section 6.6.2.3																
PRO: FACT-O TOI[10]		X		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression as per RECIST 1.1, death, withdrawal of consent, lost to follow-up, participant/guardian decision, and at EOT													X	X	X	
CCI																					
IRT Randomization				X																	

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**													**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**					
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
IRT IMP Dispensation				Arm 1 Only-Add alpelisib and olaparib dispensation Day 1 of each Cycle																	
IRT Dose Reduction(s)				Arm 1 Only-Add alpelisib or olaparib dose reduction(s) as needed																	
IRT Dosing Confirmation				ARM 2 Only-Add Dosing for Day 1 of each Cycle																	
Alpelisib dosing[11]				Once Daily																	
Olaparib dosing[12]				Twice Daily																	
Paclitaxel Infusion				X	X	X	X	X	X	X	X	X	X	X	X						
Pegylated liposomal doxorubicin				X				X				x									

Period	**Molecular Screening**	**Screening**	**Screening**	**Treatment**												**End of Treatment**	**Post-Treatment Follow-Up**			
Cycle				**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4 (subsequent cycles)**				
Visit Name	**Molecular Screening**	**Screening**	**Screening**	**C1D1**	**C1D8**	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D8**	**C3D15**	**C3D22**	**C4D1**	**End of Treatment**	**Safety Follow-up**	**Efficacy follow up, if applicable [13]**	**PRO Follow-up**	**CCI Survival Follow-up**
Days	**-**	**-28 to -1**	**-14 to -1**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**14 Days from last dose**	**30 Days after last dose**	**Follow tumor assessment**	**8 weeks after progression**	**Every 12 weeks**
(PLD) infusion																					
Meal record					X																
Alpelisib & Olaparib full PK sampling				Please refer to alpelisib and olaparib pharmacokinetic blood collection log in Table 8-12 (full PK set in alpelisib + olaparib combination arm)																	
Alpelisib & Olaparib sparse PK sampling				Please refer to alpelisib and olaparib pharmacokinetic blood collection log in Table 8-13 (sparse PK set in alpelisib + olaparib combination arm)																	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If no germline BRCA mutation was detected by local laboratory testing with the FDA-approved Myriad BRACAnalysis CDx test, this data can serve as the confirmation of no BRCA mutation. For China, central testing will be required at NVS designated laboratory for germline BRCA mutation.
[2] Not for China unless accepted by the relevant health authorities
[3] Complete physical examinations to be completed at Screening, C2D1, EOT and Efficacy Follow-up
[4] Until clinical PD or RECIST PD as per BIRC, whichever is earlier

Period	Molecular Screening	Screening	Screening	Treatment												End of Treatment	Post-Treatment Follow-Up			
Cycle				Cycle 1				Cycle 2				Cycle 3				Cycle 4 (subsequent cycles)				
Visit Name	Molecular Screening	Screening	Screening	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	C3D1	C3D8	C3D15	C3D22	C4D1	End of Treatment	Safety Follow-up	Efficacy follow up, if applicable [13]	PRO Follow-up	CCI Survival Follow-up
Days	-	-28 to -1	-14 to -1	1	8	15	22	1	8	15	22	1	8	15	22	1	14 Days from last dose	30 Days after last dose	Follow tumor assessment	8 weeks after progression	Every 12 weeks

[5] Body temperature, blood pressure and pulse

[6] All women of childbearing potential as defined in the inclusion/exclusion criteria who are not surgically sterile will have serum pregnancy testing
[7] Serum pregnancy test performed locally and source documented. During study treatment, local serum pregnancy test to be performed on Day 1 of each cycle
[8] Macroscopic Panel Dipstick: (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
[9] Additional cardiac imaging (MRI or MUGA or ECHO) during treatment is to be performed if clinically indicated signs or symptoms or as required per the local standard of care for the participant's treatment (such as PLD)
[10] Assessments of PROs should be collected prior to any clinical assessments, drug dosing or diagnostic testing.
[11] Alpelisib will be administered at 200 mg orally once daily following food on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.
[12] Olaparib will be administered at 200 mg orally twice daily irrespective of meals on a continuous dosing schedule starting on Cycle 1 Day 1 in a 28-day cycle.
[13] Every 8 weeks during the first 18 months from study randomization and every 12 weeks thereafter
[14] Confirmatory assessment should be performed ≥ 4 weeks after response is first documented
[15] Tumor assessments should be continued even after start of new antineoplastic therapy
[16]. Only for Arm 2 patients receiving paclitaxel

8.1 Screening

Molecular screening

For eligibility into the study, participants must have a “no mutation detected” status either by an already available status from the local site who have used the FDA-approved Myriad BRACAnalysis CDx test or a BRCA mutation status as centrally tested by the Novartis designated central laboratory using the FDA-approved Myriad BRACAnalysis CDx test during molecular screening.

BRCA “no mutation detected” status generated by tumor tissue, or Conformité Européenne (CE)-marked Myriad tumor BRACAnalysis or other laboratory-developed tests are not acceptable alone but if the participant already has a BRCA "no mutation detected" result from any of the aforementioned tests, participant may start the screening in parallel with the Myriad BRACAnalysis CDx confirmatory test. If a discrepancy occurs between the local and central laboratory results, then the Myriad BRACAnalysis CDx confirmatory test will supersede the local result and the patient would be screen failure.

For China, central testing will be required at NVS designated laboratory for germline BRCA mutation.

The following participants will be considered as molecular screen failure participants: (1) participants who do not have BRCA mutation results from Myriad BRACAnalysis CDx assay, (2) participants who have unknown BRCA mutation result, due to failing test or missing data.

All participants must sign the molecular screening informed consent form that will include a molecular screening description for the BRCA testing:

The steps required for participant enrollment are as follows:

1. Upon participant signature on the molecular ICF, the blood sample should be collected immediately and shipped to a Novartis designated laboratory for gBRCAnm result analysis. The sample should be shipped no less than 28 days prior to the planned randomization date to allow proper time for analyses and other screening assessments to be conducted.
2. The participant will be assigned a participant number by the investigator (see Section 6.4.1) and be registered into the IRT system.
3. Demographic information is collected in the eCRF (see Section 8.2).
4. The Novartis designated laboratory will provide the gBRCAnm results to the investigational site.
5. Once participant is confirmed as gBRCAnm via central lab or approved historical lab result, participant should be consented to main study consent and then commence screening procedures. If participant already has a local result confirming gBRCAnm, participant should also be consented to main study consent and then commence screening procedures but cannot be randomized until participant is confirmed as gBRCAnm via central lab.

Screening

All study participants must be thoroughly informed about all aspects of the study, including the study treatment, visit schedule, required evaluations, and all regulatory requirements for informed consent. Written informed consent must be obtained before any study specific assessments/procedures are performed including molecular screening and screening. If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion.

Participants enrolled will be assigned a participant number by the investigator and be registered into the IRT system once the molecular study informed consent is signed. The participant number assigned should be the next sequential participant number available in the clinical database.

For details of screening assessments, refer to Table 8-4.

The screening assessments must be performed within 28 days of first dose of study treatment to confirm participant's eligibility with the exception of the central serum pregnancy test and selected assessments which must be conducted within 14 days prior to start of study treatment as per Table 8-1 and Table 8-4. It is highly recommended to send the serum pregnancy test to the central laboratory no later than 7 days prior start of study treatment in order to receive test result prior to participant's randomization.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed. In case of re-screening, a new participant ID will be generated, however, site has to provide original participant ID in respective eCRF to link the two participants for reporting and validation.

All required screening activities must be performed when the participant is re-screened for participation in the study to satisfy the requirements defined in Table 8-4. An individual participant may only be re-screened once for the study. Once the number of participants complete molecular screening and screened and enrolled/randomized is likely to ensure target enrollment, Novartis may close the study to further screening. In this case, the participants who screen failed will not be permitted to re-screen.

A participant who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the retest result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 28 days of screening period. In this case, the participant will not be required to sign another ICF, and the original participant ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 28 days of screening period or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the participant is considered a screen failure. If the laboratory test(s) results do not satisfy the entrance criteria within the 28 day screening period and the investigator believes retest(s) are likely to satisfy the entrance criteria, then the participant can be rescreened once. Unused tumor samples for screen failure participants will be returned, unless otherwise directed. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria.

Assessments of PROs should be collected after the assessment of vitals but prior to any clinical assessments, drug dosing or diagnostic testing.

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

8.1.1 Eligibility screening

Following IRT registration at molecular screening and screening, participant eligibility will be checked according to study inclusion and exclusion criteria as described in Section 5 once all screening procedures are completed. A list of procedures to be performed during the 28-day screening period is summarized in Table 8-4. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to IRT randomization and the start of study treatment for each participant to ensure that all inclusion and exclusion criteria have been satisfied. When all screening procedures are completed and the participant's eligibility is confirmed (i.e. all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist embedded in the IRT system will be completed prior to the first dose of study drug. Please refer to Section 6.4.2 and as well as comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who signed a molecular screening ICF but are a molecular screening failure, as well as participants who are found not eligible after signing the main study consent will be considered as screening failures and data will be handled in the same manner. The reason for screen failure should be entered on the applicable eCRF. The demographic information, informed consent and Inclusion/Exclusion pages must also be completed for molecular screening and screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening phase (see Section 10.1.3). For molecular screening failures, only SAEs possibly related to a study procedure will be reported.

If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

The following participant demographics and baseline characteristics are to be collected on all enrolled/randomized participants:

- Demographic information (age, gender, participant race/predominant ethnicity (if permitted) are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities)
- Medical history (e.g., important medical, surgical, and allergic conditions from the participant's medical history which could have an impact on the participant's

evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History CRF should include the toxicity grade

- Disease baseline characteristics including diagnosis, history, extent of high-grade serous ovarian, fallopian tube or primary peritoneal cancer, 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
- Prior/concomitant therapy: all medications and significant non-drug therapies taken within 30 days before the first dose of study treatment is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures CRF page and updated on a continual basis if there are any new changes to the medication
- Tumor biopsy for biomarkers (unless archival biopsy provided as per Section 8.5.3)
- Participant QoL outcome questionnaires Functional Assessment of Cancer Therapy-Ovarian (FACT-O), CCI [redacted].

Furthermore, the following assessments will be performed to assess the eligibility of the participant:

- Vital Signs including height, weight, body temperature, blood pressure and pulse
- ECOG Performance Status
- 12-Lead ECG
- Cardiac imaging (MRI/ECHO/MUGA)
- Tumor evaluation (e.g. CT Scan/MRI, CA-125)
- Laboratory evaluations (e.g., hematology, coagulation, fasting biochemistry, fasting plasma glucose/serum lipid profile/lipase/amylase, urinalysis, HbA1C)
- gBRCA 1/2 mutation status
- Complete physical examination.

In addition, a serum pregnancy test will be performed for women of child bearing potential by central laboratory and the result will automatically be transferred to Novartis.

Participants will be stratified at randomization according to:

- Relapse within < 3 months from last platinum dose vs. 3-6 months from last platinum dose
- Prior PARP inhibitor use (yes vs. no)
- Prior bevacizumab use (yes vs. no)

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

Following protocol amendment 04, efficacy follow up is NO longer applicable for any participant.

8.3.1 Imaging tumor assessments

Following protocol amendment 03, the central collection review of imaging/clinical data and the BIRC assessment is NO longer completed for any participant.

Tumor response will be assessed locally according to the Novartis guideline version 3.2 (see Section 16.3) based on RECIST 1.1 (Eisenhauer et al 2009). The updated imaging assessment collection plan following protocol amendment 03 is presented in Table 8-7. The imaging assessment collection plan before implementation of protocol amendment 03 is presented in Table 8-8.

Table 8-7 Imaging Assessment Collection Plan

Procedure	During Treatment/Efficacy Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected
CT or MRI of other metastatic site(s) (e.g. neck)	As per local standards of care, as clinically indicated, or at any time when recurrence is suspected

Table 8-8 Imaging Assessment Collection Plan (before implementation of protocol amendment 03)

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 8 weeks (+/- 7 days) for the first 18 months and thereafter every 12 weeks (+/- 7 days) until disease progression per RECIST as assessed by BIRC, EOT*, death, withdrawal of consent, or lost to follow-up
CT or MRI of other metastatic site(s) (e.g. neck)	Mandated if suspected lesion at screening	If lesions were documented at baseline, follow same schedule as CT/MRI of chest and abdomen

* Tumor evaluation at End of treatment (EOT) is required for participants who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 8) or for participants whose previous tumor assessment did not demonstrate progressive disease (PD) and was done more than 21 days prior to end of treatment visit.

8.3.1.1 Baseline imaging assessments

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

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to randomization, including before signing the main study ICF, can be considered as the baseline images for this study. The following assessments are required at screening/baseline:

- Chest, abdomen, and pelvis CT or MRI
- CT or MRI of other metastatic sites (e.g. neck), if suspected lesions at screening.

If a participant is known to have a contraindication to CT intravenous (i.v.) 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 clinically indicated, CT or MRI of other areas (e.g. neck) of disease as appropriate should be performed.

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.

8.3.1.2 Post baseline imaging assessments

With the protocol amendment 03, the post baseline imaging assessments are now completed according to local standards of care, as clinically indicated or at any time when recurrence is suspected as described in Table 8-7.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination, CA-125 assessment by local lab on two consecutive occasions separated by at least 7 days, 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 and when possible, 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 intravenous contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (see Section 16.3).

8.3.1.3 Time points at which progression is determined locally

Following the implementation of protocol amendment 03, this sub-section is no longer applicable.

8.3.1.4 Time points without locally determined progression

Following the implementation of protocol amendment 03, this sub-section is no longer applicable.

8.3.2 CA-125 Assessment

Following the implementation of protocol amendment 03, CA-125 is now assessed only locally, per standards of care, as clinically indicated, or at any time when recurrence is suspected.

CA-125 will be assessed as part of the efficacy assessment for clinical disease progression (see Section 8.3.4 and Section 8.3.3). In the absence of a radiological or clinical evidence of progressive disease, a rise in CA-125 alone is not sufficient to declare clinical disease progression.

If a clinical disease progression is suspected, CA-125 testing should be repeated with a time-interval of not less than 1 week. To confirm clinical disease progression, a CA-125 elevation according to the modified GCIG criteria (see Section 8.3.3), must be established on 2 occasions at least 1 week apart.

8.3.3 GCIG criteria for CA-125 progression

CA-125 progression will be defined on the basis of a progressive serial elevation of serum CA-125 levels, according to the following modified GCIG criteria. CA-125 elevation without accompanying radiological changes or clinical symptoms/signs consistent with PD will not be considered as clinical disease progression.

- Patients with elevated pretreatment CA-125 (i.e. greater than upper limit of normal (ULN)) and normalization of CA-125 whilst on study treatment, must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart,

Or

- Patients with elevated pretreatment CA-125 (i.e. greater than upper limit of normal (ULN)), which does not normalize whilst on study treatment, must show evidence of CA-125 greater than, or equal to, 2 times the nadir value both during pre-treatment and on-treatment period, on 2 occasions at least 1 week apart,

Or

- Patients with pretreatment CA-125 in the reference normal range, must show evidence of CA-125 greater than, or equal to, 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA-125 progression will be assigned at the date of the first measurement that meets the criteria as noted above.

According to GCIG, participants are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody) or if there has been medical and/or surgical interference with their peritoneum or pleura (e.g., paracentesis) during the previous 28 days. If clinical disease progression is

suspected, a second CA-125 test should be done at least 28 days after the procedure or at the latest at the next planned visit.

8.3.4 Clinical disease progression

Due to the pelvic location of the primary tumor and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of disease progression. Thus, as a supplemental analysis, PFS will be assessed based on clinical disease progression as assessed by BIRC (locally as per amendment 03), where clinical disease progression will be considered if at least 1 of the following radiological or clinical criteria and GCIG criteria for CA-125 progression are met:

1. Additional diagnostic tests (e.g. histology/cytology, ultrasound, endoscopy, or any other imaging technique) identify new lesions or determine that existing lesions qualify for unequivocal progression AND CA-125 progression according to GCIG criteria.
2. Definitive clinical signs and symptoms of disease progression, unrelated to nonmalignant or iatrogenic causes ([i] intractable cancer-related pain; [ii] malignant bowel obstruction/worsening dysfunction; or [iii] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125 progression according to GCIG criteria.

Clinical disease progression will not be diagnosed solely based on CA-125 progression in the absence of at least 1 of the criteria defined above.

8.3.5 Progression Free Survival

For PFS, the disease progression will be determined based on BIRC (local as per amendment 03) assessment using RECIST 1.1, defined as the time from the date of randomization to the date of the first radiologically documented progression or death due to any cause.

Definition of Progression

For participants with measurable disease at randomization, progression is defined in Section 16.3.

For participants with non-measurable disease at randomization, progression is defined as any of the following:

- The appearance of >= one new measurable lesion
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytologic proof of neoplastic origin, in the opinion of the treating physician (in this circumstance, explanation must be provided)

Of note, the following participants (with measurable or non-measurable disease) should also be considered as experiencing progression although it will not be included in the primary efficacy analysis:

a. Global deterioration in health status attributable to the disease, requiring a change in therapy without objective evidence of progression. Participants should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression even after discontinuation of treatment.

8.3.6 Appropriateness of efficacy assessments

The measurements are standard based on the Novartis RECIST guideline, version 3.2 (Eisenhauer et al 2009).

8.4 Safety

Following the implementation of protocol amendment 03, all laboratory assessments will be performed locally. Central laboratory analysis will no longer be required for this study.

Safety assessments are specified in the Table 8-4and Table 8-9with the assessment schedule detailing when each assessment is to be performed.

Safety will be monitored by assessing physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, body weight, ECG, cardiac function evaluation by MRI/ECHO/MUGA scan, laboratory testing (hematology, serum chemistry, coagulation and urinalysis), pregnancy tests, as well as routine safety monitoring and collecting of AEs and SAEs at every visit.

For details on AE collection and reporting, refer to Section 10. Before implementation of protocol amendment 03, all safety assessments should be completed as per Table 8-6. From protocol amendment 03 implementation, all safety assessments should be completed as per Table 8-5.

CTCAE Version 4.03 will be used throughout the study to allow pooling of safety data at alpelisib program level.

As per Section 4.5.3, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 3 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-9 Assessments & specifications

Assessment	Specifications
Physical examination	At screening, C2D1, EOT (or as needed) and Efficacy Follow-up complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Additionally include examination of breasts and loco-regional lymph nodes. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will be at all visits as indicated in Table 8-5during treatment except where a complete physical examination is required. It will include at least the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). If indicated based on symptoms, additional exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-5

Performance status:

The performance status will be assessed according to the ECOG Performance status scale as described in Table 8-6(before protocol amendment 03 implementation), Table 8-5 (post protocol amendment 03 implementation) and Table 8-10.

Table 8-10 ECOG performance status

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

8.4.1 Laboratory evaluations-

Clinical laboratory analyses in Table 8-11(hematology, coagulation, full fasting chemistry, HbA1C and urinalysis) are to be performed by local laboratory.

Unscheduled local laboratory assessments may be performed if medically indicated to assess a (potential) adverse event and recorded in the eCRF, if required according to the visit evaluation schedule, for documentation of the adverse event for a treatment decision and any clinically significant laboratory values per investigator's discretion.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded in eCRF page. Additional analyses are left to the discretion of the investigator. Visit window of +/-3 days are allowed.

If warfarin is co-administered with olaparib, then additional INR testing is recommended. (See Section 6.2.1.1).

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a participant has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well.

The investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

Table 8-11 CCI



Table 8-12 Clinical laboratory parameters collection plan (before implementation of protocol amendment 3)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils *(absolute value preferred, percentages are acceptable*)
Fasting Chemistry (Full)	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Sodium, Potassium, Creatinine, Creatine kinase (CK), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase (fasting), Lipase (fasting), Glucose (fasting)
Fasting Chemistry (Partial)	Creatinine, Creatine Kinase, ALT, AST, Total Bilirubin
Fasting lipid panel	Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	International normalized ratio [INR], Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Additional tests	HbA1c
Pregnancy Test	Serum (See Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

Electrocardiogram (ECG) monitoring will be conducted at a frequency that is in accordance with the prescribing information for paclitaxel and pegylated liposomal doxorubicin. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

ECGs will be performed and evaluated locally.

Figure 8-1 Timing of study procedures



The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine. At screening, in order for an accurate evaluation of baseline QTcF, a total of three 12-lead ECGs will be performed within 7 days prior to randomization (at screening between Day -28 and Day -1). At all other visits, single 12 lead ECGs are collected with ECG machines available at the site. The original ECG(s) and a certified copy should be printed on non-heat-sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms) the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

A standard 12 lead ECG will be performed approximately every 12 weeks, in accordance with the prescribing information for paclitaxel and pegylated liposomal doxorubicin, as presented in Table 8-13. Of note, more frequent ECG monitoring may be considered if at increased risk for ECG abnormalities due to the use of drugs that prolong the QT interval and/or induce Torsades de Pointes.

Table 8-13 ECG Collection Plan

Cycle	Day	Time	Number of ECG Replicates
Screening	-28 to -1	Anytime	12 lead, triplicate
Cycle 1 and every 12 weeks thereafter	1	Pre-dose	12 lead, single
EOT	NA	Anytime	12 lead, single
Unscheduled (as clinically indicated or as deemed appropriate by the investigator e.g. if the participant takes drugs that prolog QT interval and/or induce Torsades de Pointes)	NA	Anytime	12 lead, single or double to confirm safety finding

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents

at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Please refer to Figure 8-1 for the timing of ECG study procedures.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated.

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

Paper ECGs should be appropriately labeled and the original kept in the source documents at the study site. If an unscheduled ECG is performed at an external medical facility, a copy of the ECG should be obtained and a copy kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

8.4.2.1 Cardiac imaging - MRI, ECHO or MUGA

In this study, the left ventricular heart function will be evaluated by cardiac imaging (MRI or ECHO or MUGA) at screening to confirm eligibility and at EOT.

Additional cardiac imaging during treatment is to be performed if clinically indicated signs or symptoms or as required per the local standard of care for the participant's treatment (such as PLD). The same imaging should be used.

8.4.3 Pregnancy and assessments of fertility

All women of childbearing potential as defined in the inclusion/exclusion criteria who are not surgically sterile will have serum pregnancy testing as follows:

- At screening, within 14 days of first dose of study treatment (central laboratory)
- During study treatment, on Day 1 of each cycle (local laboratory or per local guidelines)
- At the EOT visit (local laboratory)
- During the 30 days safety follow-up visit (local laboratory or per local guidelines)

If serum test is positive, the participant must be discontinued from the study treatment.

Results will be required to be retained as source documentation.

Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A

communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment (Follicle Stimulating Hormone (FSH), estradiol) to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Following the implementation of protocol amendment 03, PRO questionnaires will no longer be collected.

8.5.2 Pharmacokinetics

Following the implementation of protocol amendment 03, PK sample collection will no longer be performed. The samples already collected will be assayed for PK concentrations. The procedures below are for samples collected prior to implementation of protocol amendment 03. The pharmacokinetics of alpelisib in combination with olaparib have been assessed in a Phase Ib study (Konstantinopoulos et al 2019). No pharmacokinetic interactions were detected when alpelisib and olaparib were co-administered but sampling in the study was sparse. To assess this further, post-dose PK samples over the course of CCI hours will be collected at steady-state in a sub-set of approximately CCI participants of the alpelisib and olaparib combination arm over the course of a CCI on Day CCI during Cycle CCI to compare exposure against historical data.

Alpelisib/Olaparib pharmacokinetic blood sampling schedules

PK samples will be collected at the visits defined in the Assessment Schedule and as defined in Table 8-14andTable 8-15. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment.

For the full PK subset at selected sites, plasma samples will be taken at CCI

The first approximately [redacted] participants enrolled in the alpelisib and olaparib combination arm will be assigned to the full PK subset (taken into account the ability of clinical sites to comply with the instructions in the laboratory manual concerning the preparation of plasma samples). [redacted].

In all remaining participants in the olaparib/alpelisib arm, PK samples will be collected [redacted], independent of the study part, to characterize the exposure of alpelisib in the participants with HGSOC, when the drugs are administered together. [redacted]

8.5.2.1 Pharmacokinetic blood collection and handling

Complete instructions for sample processing, handling and shipment will be provided in the [CBYL719K12301 Laboratory Manual].

On days and time points when PK, biochemistry, hematology or other blood samples are to be performed, the PK sample must be drawn last. If plasma samples containing EDTA as anticoagulant (see below) are collected prior to chemistry tests it may cause medical interference with chemistry analysis if samples are cross-contaminated. For post-dose PK samples, only the time window specified in the blood collection log tables are allowed, while other pre-dose PK samples may be obtained within 1 day from the scheduled date or visit.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein in accordance with the assessment schedule and institutional guidelines. At the specified time points, blood draws in the volume specified in the blood collection log tables will be collected into tubes containing tripotassium ethylenediaminetetraacetic acid (K3-EDTA) (both alpelisib and olaparib).

Both alpelisib and olaparib plasma samples tubes will be centrifuged to separate plasma and plasma will be immediately split and transferred into separate pre-labeled tubes as primary and backup samples. Plasma samples will be stored frozen in an upright position until shipment to the bioanalytical lab for analysis.

[redacted]

Exact dates and clock times of drug administrations and actual blood draws will be collected on the appropriate eCRF pages. The time of the meal prior to PK sampling, where post dose time points are collected for alpelisib or olaparib (for full PK set only) on [redacted] should be recorded in the appropriate alpelisib CRF page. On days of PK collection and on the day of previous administration the exact time of dosing, date sample taken and actual time of sampling must be entered on the CRF.

To ensure compliance with sampling procedures on the days of PK collection, participants will take their alpelisib and olaparib doses at the clinic under the supervision of the investigator or his/her designee. Participants who forget to postpone their dose until they arrive at the site on

pre-dose sampling days, instead take their medication at home will not participate in PK analysis for that day; they should not have blood samples collected. PK assessment for these participants should be postponed to the next day if possible. Dosing information before alpelisib and olaparib PK sampling may be recorded, if feasible, at every PK visit for PK analysis. Any sampling problems must be noted on the CRF and on appropriate source documentation.

If vomiting occurs within CCI [redacted] where post-dose time points are collected, the time (using the 24 hrs clock) of vomiting should be recorded in a separate section of the CRF and on the transmittal forms, which accompany the sample. No additional study medication should be taken in an effort to replace the material that has been vomited.

If the participant experiences an AE related to one or both drugs that fits the criteria of a SAE, or discontinues both drugs due to related toxicities, an unscheduled PK blood sample must be obtained whenever possible and as soon as possible after the last dose of alpelisib (preferably within 2 weeks after the last dose.)

CCI [redacted]



8.5.2.2 Analytical method

Plasma concentrations of alpelisib and olaparib will be measured by a designated CRO using CCI [redacted]. The lower limit of quantitation (LLOQ) is currently CCI ng/mL for alpelisib and CCI ng/mL for olaparib. Values below the assay LLOQ will be reported as 0 ng/mL. All concentrations below the LLOQ or missing data will be labeled as such in the concentration data listings.

8.5.3 Biomarkers

PI3K pathway inhibition may induce a functional HRD state and, therefore, sensitize or potentially resensitize tumors to PARP inhibitors in participants with no germline BRCA mutation detected (gBRCAnm) (Konstantinopoulos et al 2019). Investigating aberrations in biomarkers of the PI3K pathway, HRR status and other DNA damage/repair pathways in participants enrolled in this study will allow for the assessment of the potential predictive value of biomarkers for benefit from alpelisib given in combination with olaparib for gBRCAnm HSGOC cancer. In addition, mechanisms of resistance to study treatment will also be explored.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g. inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis.

Additional biomarkers or methods may be utilized if indicated by new findings from the literature as well as from Novartis internal data.

A summary of biomarker assessments and biomarker sample collection plan has been provided in Table 8-16. Tumor and blood samples will be collected for exploratory biomarker analysis from all participants, except those enrolled in China. Patients enrolled in China only need to provide a blood sample for molecular screening to determine BRCA non-mutation status prior to randomization. All assessments will be performed by a Novartis designated laboratory.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-4).

Instructions for collection, processing and shipment of all biomarker samples can be found in the central laboratory documents. Required sample collection information must be entered on the appropriate sample collection eCRF pages and central laboratory requisition forms.

Table 8-16 Biomarker sample collection

Sample Type	Volume	Visit	Time point
Tumor samples**			
Newly obtained or archival biopsy or tumor block (preferably within 3 years) or at least 12-16 slides at 5 µm thickness (12 slides minimum from a surgical specimen, 16 slides minimum from a biopsy) if medically feasible	1 block or min.12-16 slides	Screening	Screening
Blood samples			
EDTA blood for gBRCAnm testing*	1 x 9 mL***	Molecular screening	Molecular screening
EDTA plasma for circulating DNA (ctDNA)**	2 x 10 mL	C1D1	Pre-dose
	2 x 10 mL	C2D1	Pre-dose
	2 x 10 mL	Every 4 cycles from C4D1 onwards	Pre-dose
	2 x 10 mL	End of Treatment	Anytime
Skin Samples ** to be done and assessed locally at the investigator's discretion as per protocol amendment 03			
skin biopsy (see Section 6.6.2.3)	NA	At appearance of G4 skin toxicity or any grade of suspected severe cutaneous reactions	Anytime
skin biopsy (optional)	NA	At appearance of G3 skin toxicity	Anytime

* All participants including those enrolled in China are required to submit this sample
** Not applicable to patients enrolled in China unless accepted by the relevant health authorities.
*** Except in China (1 x 2 mL will be collected)

8.5.3.1 Additional biomarker assessments

8.5.3.1.1 Mandatory blood collection for participant enrollment

For participants in the molecular screening study approximately 9 mL of blood will be collected (except in China: 2 mL will be collected) for the gBRCA mutation test.

All participants (for all countries except China) will be in the screening based exclusively on the FDA-approved Myriad BRACAnalysis CDx™ test result. For China, central testing for germline BRCA mutation (gBRCAnm) will be required at the NVS designated laboratory.

As an enrollment criteria, germline BRCA 1/2 mutation status will be assessed centrally using whole blood specimens at the Novartis designated central laboratory: Myriad Genetic Laboratories. If a participant's BRCA 1/2 mutation status is already available and was provided by a local laboratory using exclusively the same FDA-approved CDx™ test, the mutation status may be used for enrollment into this study and must be documented in the source documents before the participant is consented. In such cases, central testing and confirmation of BRCA 1/2 mutation status by the Novartis designated laboratory is not required prior to randomization. gBRCA 1/2 mutation results generated by tumor tissue, research use only, or other CE-IVD laboratory-developed tests are not acceptable alone but if participant already has a BRCA "no mutation detected" result from any of the aforementioned tests, participant may start the screening procedures in parallel with the BRACAnalysis CDx confirmatory test in order to save time. If a discrepancy occurs between the local and central laboratory results, then the Myriad BRACAnalysis CDx confirmatory test will supersede the local result and the patient would be screen failure.

In accordance with the NCCN Guidelines for Ovarian Cancer (Armstrong et al 2019) and the validated FDA-approved Myriad CDx™ Instructions for Use (IFU), only the participants with the CDx™ test result of “No Mutation Detected,” (i.e. gBRCAnm) using whole blood specimens, will be selected as eligible for randomization into the study. The participants with the results “Genetic variant, favor polymorphism” and “Genetic variant of uncertain significance (VUS)” will be selected as ineligible for randomization into the Study CBYL719K12301 study. The CDx™ test result “no mutation detected” includes “results with no variants differing from the wild type sequence or polymorphic genetic variants”. In the event that it is not medically feasible to submit the required samples in the opinion of the investigator, the participant may still be eligible to participate in the study provided that all other eligibility criteria are met.

8.5.3.1.2 Exploratory analysis in tumor samples

A mandatory recent archival tumor sample (preferably within 3 years) or newly obtained sample must be provided if medically feasible (excluding participants to be enrolled in China). Blocks are preferred. If not, at least 12-16 slides (12 slides minimum from a surgical specimen, 16 slides minimum from a biopsy) must be provided instead.

Approximately 50% of high-grade serous ovarian carcinomas harbour genetic or epigenetic alterations in the HRR pathway (Cancer Genome Atlas Research Network 2011). Platinum sensitivity has been used as an indirect predictive marker of homologous repair deficiency (HRD) and response to PARP inhibitors (Rafii et al 2017). BRCA1/2 mutations predict

response to PARP inhibitors as HRD testing; yet these tests remain limited in their ability to select all patients who will derive treatment benefit. This study will explore the HRR status and the somatic BRCA status and correlate them to better understand and extend the substantial clinical benefits that have been seen with PARP inhibitors.

Tumor tissue sample will be used for exploratory biomarker analyses related to PIK3CA, HRR status and somatic BRCA (sBRCA). This may include: 1) additional mutation analysis of the PIK3CA genes by a broader NGS panel and assessment of their potential impact on clinical outcome; 2) the identification of potential biomarkers that may be predictive of benefit from treatment with alpelisib in combination with olaparib, and 3) the investigation of potential resistance mechanisms to the study treatment.

8.5.3.1.3 Exploratory analysis in blood samples

Exploratory analysis in blood samples may include but are not limited to circulating DNA (ctDNA) and the PI3K pathway activation. Approximately 20 mL of plasma will be collected for ctDNA at pre-dose at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, and then Day 1 of every four cycles until end of treatment.

ctDNA is expected to allow capturing heterogeneity and real time status of the tumor (De Mattos-Arruda et al 2014). Recent advancements in ctDNA technology enables reliable detection of molecular alterations, including PIK3CA, through either targeted or multiplex approaches and previous studies successfully detected PIK3CA mutations in ctDNA (Board et al 2010, Higgins et al 2012). However, the potential predictive value of baseline PIK3CA status determined in ctDNA still needs to be confirmed in the clinical setting. The remaining blood samples from baseline will be utilized to test for mutations in genes that are relevant for PI3K signaling and other relevant pathways in ovarian cancer.

This study will also explore the concept of using ctDNA as a surrogate approach to monitoring participants' responses to treatment and disease progression by assessing the PIK3CA mutations in ctDNA from blood samples taken at pre-treatment and over the course of treatment as well as at time of disease progression.

Analysis of biomarkers (other than PIK3CA) relevant to cancer may be also performed on ctDNA samples collected at pre-treatment and during the course of the study and at the time of progression in order to explore additional biomarkers that may be predictive of disease response or resistance.

8.5.3.2 CCI

CCI

8.5.3.3 Optional Additional CCI

CCI

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment (alpelisib/olaparib or paclitaxel or pegylated liposomal doxorubicin (PLD) for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances.

- Adverse event or laboratory abnormalities requiring permanent discontinuation of study treatment as per Section 6.6.1
- Progressive disease as per RECIST 1.1 as per BIRC (or local assessment as per amendment 03) (see criteria in Section 8.3)
- Protocol deviation that results in significant risk to participants' safety
- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendation in the prohibited treatment Section 6.2.2.
- Any situation in which continued study participation might result in a safety risk to the participant
- Study terminated by Sponsor

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information. The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

For participants who already discontinued the treatment and currently are in efficacy follow up and for those who will discontinue from study treatment for reasons other than documented disease progression per RECIST 1.1 as assessed by BIRC (locally as per amendment 03), death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor

assessments must continue to be performed as per Table 8-4until documented disease progression assessment, death, lost to follow-up, discontinuation from study or withdrawal of consent/ opposition to use data/biological samples irrespective of initiation of new antineoplastic therapy. Note: this requirement no longer applies for Amendment 04 due to removal of efficacy follow-up.After discontinuation from study treatment, a safety follow-up visit within 30 days after the last dose of study treatment will be conducted. For reasons other than documented progressive disease per RECIST 1.1, death, lost to follow-up, or withdrawal of consent, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

New / concomitant treatments

- Adverse Events / Serious Adverse Events

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

For participants who discontinue from study treatment for reasons other than documented disease progression per RECIST 1.1 as assessed by BIRC (locally as per amendment 03), death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor assessments must continue to be performed as per Table 8-4until documented disease progression assessment, death, lost to follow-up, discontinuation from study or withdrawal of consent/ opposition to use data/biological samples irrespective of initiation of new antineoplastic therapy. Note: this requirement no longer applies for Amendment 04 due to removal of efficacy follow-up.

9.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.4 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent /opposition to use data/biological samples occurs only when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples) and
- No longer wishes to receive study treatment
- **and**
- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.5 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their study completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to participants who in the opinion of the Investigator are still deriving clinical benefit. Since the primary analysis of PFS did not demonstrate treatment benefit, the follow-up for OS will not be performed. .

9.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety.

Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment (instructions will be provided to the Investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit) (see Section 9.1.1). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety.

Should early termination be necessary, participants must be seen as soon as possible (instructions will be provided to the investigator for contacting the participant, when the participant should stop taking drug and when the participant should come for a final visit) and treated as a prematurely withdrawn participant (see Section 9.1.1). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.6.1 Follow up for safety evaluations

All participants who discontinue study treatment, including those who refuse to return for an EOT visit, will be contacted for safety evaluations (i.e., assessment of adverse events and/or Serious Adverse Events, concomitant medications) 30 days after the last dose of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. participant whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

If participants refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the participant should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

9.6.2 Follow-up for efficacy evaluations

Following the implementation of protocol amendment 04, efficacy follow up is NO longer applicable for any participant.

For participants who already discontinued the treatment and currently are in efficacy follow-up and for those who will discontinue from study treatment for reasons other than documented disease progression per RECIST 1.1 as assessed by BIRC (locally as per amendment 03), death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor assessments must continue to be performed as per Table 8-1 until documented disease progression assessment, death, lost to follow-up, discontinuation from study or withdrawal of consent/ opposition to use data/biological samples irrespective of initiation of new antineoplastic therapy.

9.6.3 Survival follow-up CCI

Following the implementation of protocol amendment 03, this section is no longer applicable.

Participants will enter the survival follow-up period once they complete the safety follow-up period and efficacy follow-up period after treatment discontinuation (whichever is longer). Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since study treatment discontinuation and date of progression on subsequent therapies will also be collected during these phone calls. Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information will be documented in the source documents and relevant CRFs.

CCI

9.7 Optional Additional CCI

CCI

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator and any qualified designees are responsible for managing the safety of individual participants and for appropriately treating and/or referring the participant to appropriate care and follow up for all medical events occurring in participants. They are also responsible for detecting, recording and reporting medical events that meet the definition of an AE or SAE.

Information about adverse drug reactions and how to manage them may be found in the IB. Information about adverse drug reactions can also be found in the product information for marketed products.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

AEs which occur after signature of the molecular screening consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and Section 10.1.3 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events. If molecular screening and main screening procedure occur in parallel all AEs per the descriptions below (inclusive of SAEs) will be captured as adverse events.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Terminology Criteria (CTC) grade: Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, including Grade 5 (AEs leading to deaths).
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of

underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome
   - not recovered/not resolved
   - recovered/resolved
   - recovered/resolved with sequelae
   - recovering/resolving
   - fatal, unknown.

If the event worsens the event should be reported a second time in the CRF 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 CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Adverse events separate from the progression of malignancy (for 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.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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 participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis immediately, without undue delay, under no circumstances later than' safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded in the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report

When the molecular screening occurs before the main screening assessments, SAEs that occur during the molecular screening period will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy).

When the molecular screening and the main screening assessments occur in parallel, SAEs that occur during the screening period will be reported regardless of relationship to study procedure.

SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

For participants who failed the molecular screening or screening, SAEs will be collected until the time the participant is deemed a molecular screening or screen failure.

All follow-up information for the SAE including information on 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 must be reported separately as a new event.

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 study treatment, a Chief Medical Officer (CMO) & Patient Safety (PS) 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 study treatment 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 (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment unless otherwise specified by local law/regulations.

Any case of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) occurring after the 30 day follow up period should be reported as SAE regardless of investigator's assessment of causality or knowledge of the treatment arm.

Any potential Hy's Law case will be handled as a serious adverse event associated with the use of the study treatment (assessing it as medically significant in the absence of any other seriousness criteria) and must be reported as SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded and even if abnormal transaminases values at baseline).

Reporting will include all available information, especially that needed for evaluating the severity and likelihood that the study treatment caused the reaction. The investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The trial participant must be given adequate time asked to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent 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 and reported by the investigator to the 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.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors, including study treatment overdose are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors, including study treatment overdose and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF, irrespective of it being associated with AE/SAE.

For more information on AE and SAE definition and reporting requirements, please see the respective Section 10.1.1 and Section 10.1.2.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs.

Please refer to Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below:

- These liver chemistry repeats will be performed using the local laboratory. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator’s discretion: 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

Additional details on actions required in case of liver events are outlined in Table 16-2 and Table 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBIL, PT/INR, ALP and GGT) to confirm elevation. All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be formed prior to the randomization of the first participant and will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate this trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial (i.e. not being members of the DMC), a patient advocate 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 steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). 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 Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site. Data collected by third parties (such as IRT, safety laboratory results, biomarkers, PK and PROs) will be sent electronically to Novartis.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Safety laboratory assessments, pharmacokinetic (PK) and biomarker (blood and tissue) samples drawn during the course of the study will be collected from the investigator sites and sent to the Novartis designated central laboratory for processing. The laboratory results will be sent electronically to Novartis (or a designated CRO). Following protocol amendment 03, safety laboratory assessments will be processed locally. CCI [redacted] will no longer be collected.

Prior to protocol amendment 03, imaging data used for tumor assessments were to be collected at the sites and transmitted to a designated vendor for centralized analysis, quality control, as well as further processing and data reconciliation. It will be prospectively reviewed by a blinded independent review committee (BIRC).

Following protocol amendment 03, imaging data used for tumor assessments will be collected at the sites and assessed locally per local standard of care, as clinically indicated, or at any time when recurrence is suspected.

PRO data collected using an electronic tablet device will be documented into a separate study-specific database supplied and managed by a designated vendor. The PRO database will be accessible to study sites and Novartis personnel (or a designated CRO) for data management. All PRO data will be sent electronically to Novartis personnel (or a designated CRO). Following implementation of protocol amendment 03, PRO questionnaires will no longer be administered to participants.

Randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis//CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary efficacy and safety analyses for this study will be performed after observing approximately 224 PFS events per BIRC assessment. The primary CSR will be produced after the primary PFS analysis.

Since the primary endpoint of PFS per BIRC was not met at the final PFS analysis, CCI [redacted]

Any additional data for participants continuing to receive study treatment past the final PFS analysis, as allowed by the protocol, will be further summarized in a study report at the time of study close-out.

It is planned that the data from all centers participating in the study will be combined, so that an adequate number of participants are available for analysis. Novartis and/or a designated CRO will perform all analyses. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) is comprised of all participants to whom study treatment has been assigned by randomization. According to the intent to treat (ITT) principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The FAS will be the primary population for all efficacy analyses.

The Safety Set includes all participants who received at least one dose of study treatment (i.e. at least one dose of any component of alpelisib, olaparib, paclitaxel, or pegylated liposomal doxorubicin). Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The Pharmacokinetic Analysis Set (PAS) consists of all participants who receive at least one dose of alpelisib or olaparib and provide at least one evaluable PK concentration.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and Safety Set.

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

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

12.3 Treatments

The Safety set will be used for the following analyses. 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 duration of exposure to alpelisib, olaparib, paclitaxel, and pegylated liposomal doxorubicin as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

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

12.4 Analysis supporting primary objectives

The primary objective is to determine whether treatment with alpelisib in combination with olaparib prolongs PFS compared to treatment with standard-of-care chemotherapy (paclitaxel

or pegylated liposomal doxorubicin) in participants with gBRCAnm, platinum-resistant or refractory high grade serous ovarian cancer.

12.4.1 Definition of primary endpoint(s)

The primary endpoint (variable attribute of the primary estimand; refer to Section 2.1) is progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a participant has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in Section 16.3 for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression in the primary efficacy analysis. PFS will be assessed via BIRC radiology assessment according to RECIST 1.1. Censoring conventions (i.e. handling of missing values/censoring/discontinuations) are provided in Section 12.4.4. PFS as assessed per local investigator assessment will be analyzed as a sensitivity analysis of the primary estimand.

12.4.2 Statistical model, hypothesis, and method of analysis

In this study, the primary efficacy analysis will be the comparison of PFS between the two treatment groups using a stratified log-rank test at an overall one-sided 2.5% level of significance.

Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

$H_{01}: \theta_1 \geq 0$ vs. $H_{a1}: \theta_1 < 0$

where θ_1 is the log-hazard ratio (alpelisib + olaparib arm vs. standard-of-care chemotherapy (paclitaxel or pegylated liposomal doxorubicin) arm) of PFS.

The primary efficacy endpoint of PFS (variable attribute of the primary estimand; refer to Section 2.1) will be analyzed at the interim look and final look of a group sequential design based on the FAS according to the treatment group participants were randomized to and the strata they were assigned to at randomization (strata formed using the randomization factor as obtained via IRT). PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression model will be used to estimate the hazard ratio of PFS, along with 95% confidence interval.

12.4.3 Handling of intercurrent events of primary estimand

The primary estimand will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment**: tumor assessment data collected after discontinuation of study treatment will be used for the primary analysis (treatment policy strategy).

12.4.4 Handling of missing values not related to intercurrent event

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

If a PFS event is observed after one or more missing or non-adequate tumor assessments, the actual date of event will be used (see RECIST 1.1 in Section 16.3).

12.4.5 Sensitivity analyses

As a sensitivity analysis performed in the FAS, the hazard ratio and 95% confidence interval for PFS as per BIRC will be obtained from a stratified and covariate unadjusted Cox model with stratification factors derived from the clinical database, in case at least 5% of the participants have discrepancies between strata at randomization (using IRT data) and strata derived from the eCRF data. This analysis will also include Kaplan-Meier median with its 95% confidence interval.

In addition, the hazard ratio and 95% confidence interval for PFS as per BIRC will also be obtained from an unstratified and covariate unadjusted Cox model.

Furthermore, PFS per local review will be analyzed using a stratified Cox model, with the same analysis conventions as the primary efficacy analysis, and the treatment effect will be summarized by the hazard ratio with its 95% confidence interval. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group.

12.4.6 Supplementary analysis

As supplementary analyses, subgroup analyses will be performed on each level of randomization stratification factors. If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will also be performed. Important subgroups will be specified in the Statistical Analysis Plan (SAP).

Furthermore, as supplementary analyses of the primary endpoint of PFS based on BIRC assessment using RECIST 1.1,

- PFS based on BIRC assessment using both RECIST 1.1 and clinical criteria;
- PFS based on local investigator assessment using both RECIST 1.1 and clinical criteria;

will be analyzed by using a stratified Cox model, and the treatment effect will be summarized by the hazard ratio with its 95% confidence interval.

In addition, the number of participants censored and reasons for censoring will be summarized by treatment group using descriptive statistics, presented separately for local review and blinded independent central review based on different criteria (RECIST 1.1 and/or clinical criteria). Further supplementary analyses will be provided in the SAP.

12.5 Analysis supporting secondary objectives

The secondary objectives of this study are to compare the two treatment groups with respect to overall survival (OS), and to evaluate the overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), duration of response (DOR), time to definitive deterioration in quality of life, time to definitive deterioration in ECOG performance status, pharmacokinetics, and safety.

OS is the key secondary endpoint (variable attribute of the key secondary estimand). A hierarchical testing strategy will be used to control the overall type I error rate, where OS will only be formally tested and interpreted if the primary analysis of PFS is statistically significant.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Key secondary estimand

OS is defined as the time from date of randomization to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date).

Assuming proportional hazards model for OS, the following statistical hypotheses will be tested only if PFS is statistically significant:

$H_{02}: \theta_2 \geq 0$ vs. $H_{a2}: \theta_2 < 0$

where θ_2 is the log-hazard ratio (alpelisib + olaparib arm vs. standard-of-care chemotherapy (paclitaxel or pegylated liposomal doxorubicin) arm) of OS. The analysis to test these hypotheses will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance.

The final OS analysis will not be performed at the time point of the final PFS analysis, but after additional follow-up. Therefore, a three-look group sequential design is considered for OS.

OS will be hierarchically tested in the following way:

- The time point for the first OS interim analysis will be at the time of final PFS analysis after approximately 50% of deaths (126 deaths) are expected to have been recorded in the clinical database. If PFS is statistically significant at this stage, OS will also be tested. If PFS is not statistically significant at this stage, then OS will not be tested.
- If OS is not statistically significant at the first interim analysis, the second OS analysis will be planned after approximately 75% of deaths (189 deaths) have been recorded in the clinical database. If OS is not statistically significant at this stage, a final analysis is planned at the time approximately 252 deaths have been recorded.

The type I error probability will be controlled by using a Lan-DeMets (O'Brien and Fleming 1979 alpha spending function for OS which is independent of the one used for PFS. This guarantees the protection of the overall type I error ($\alpha = 2.5\%$) across all hypotheses and the repeated testing of the OS hypotheses at the interim and the final analyses (Glimm et al 2010).

OS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier

method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

The analysis of key secondary estimand will account for different intercurrent events as explained in the following:

- **Discontinuation of study treatment**: OS will take into account all deaths irrespective of the study treatment discontinuation reasons (treatment policy strategy).

The sensitivity and supplementary analyses for the key secondary estimand will be provided in the SAP.

12.5.1.2 Other secondary efficacy endpoints

Overall response rate (ORR) with confirmed response is defined as the proportion of participants with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), as per BIRC assessment according to RECIST 1.1 (see Section 16.3 for details).

ORR with confirmed response will be calculated based on the FAS according to the intent-to-treat (ITT) principle; however participants with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. ORR with confirmed response will be presented by treatment group along with approximate 95% confidence intervals. As a sensitivity analysis, ORR with confirmed response as assessed by local investigator review will be calculated by treatment group and presented along with the approximate 95% confidence intervals. In addition, the following ORR will also be calculated and presented by treatment group together with approximate 95% confidence intervals:

- ORR with confirmed response for participants with measurable disease at baseline,
- ORR with unconfirmed response based on the FAS,
- ORR with unconfirmed response for participants with measurable disease at baseline.

Clinical benefit rate (CBR) with confirmed response is defined as the proportion of participants with a best overall response of confirmed CR or PR, or SD lasting for a duration of at least 24 weeks. CR, PR and SD are defined as per BIRC assessment according to RECIST 1.1 (see Section 16.3 for details).

CBR with confirmed response will be calculated based on the FAS and according to the ITT principle; however participants with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. CBR with confirmed response and its 95% confidence interval will be presented by treatment group. As a sensitivity analysis, CBR with confirmed response as per local investigator review will be presented by treatment group, along with 95% confidence intervals. In addition, the following CBR will also be calculated and presented by treatment group together with approximate 95% confidence intervals:

- CBR with confirmed response for participants with measurable disease at baseline,
- CBR with unconfirmed response based on the FAS,
- CBR with unconfirmed response for participants with measurable disease at baseline.

Time to response (TTR) is defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data as per BIRC assessment and according to RECIST 1.1 (see Section 16.3 for details).

All participants in the FAS will be included in TTR calculations. Participants without a confirmed CR or PR will be censored at the study maximum follow-up time (i.e. LPLV-FPFV) for participants with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be listed and summarized by treatment group.

Duration of response (DOR) with confirmed response only applies to participants whose best overall response is confirmed complete response (CR) or confirmed partial response (PR) according to RECIST 1.1 based on tumor response data per BIRC assessment. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Participants continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment. DOR with confirmed response will be listed and summarized by treatment group for all participants in the FAS with confirmed BOR of CR or PR. As a supplemental analysis, DOR with unconfirmed response based on the FAS will also be listed and summarized by treatment group.

Time to definitive deterioration in ECOG PS is defined as the time from the date of randomization to the date when ECOG PS has definitively deteriorated by at least one category compared with baseline. Deterioration is considered definitive if there is no subsequent improvement in ECOG PS back to the baseline category or above. Participants will be censored if no definitive deterioration in ECOG PS is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last PS assessment prior to cut-off/start of new anti-neoplastic therapy.

Time to definitive deterioration in ECOG PS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for the time to definitive deterioration in ECOG PS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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

summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE version 4.03 grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The number (and proportion) of participants with AESI will be summarized by dose/treatment. AESI consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). AESI will be defined at the project level and may be regularly updated. The grouping of AEs in AESI according to project standards will be specified in the Case-Retrieval Sheet and/or the SAP.For

each specified AESI, the number and percentage of participants with at least one event part of the AESI will be reported by treatment group.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time. If ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced by treatment group.

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

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

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 is not applicable for laboratory data.

For laboratory tests where grades are not defined by CTCAE Version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE Version 4.03 grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE Version 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE Version 4.03 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE Version 4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other exploratory analyses, for example, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

12.5.3 Pharmacokinetics

Descriptive summary statistics of alpelisib and olaparib plasma concentration data will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), standard deviation, CV (arithmetic and geometric), median, minimum, and maximum. The geometric mean and arithmetic mean (SD) plots will also be graphically presented for concentration-time data (concentration time profiles).

Plasma samples will be assayed for alpelisib and olaparib concentrations with a LLOQ of approximately CCI ng/mL for alpelisib and approximately CCI ng/mL for olaparib. All concentrations below the LLOQ will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV.

For the first approximately CCI participants randomized in the alpelisib and olaparib combination arm, extensive PK sampling for alpelisib and olaparib will be performed as detailed in Section 8.5.2.

For these participants, PK parameters (if available) of alpelisib and olaparib, including but not limited to those listed in Table 12-1, will be calculated from the individual concentration-time profile. Any missing PK parameter data will not be imputed. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Clast and Tlast will be listed but not summarized.

PAS will be used in all pharmacokinetic data analysis and PK summary statistics

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC%Extrap[1]	Area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCtau[2]	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
Clast	Last measurable concentration (mass x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})

Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time).
Tlast	Last measurable concentration sampling (time)
Rsqadj[1]	Square of the correlation coefficient associated with lambda_z

[1] AUC%Extrap and Rsqadj will be used in the interpretation of the primary PK parameters and therefore will be included in the listings only.
[2] For alpelisib the dosing interval is 24 hrs, while for olaparib it is 12 hrs

12.5.4 Patient reported outcomes

The FACT-O TOI score of the FACT-O and time to 5-point definitive deterioration in the FACT-O TOI score are identified as the primary PRO variables of interest. The FAS will be used for analyzing PRO data.

No multiplicity adjustment will be applied.

PRO scores in the FACT-O will be analyzed using a repeated measures model for longitudinal data to assess the treatment effect over time, including terms for treatment, study stratification factors, time of visit (in weeks counting from the time of randomization to the time of a particular post-baseline measurement), treatment-by-time of visit interaction, and baseline score. The differences in least square means between treatment and control group, and the corresponding 2-sided 95% confidence interval (CI) at selected time points will be presented.

Definitive deterioration is defined as the time from the date of randomization to the date of event defined as at least 5-point worsening from baseline with no later improvement above this threshold observed during the course of the treatment or until death due to any cause, in the FACT-O TOI score. If a participant has not had an event prior to analysis cut-off or start of another anticancer therapy, time to deterioration will be censored at the date of the last adequate PRO evaluation.

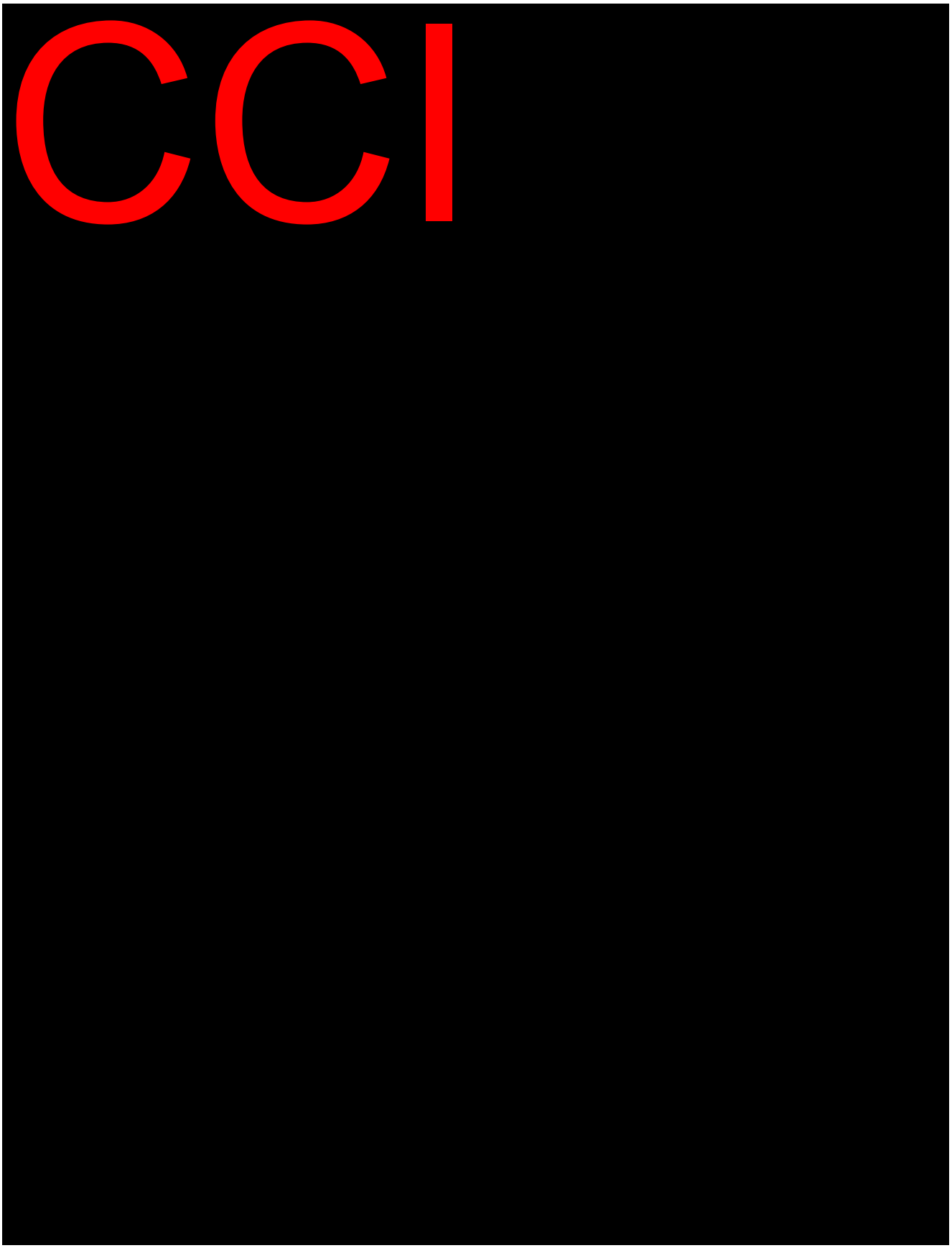
Time to 5-point definitive deterioration will be estimated using the Kaplan-Meier method. The median time along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression model will be used to estimate the hazard ratio of time to definitive deterioration, along with 95% confidence interval (using the same strata information as above).

Descriptive statistics will be used to summarize the PRO scores and absolute change from baseline score scales at each scheduled assessment.

12.6 Analysis of exploratory endpoints

12.6.1 CCI

CCI


CCI



12.6.3.1 Outline of the data analysis

Additional analyses that may be performed after the completion of the end-of-study Clinical Study Report (CSR) will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

The following exploratory endpoints may be assessed and the details of the analysis may be outlined in a biomarker SAP:



12.6.3.2 Data handling principles

Detailed data handling methods will be addressed in the Statistical Analysis Plan.

12.6.3.2.1 Analysis sets

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on participants with biomarker data.

12.6.3.2.2 Basic tables, figures and listings

Unless otherwise stated, as project standard, all biomarker data collected will be listed and summarized. In the event of the collection of large biomarker data such as next generation sequencing (NGS), gene expression or protein expression panels, some pragmatic considerations will be applied to limit output, as these may easily top thousands, if not tens of thousands of pages offering little to no scientific value.

Depending on the endpoint of interest, graphical displays such as box plots or strip plots may be used to assess the relationship of different biomarkers with clinical benefit. These may be separated by treatment group and include either baseline or change from baseline values, where applicable.

For categorical markers such as mutation status, 2x2 contingency tables may be used to assess the relationship with clinical benefit. Kaplan-Meier curves may be generated given the number of PFS events warrant such an assessment.

12.7 Interim analyses

Progression free survival (PFS)

One interim analysis is planned after approximately 90 of the 224 targeted PFS events (i.e., at approximately 40% information fraction) have been documented (expected around 13.9 months from the date of first participant randomized in the study). The primary intent of the interim analysis is to stop early for lack of efficacy (futility);CCI

A gamma spending function ($\gamma = 2.5$) as implemented in East 6.4 will be used as a beta-spending function to determine the non-binding futility boundary.

Based on the choice of beta-spending function described above and if the interim analysis is performed exactly at 90 PFS events, the futility boundary in terms of the p-value scale (or the Z-statistic scale) at the interim is calculated as p = 0.236 (or Z = -0.72). The observed (i.e., nominal) p-value has to be greater than the p-value scale futility boundary of 0.236 (or the observed z-statistic has to be > Z-statistic scale boundary of -0.72) to conclude lack of efficacy (futility).

Since the observed number of events at the interim analysis may not be exactly equal to the planned 90 PFS events, the futility boundary will need to be re-calculated using the pre-specified β-spending function and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic) at the interim analysis will then be compared against the re-calculated futility boundary.

If the study continues to the final PFS analysis, the final PFS analysis will be performed when approximately 224 PFS events have been documented. If exactly 90 events are observed at the interim analysis, the study continued and exactly 224 events are obtained at the final analysis, the observed p-value will have to be less than 0.025 to declare statistical significance. In practice, the final analysis will be based on the actual number of PFS events documented at the cut-off date for the final PFS analysis. The statistical properties of the group sequential design are summarized in Table 12-2 below:

Table 12-2 Simulated probabilities to stop for lack of efficacy (futility) at the interim or final PFS analysis

			Simulated cumulative probabilities (%)		Simulated incremental probabilities (%)	
Scenario	**Look**	**# PFS events**	**Stop for efficacy**	**Stop for futility**	**Stop for efficacy**	**Stop for futility**
Under H_0 (HR=[redacted])	Interim	90	[redacted]			
	Final	224				
Under H_a (HR=[redacted])	Interim	90				
	Final	224				
Under other H_a (HR=[redacted])	Interim	90				
	Final	224				

Note: Simulation is performed in East 6.4 with number of simulations = 10,000 and randomization seed = 2020
[redacted].

The interim analysis will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analysis will be provided to the DMC by the independent statistician.

Key secondary endpoint: Overall survival (OS)

A hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint PFS is statistically significant.

A maximum of three analyses is planned for OS; at the time of the final analysis for PFS (provided PFS is significant), at which point a total of approximately 126 deaths are expected and at the time when approximately 189 deaths are expected (expected approximately 31 months from date of first participant to be randomized) as well as a final analysis for OS when approximately 252 deaths are expected (expected approximately 44 months from date of first participant to be randomized).

An α-spending function according to Lan-DeMets (O'Brien and Fleming 1979) as implemented in East 6.4 (Lan KK and DeMets DL 1983), independent of the one used for the PFS, along with the testing strategy outlined below will be used to maintain the overall type I error probability. This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm et al 2010).

The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favoring the test treatment arm. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

The projected timing of interim analysis is summarized in Table 12-3.At the time of final PFS analyses, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. All participants will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

Table 12-3 Estimated timelines for interim and final analyses

Months after randomization of the first participant (approximation)	# PFS Events	Cumulative Power against a hazard ratio of CCI	# OS events	Cumulative Power[b] against hazard ratio of CCI
14	90 (40 %)	CCI	-	CCI
22	224 (100 %)		126 (50 %)[a]	
31	-		189 (75 %)[a]	
44	-		252 (100 %)[a]	

[a] CCI

Note: Simulation is performed in East 6.4 with number of simulations = 10,000 and randomization seed = 2020

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable PFS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on the AURELIA study (Pujade-Lauraine et al 2014), the median PFS in the control arm of current study is assumed to be around 3.4 months for the purpose of sample size calculation. It is expected that treatment with alpelisib + olaparib will result in a 40% reduction in the hazard rate for PFS, i.e. an expected hazard ratio of 0.60 (which corresponds to an increase in median PFS to 5.7 months under the exponential model assumption).

Then in order to ensure 93.5% power to test the null hypothesis: PFS hazard ratio = 1, versus the specific alternative hypothesis: PFS hazard ratio = 0.60, it is calculated that a total of 224 PFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 2-look group sequential design with a gamma spending function (with $\gamma = 2.5$) using an information fraction of 40% to define a non-binding futility rule at the interim analysis.

Assuming that enrolment will continue for approximately 19.2 months at a stepwise rate: (1) 8 participants per month for the first 6 months; (2) 18 participants per month from 6 months to 12 months; and (3) 28 participants per month after 12 months, as well as a 20% overall dropout rate by the time of the final PFS analysis, a total of 358 participants will need to be randomized to observe the targeted 224 PFS events at approximately 22.4 months after the randomization date of the first participant. These calculations were made using the software package East 6.4.

12.8.2 Secondary endpoint(s)

OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable PFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 12.5.1. Based on the available data from AURELIA study (Pujade-Lauraine et al 2014), the median OS in the control arm is expected to be around 13.3

months. It is hypothesized that treatment with alpelisib will result in a [CCI]% reduction in the hazard rate for OS, i.e., an expected hazard ratio of [CCI] (which corresponds to an increase in median OS to [CCI] months under the exponential model assumption). Then in order to ensure [CCI]% power to test the null hypothesis: OS hazard ratio = [CCI] versus the specific alternative hypothesis: OS hazard ratio = [CCI], it is calculated that a total of 252 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a Lan-DeMets (O'Brien and Fleming 1979) alpha spending function using information fractions of 50%, 75% and 100%.

Based on the same number of participants that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (i.e. 358 participants), and assuming a 5% annual dropout rate by the time of the final OS analysis, it is estimated that these 252 deaths will be observed approximately 43.5 months after the randomization date of the first participant. Therefore the cut-off date for the final analysis of OS will be approximately 21 months after the cut-off date for the final analysis of PFS. These calculations were made using the software package East 6.4.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as Clinicaltrials.gov and as required in CTIS public website. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the

Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EU CTIS public website etc.).

Summary result of primary and secondary endpoints will be disclosed based upon the global Last Patient, Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant Engagement

Not applicable.

13.6 Data protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

Any data security breach that may impact the confidentiality and protection of study participants' data is recorded and investigated by Novartis as required by applicable laws or regulations and as adequate to the nature of the breach.

Upon identification of any potential data security breach, a Novartis team will perform an initial assessment. Depending on the nature and type of breach, including the categories of data impacted, the data security breach management process may include investigation of the root cause of the incident, and, on a basis of its outcome, determination of the adequate mitigation actions to address any immediate impact, and corrective and preventive measures to prevent recurrence and mitigate any adverse effects, as applicable. The data security breach will be reported to the regulatory authorities and Ethic Committees or IRBs as required by the applicable laws or regulations.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participants included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × 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 Total bilirubin > 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*
If ALT or AST abnormal at baseline:	● ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

*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 ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

	ALT	TBIL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBIL	None	● **No change to study treatment** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and Glutamate dehydrogenase (GLDH) in 48-72 hours. ● Follow-up for symptoms.
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBIL	None	● Interrupt study drug ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies. ● Study drug can
	If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
	If normal at baseline: ALT > 8 x ULN	Normal	None	

	ALT	TBIL	Liver Symptoms	Action
ALT increase with bilirubin increase:				be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 3 x ULN	TBIL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[c] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Discontinue the study treatment immediately ● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBIL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) 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.

16.2 Appendix 2: Guidelines for the treatment of study drug combination induced diarrhea

16.2.1 Guidelines for the treatment of study drug induced diarrhea

Mild to moderate diarrhea has been reported within the ongoing studies of single-agent BYL719. 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 BYL719-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 6-4).

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, applesauce, 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 eCRF.

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 eCRF.

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 patients 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). Enteric acting steroids/systemic steroids may be given if clinically indicated for the management of colitis. 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 - bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis
- Sigmoidoscopy - reassessment of colitis
- Biopsy: Histopathological examination of colonic mucosa and immunophenotyping may be performed to confirm the etiology of colitis.

16.2.2 Guidelines for the treatment of study drug 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 BYL719 metabolism (see Section 6.2 and Section 16.4).

16.3 Appendix 3: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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Authors (Version 3.1):	
Authors (Version 3):	
Authors (Version 2):	
Authors (Version 1):	

Table 16-4 Glossary

CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
eCRF	Electronic Case Report Form
FPFV	First participant first visit
ITT	Intent-to-treat
LPLV	Last participant last visit
MRI	Magnetic resonance imaging
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

16.3.1 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 16.3.2 and the definition of best response in Section 16.3.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.3.3.2 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 16.3.4 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.

16.3.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria by (Therasse et al 2000) and revised RECIST guidelines (version 1.1) by (Eisenhauer et al 2009).

16.3.2.1 Definitions

16.3.2.1.1 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 participants without measurable disease, even if not expected as per eligibility criteria in this protocol, see Section 16.3.3.2.9.

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 5 mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes >=15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring >=10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, 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.

16.3.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the participant 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 participants be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how participants with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.3.3.2.9.

16.3.2.2 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 participants, 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 participant 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. Ultrasound 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, Prostate Specific Antigen (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 participant 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).

16.3.2.3 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 eCRF (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) should be at least 10 mm in longest diameter. See Section 16.3.2.1.1.
- Nodal target: See Section 16.3.2.1.1. 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.

16.3.2.4 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 16-5 and non-target lesions Table 16-6 identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together Table 16-7 as well as the presence or absence of new lesions.

16.3.2.4.1 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

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.

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.

16.3.2.4.2 Determination of target lesion response

Table 16-5 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% reduce 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 16.3.2.2).

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 eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-5 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 participants who have not achieved target response of CR. For participants who have achieved CR, please refer to last bullet in this section.

- For those participants 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.

16.3.2.4.3 Determination of non-target lesion response

Table 16-6 Response criteria for non-target lesions

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

16.3.2.4.4 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 eCRF 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 participant in which case the response should be UNK, as for any of this participant's assessment Section 16.3.2.5.
- 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 16.3.2.2.

16.3.2.5 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 16-7.

Table 16-7 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 16.3.2.4

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.

16.3.3 Efficacy definitions

The following definitions primarily relate to participants who have measurable disease at baseline. Section 16.3.3.2.9 outlines the special considerations that need to be given to participants with no measurable disease at baseline in order to apply the same concepts.

16.3.3.1 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 participant'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 participant 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) > 6weeks 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 based on a 6 week tumor assessment frequency taking into account assessment windows.

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 participant 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 participant 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 participant. 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 participant 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 participant 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 overall lesion responses.

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

Overall response rate (ORR) is the proportion of participants 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 participants with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize participants 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 participants 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 participants 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 (Dent et al 2001) and counts all participants 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. participants 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, participants 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 intent-to-treat(ITT) approach).

16.3.3.2 Time to event variables

16.3.3.2.1 Progression-free survival

Usually in all Oncology studies, participants 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 participant 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.

16.3.3.2.2 Overall survival

All participants should be followed until death or until participant has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the participant was last seen alive / last known date participant 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 participant is not known to have died, survival will be censored at the date of last known date participant alive.

16.3.3.2.3 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 participant has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.3.3.2.4 CCI



CCI

16.3.3.2.5 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 participants who did not experience treatment failure will be censored at last adequate tumor assessment.

16.3.3.2.6 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 participants: a good risk group and a poor risk group. Good risk participants tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk participants 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 participants. Less potent agents induce a response mainly in good risk participants only. This is described in more detail by (Morgan 1988).

It is recommended that an analysis of all participants (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 participants (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-participant analysis of these endpoints are not appropriate since the status of participants throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For participants 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 participants 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 participants 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.

16.3.3.2.7 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 16.3.3.2.6. It is recommended that an analysis of all participants (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 participants should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all participants, participants 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 participants 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 participant 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 participants have not yet progressed so they theoretically still have a chance of responding

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

16.3.3.2.8 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 backdating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol Section 16.3.3.2.8.

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 participant 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 participant 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.

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

It is possible that participants with only non-measurable disease present at baseline are entered into the study, 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 participants 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 participants with measurable disease at baseline, participants without measurable disease should also be incorporated in an appropriate manner. The overall response for participants with non-measurable disease is derived slightly differently according to Table 16-8.

Table 16-8 Overall lesion response at each assessment: participants 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 16.3.2.4.3

In general, the **non-CR/non-PD response** for these participants is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response participants 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 participants 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 participants with only non-measurable disease at baseline, handling participants with a best response of CR as "responders" with respect to ORR and all other participants as "non-responders".

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

16.3.3.2.10 Sensitivity analysis

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 participant being lost to follow-up? It is important that the protocol and SAP 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 16.3.3.2.8, and using the FDA guideline on endpoints (FDA 2007) as a reference, the following analyses can be considered:

Table 16-9 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
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 16.3.3.2.8.

2 =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.3.3.2.8.

3 =The rare exception to this is if the participant 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.

Situation	Options for end-date (progression or censoring)1 (1) = default unless specified differently in the protocol or RAP	Outcome
(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 participants 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 participant 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 16-5 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.

16.3.4 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).

16.3.4.1 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).

16.3.4.2 End of treatment phase completion

Participants **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For participants 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 participant, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 14 days of the last study treatment.

Participants may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/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 participant from trial.

16.3.4.3 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.

Participants 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
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.3.4.4 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 participants with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.3.4.5 Programming rules

The following should be used for programming of efficacy results:

16.3.4.5.1 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.

16.3.4.5.2 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 16.3.3.2.8). 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.

16.3.4.5.3 Incomplete dates for last known date subject 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.

16.3.4.5.4 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)’.

16.3.4.5.5 Study / project specific programming

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

16.3.4.5.6 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
- Died
- Unknown

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 16-5)
- 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 16.3.3.2.8. 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 participants 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.

16.3.5 References (available upon request)

16.4 Appendix 4: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the participant 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 alpelisib. Please note that all lists in Appendix 5 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 6.2. In doubt, please the contact medical monitor with any questions.

16.4.1 Prohibited Medication

Strong and moderate inducers of CYP3A4

This list of CYP inducers was compiled from the University of Washington's Drug Interaction Database (Updated July 2020). This list is only meant to be used as a guide.

Table 16-10 List of prohibited strong and moderate inducers of CYP3A

Category	Drug Name
Strong CYP3A Inducers	Apalutamide, Avasimibe[1], Carbamazepine, Enzalutamide, Ivosidenib, Lumacaftor, Mitotane, Phenobarbital, Phenytoin, Rifapentine, Rifampin (Rifampicin), St. John's wort (hypericum perforatum)[1]
Moderate CYP3A inducers	Bosentan, Dabrafenib, Daclatasvir/asunaprevir/beclabuvir, Efavirenz, Elagolix, Etravirine, Genistein[2], Lersivirine Lesinurad, Lorlatinib, Modafinil, Nafcillin, Tipranavir/ritonavir, lopinavir, Rifabutin, Semagacestat, Talviraline, Telotristat, Thioridazine

[1] Herbal product
[2] Food product

Strong and moderate inhibitors of CYP3A4

This list of CYP inhibitors was compiled from the University of Washington's Drug Interaction Database (Updated July 2020). This list only meant to be used as a guide.

Table 16-11 List of prohibited strong and moderate inhibitors of CYP3A

Category	Drug Name
Strong CYP3A inhibitors	Ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[3], indinavir/ritonavir[3], tipranavir/ritonavir[3], ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir[3], elvitegravir/ritonavir[3], saquinavir/ritonavir[3], lopinavir/ritonavir[3], itraconazole, voriconazole, mifepristone, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice[2], ceritinib, conivaptan, nefazodone, nelfinavir, idelalisib, saquinavir, ribociclib, boceprevir, atazanavir/ritonavir[3], darunavir/ritonavir[3], tucatinib
Moderate CYP3A inhibitors	ACT-539313, Aprepitant, Amprenavir, Atazanavir, Casopitant, Cimetidine, Ciprofloxacin, Crizotinib, Cyclosporine, Darunavir, Diltiazem, Dronedaron, Duvelisib, Erythromycin, Faldaprevir, Fedratinib, Fluconazole, Grapefruit juice[2], Imatinib, Isavuconazole, Istradefylline, Letermovir, Netupitant, Nilotinib, Ravuconazole, Tofisopam, Verapamil, *Schisandra sphenanthera* (nan wu wei zi / magnolia vine)[1], Asafoetida resin (*Ferula asafoetida*)[1]

[1] Herbal product
[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

Category	Drug Name
[3] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the University of Washington's (UW) DDI Database.	

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 16-12 List of prohibited BCRP inhibitors

Category	Drug Name
BCRP inhibitors - Evidence for DDI potential shown in vivo	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], Paritapravir[2], Tipranavir[2]

[1] Lee et al 2015
[2] Novartis PK Sciences DDI List (January, 2018)

16.4.2 Permitted medication to be used with caution

This list was compiled from the University of Washington's Drug Interaction Database (Updated August 2020) and the Novartis PKS Internal DDI Memorandum (January 2018). This list is only meant to be used as a guide and is not comprehensive

Table 16-13 List of CYP450 substrates to be used with caution

Category	Drug names
CYP3A4 substrates	
Narrow therapeutic index substrates of CYP3A	alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
Sensitive substrates of CYP3A	alpha-dihydroergocryptine, atorvastatin, avanafil, avapritinib, blonanserin, bosutinib, brotizolam, budesonide, buspirone, cobimetinib, darifenacin, dasatinib, dronedarone, ebastine, eletriptan, entrectinib, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, ubrogepant, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, ticagrelor, tilidine, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, vilaprisan, voclosporin, zanubrutinib
CYP2C9 substrates	
Narrow Therapeutic index substrates of CYP2C9	(S)-Warfarin
Sensitive substrates of CYP2C9	benzbromarone, celecoxib, glimepiride, glipizide, (R)/(S)-ibuprofen, lornoxicam, meloxicam, piroxicam, tolbutamine
CYP2B6 substrates	
Narrow Therapeutic index substrates of CYP2B6	Not Applicable
Sensitive substrates of CYP2B6	bupropion

Category	Drug names
Transporter substrates	
Substrates of BCRP	atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, methotrexate[1], mitoxantrone, pitavastatin[1a], rosuvastatin[1a], irinotecan, ethinyl estradiol, simvastatin, sofosbuvir[1], sulfasalazine[1], tenofovir[1], topotecan[1], venetoclax
Substrates of OATP	aliskiren, ambrisentan, anacetrapib, atenolol, atorvastatin, bromocriptine, caspofungin, celiprolol, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, rosuvastatin, paclitaxel, paritaprevir, pitavastatin, pravastatin, repaglinide, simvastatin, valsartan, olmesartan, telmisartan, montelukast, ticlopidine, thyroxine
Substrates of MATE ½	acyclovir, cephalexin, ganciclovir, fexofenadine[1], glycopyrronium[1], metformin[1], pindolol, pilsicainide, procainamide, ranitidine, topotecan, varenicline
OCT1/2 substrates	6-beta-hydroxycortisol, amantadine, carboplatin, cephalexin[2], cisplatin, dofetilide[2], ipratropium, lamivudine, linagliptin, metformin, oxaliplatin, oxybutynin, phenformin, picoplatin, pilsicainide[2], pindolol[2], sorafenib, procainamide[2], ranitidine[2], thiamine, tropisetron, trospium, varenicline[1], umeclidinium, zidovudine[2]
OAT1/3 substrates	acyclovir, adefovir, anagliptin, beta-lactam antibiotics, bumetanide, captopril, cefonicid, cefaclor, cephradine, chlorothiazide, cidofovir, cimetidine, dapagliflozin, famotidine, furosemide, ganciclovir, ibuprofen, methotrexate, olmesartan, pemetrexed, pitavastatin, pravastatin, quinapril, ranitidine, rosuvastatin, tetracycline, tenofovir, topotecan, valsartan, zidovudine

[1] Evidence of DDI *in vivo*. Others report as substrates *in vitro*.
[1a] Potential *in vivo* substrate
[2] Used clinically used as substrates or inhibitors
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).