NOVARTIS

Clinical Development

BYL719 (alpelisib)

Study number: CBYL719X2402 / NCT03056755

A phase II, multicenter, open-label, three-cohort, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2-negative advanced breast cancer (aBC), who have progressed on or after prior treatments

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20-Jun-2017	Prior to DB lock	Creation of final version	N/A - First version	NA
06-Dec-2018	Prior to DB lock	Protocol amendment	Change is study design to include premenupausal women	Section 1.1
			Addition of interim analysis (IA)	Section 1.1
			Rule of data-cut off for IA was added	Section 2.1
			Q1 and Q3 was added in the list of summary statistics	Section 2.1
			Change of definition of investigational drug, Date of first administration of study treatment, Date of last administration of study treatment, Last date of exposure to study drug/treatment	Section 2.1
			Child bearing status at baseline was added in demography	Section 2.3
			Clarfication of few definition and removed some redundant text	General
			Removed a part of analysis on ANP	Section 2..2
			Removed figure on hepatic function test	Section 2.8.3
			Added section on IA with analysis to be	Section 2.14

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			performed during the IA	
			Updated one criteria number of PPS from TR02 to TR26.	
07-Nov-2019	Prior DB lock	Protocol amendment 3 & 4	Study design was updated to include Cohort C and second IA was added as per protocol amendment 3.	Section 1.1
			Study objective was updated to include Cohort C and Overall survival was added as secondary objective.	Section 1.2
			Updated the wording for the analysis cut-off date for the second interim analysis and for the primary analysis.	Second 2.1
			Defintion of PPS was updated and deleted the numbering.	Section 2.2
			Subgroup analysis was updated to focus on specific variables for primary endpoint, PFS, overall response rate, and clinical benefit rate.	Section 2.2.1
			Updated analysis to include Cohort C.	Section 2.5
			Overall survival was added to secondary objective.	Section 2.7
			Second IA was added to IA plan.	Section 2.14
			Sample size calculation was updated with at	Section 3.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			least 112 patients per cohort with one-sided 2.5% significance level and 95% power.	
03-Mar-2021	Prior to DB lock	Addition analyses to describe and assess the impact of COVID-19 pandemic.	Added new protocol deviation for COVID-19 related PDs.	Section 2.3 Protocol deviations
			Added sensitivity analysis for primary endpoint and COVID-19 related AEs table.	Section 4.1 Impact of COVID-19
24-Mar-2022	Prior to DB lock	Protocol amendment 5	Study design/objectives was updated to include extension phase and third IA was added as per protocol amendment 5.	Section 1.1, Table 1-1, Section 2.7, Section 2.14, Section 3.1
			Data analysis was updated to include extension phase and third IA was added as per protocol amendment 5.	Section 2.1, Section 2.8.5
			Updated List of Abbreviations.	
			Updated the "last contact date data sources" .	Table 2-1
			Updated the Safety set and Safety set in Extension Phase	Section 2.2, Section 2.4
			Updated the Demographics subgroup	Section 2.2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated the Patient disposition and Patient disposition in Extension Phase	Section 2.3
			Clarified the definition of secondary efficacy endpoints	Section 2.7

Refer to the available oncology statistical guidance documents as appropriate for oncology

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List of abbreviations

aBC	Advanced Breast Cancer
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Aromatase Inhibitor
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BC	Breast Cancer
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CBR	Clinical Benefit Rate
CDK4/6	Cyclin-Dependent Kinases 4 and 6
CDKi	Cyclin-Dependent Kinase inhibitor
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DAR	Dosage Administration Record
DI	Dose Intensity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form; the term CRF can be applied to either EDC or Paper
EDC	Electronic Data Capture
EOT	End of Treatment
EOS	End of Study
ER	Estrogen Receptor
ET	Endocrine Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration

FG	Fasting Glucose
FPFT	First Patient First Treatment
HbA1c	Glycosylated Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
HR+	Hormone Receptor Positive
IA	Interim Analysis
ICF	Informed Consent Form
IHC	Immunohistochemistry
IRT	Interactive Response Technology
LPFT	Last Patient First Treatment
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
mBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
[redacted]	Next Generation Sequencing
o.d.	Once Daily
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PFS2	Progression-Free Survival in next-line treatment
PgR	Progesterone Receptor
PI3K	Phosphatidylinositol-3-kinase
PIK3CA	Gene which encodes the p110alpha catalytic subunit of PI3K
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PROS	Patient-reported Outcomes
PS	Performance Status
PSDS	Post-Study Drug Supply
PT	Preferred Term
qd	Qua'que di'e / once a day
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia method
RECIST	Response Evaluation Criteria in Solid Tumors
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Stable Disease
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TA	Tumor Assessment
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
TBL	Total Bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WoC	Withdrawal of Consent

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CBYL719X2402, a phase II, multicenter, open-label, three-cohort, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2- negative advanced breast cancer (aBC), who have progressed on or after prior treatments.

The content of this SAP is based on protocol CBYL719X2402 V05. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock.

1.1 Study design

This is a phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC harboring PIK3CA mutation(s) in the tumor whose disease has progressed on or after prior treatments. Gonadal suppression must be achieved with either goserelin or leuprolide in men (cohort B) and premenopausal women patients.

Patients must have the PIK3CA mutation to be eligible for the trial. Patients will be required to sign a molecular pre-screening consent to have their mutational status either analyzed by providing adequate tumor tissue or if PIK3CA status is known, providing tumor tissue to confirm PIK3CA mutational status using a Novartis designated central laboratory. This will be conducted during a pre-screening phase prior to enrolling into the trial by Day -21. Approximately 1300 patients are expected to be pre-screened to identify PIK3CA mutational status. Those patients that harbor the PIK3CA mutation are eligible for the study and will then have the opportunity to sign the main ICF to begin screening procedures to determine eligibility. Overall approximately 340 patients (112 in each cohort), with HR+, HER2-negative aBC harboring a PIK3CA mutation in tumor tissue, that has progressed on or after prior treatments are expected to be enrolled.

The study will be composed of 2 phases:

Core Phase: includes treatment phase for all patients from First Patient First Treatment (FPFT) until 18 months post Last Patient First Treatment (LPFT) + 1 month Safety follow-up (total 19 months post LPFT)

Extension Phase: includes treatment phase starting at the end of the treatment Core Phase until Last Patient Last Visit (LPLV) (up to 12 months); The extension treatment phase is only for patients who are continuing to benefit from treatment at the end of the Core Phase who are not eligible for PSDS (Post-Study Drug Supply) in their country based on local regulations. Patients will continue on their existing treatment assigned in the Core Phase until discontinuation or Last Patient Last Treatment (LPLT) of the Extension Phase. Note: If PSDS becomes available for a patient, the patient should be discontinued from the study and access treatment via PSDS.

Patients who are benefiting from treatment and are eligible for PSDS will exit the trial at the end of the Core Phase.At the start of the Core Phase, patients will be assigned to a cohort based on previous therapy (AI or fulvestrant) as indicated below:

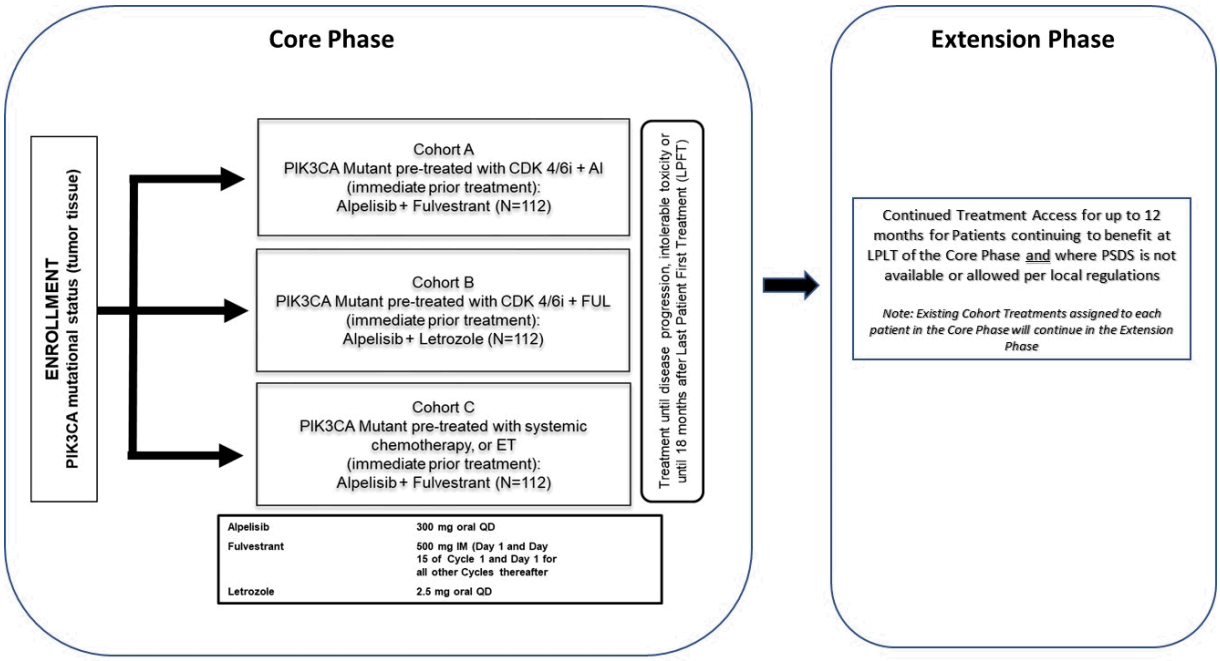
Cohort A: Patients who received any CDK 4/6 inhibitor plus any AI as immediate prior treatment will receive alpelisib + fulvestrant

Cohort B: Patients who received any CDK 4/6 inhibitor plus fulvestrant as immediate prior treatment will receive alpelisib + letrozole

Cohort C: Patients who received systemic chemotherapy or ET (as monotherapy or in combination with targeted treatment except CDK 4/6i + AI) as immediate prior treatment will receive alpelisib + fulvestrant

Note: In Cohort C, ET includes letrozole, fulvestrant and CDK4/6 inhibitor plus fulvestrant.

Figure 1-1 Study Design



Treatment crossover between cohorts will not be permitted in this study.

The primary objective of the study is to assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 separately in Cohorts A and C (alpelisib in combination with fulvestrant) and Cohort B (alpelisib in combination with letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after prior treatments.

The primary analysis for each cohort will be performed 6 months after the last patient enrolled in that specific cohort has started treatment. The final analysis will be performed after LPLV of the study which include cumulative data (eg safety and clinical benefit) since the start of Core Phase for the patients who enter the Extension Phase.

Prior to the final analysis, cohort specific analyses maybe performed when all patients included in the corresponding cohort have approximately 18 months of follow-up.

Three Interim Analyses (IA) are planned for this study. The first IA will be performed after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at least 6 months of follow up. The second IA will be performed when approximately [redacted] patients (50% enrolled patients) have been treated in the study (regardless of cohort) and have at least 6 months of follow-up. The third IA will be performed after the Core Phase has ended.

1.2 Study objectives and endpoints

Table 1-1 Study objectives

Objective	Endpoint	Analysis
Primary		Refer to Section 2.5
To assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 in cohorts A and C (alpelisib in combination with fulvestrant) and cohort B (alpelisib in combination letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after prior treatments.	The primary endpoint of this study is the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1 in each cohort	
Secondary		Refer to Section 2.7
To assess PFS based on local investigator assessment for each cohort.	PFS based on local investigator assessment using RECIST v1.1 in each cohort	
To assess PFS on next-line treatment (PFS2) for each cohort.	PFS2 based on local investigator assessment in each cohort	
To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment for each cohort.	ORR based on local investigator's assessment according to RECIST v1.1 in each cohort Clinical Benefit Rate (CBR) based on local investigator's assessment according to RECIST v1.1 in each cohort	
To assess duration of response (DOR) in patients with confirmed complete response (CR) or PR for each cohort.	Duration of Response is the time from the date of first documented response (confirmed CR or PR) to the date of first documented progression or death	
To assess Overall Survival (OS) for each cohort	Overall Survival is defined as the time of start of treatment to date of death or lost to follow-up.	
To evaluate the safety and tolerability of the combination for each cohort.	Type, frequency and severity of adverse events per CTCAE v4.03 Type, frequency and severity of laboratory toxicities per CTCAE v4.03	

To evaluate clinical benefit as assessed by the Investigator during the Extension Phase	Proportion of patients with clinical benefit as assessed by the Investigator at scheduled visits

[redacted]

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cut-off date for the first interim analysis of study data will be established after at least [redacted] patients receiving Alpelisib + Fulvestrant (cohort A) have at least 6 months of follow-up. The analysis cut-off date for the second interim analysis of study data will be established after at least [redacted] patients have been treated (regardless of cohort) and have at least 6 months of follow-up on study. The third IA will be performed after the Core Phase has ended.

The analysis cut-off date for the primary analysis of each cohort will be established 6 months after the last patient enrolled in that cohort has started treatment. The final analysis will be performed after LPLV of the study which include cumulative data (eg safety and clinical benefit) since the start of Core Phase for the patients who enter the Extension Phase.

All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

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

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed. Protocol deviations, number of patients in analysis populations and discontinuations from study treatment will be summarized by country.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables separately for each cohort a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, Q1, median, Q3, minimum, and maximum) separately for each cohort.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, will refer to the alpelisib (BYL719) only. Whereas, ***study treatment*** will refer to the combination drugs and includes investigational drug (alpelisib) as well as fulvestrant or letrozole and for men (cohort B) and premenopausal women goserelin or leuprolide as applicable in each of the study cohorts. Cohorts A and C include alpelisib/fulvestrant and cohort B includes alpelisib/letrozole.

The term investigational treatment may also be referred to as ***study treatment*** which is used througouht this document.

The term study drug can be used to refer to investigational and components of study treatment (fulvestrant or letrozole alpelisib and for men (cohort B) and premenopausal women goserelin or leuprolide as applicable).

Date of first administration of investigational drug

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

Date of last administration of investigational drug

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

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment (alpelisib or letrozole/fulvestrant or goserelin/leuprolide for men (cohort B) and premenopausal women as applicable) was administered as per the Dosage Administration (e)CRF. Example: if 1st dose of alpelisib is administered on 05-Jan-2015, and 1st dose of fulvestrant is administered on 03-Jan-2015, then the date of first administration of study treatment is on 03-Jan-2015.

The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of **any component** of study treatment was administered as per Dose Administration (e)CRF. Example: if the last alpelisib dose is administered on 15-Apr-2014, and the last dose of letrozole is administered on 17-Apr-2014, then the date of last administration of study treatment is on 17-Apr-2014. The date of first administration of study treatment will also be referred as start of study treatment.

Last date of exposure to study drug/treatment

The study treatment schedule is organized in cycles of 28 days.

The ***last date of exposure to study treatment*** is derived to be the latest date of the last date of exposure to alpelisib or letrozole/fulvestrant. The last date of exposure to study drugs will be derived as follows.

Alpelisib and letrozole

Alpelisib and letrozole are administered daily on a continuous once daily dosing schedule. Hence, the ***last date of exposure to alpelisib or letrozole*** is the date of last administration of alpelisib or letrozole, respectively.

Fulvestrant

Fulvestrant is administered on

1. Cycle 1 Day 1
2. Cycle 1 Day 15, and
3. The first day of every cycle thereafter (e.g. Cycle 2 Day 1, Cycle 3 Day 1 etc.)

Due to the irregularly spaced fulvestrant dose administration, the ***last date of exposure to fulvestrant*** is calculated using a different method depending on the cycle at which fulvestrant was discontinued:

1. If the patient discontinues fulvestrant between Cycle 1 Day 1 and Cycle 1 Day 14 inclusive:
   - The last date of exposure to fulvestrant is calculated as (last date of administration of fulvestrant) + (length of time interval to next scheduled dose - 1) i.e. [last date of fulvestrant administration+ (14-1)].

- If the patient died or was lost to follow-up within last date of administration of fulvestrant + 13 days, the last date of exposure to fulvestrant is the date of death or the date of last contact, respectively.

2. If the patient discontinues fulvestrant between Cycle 1 Day 15 and Cycle 2 Day 1:
   - The last date of exposure to fulvestrant is calculated as (last date of administration of fulvestrant) + (length of time interval - 1) i.e. [last date of fulvestrant administration+ (14-1)].
   - If the patient died or was lost to follow-up within last date of administration of fulvestrant + 13 days, the last date of exposure to fulvestrant is the date of death or the date of last contact, respectively.
3. If the patient discontinues fulvestrant on or after Cycle 2 Day 1, then:
   - the last date of exposure to fulvestrant is calculated as (last date of administration of fulvestrant) + (length of time interval - 1) i.e. [last date of fulvestrant administration+ (28-1)].
   - If the patient died or was lost to follow-up within last date of administration of fulvestrant + 27 days, the last date of exposure to fulvestrant is the date of death or the date of last contact, respectively.

Goserelin and Leuprolide

Goserelin and leuprolide were administered (for pre menopausal women and men (cohort B)) on the first day of every cycle (e.g. Cycle 1 Day 1, Cycle 2 Day 1 etc.)

The ***last date of exposure to*** Goserelina or leuprolide is calculated as follows:

- (last date of administration of Goserelina or leuprolide) + (length of time interval - 1) i.e. [last date of Goserelina or leuprolide administration+ (28-1)].
- If the patient died or was lost to follow-up within last date of administration of Goserelina or leuprolide + 27 days, the last date of exposure to Goserelina or leuprolide is the date of death or the date of last contact, respectively.

Study day

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

The study day is defined as:

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

The reference date for all assessments (safety, efficacy, etc) is the start of any component of the study treatment.

Time unit

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

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment.

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

On-treatment assessment/event and observation periods

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

- ***pre-treatment period***:

  from day of patient's informed consent to the day before first administration of study treatment.

- ***on-treatment period***:

  from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date).

- ***post-treatment period***:

  starting at day 31 after last administration of study treatment.

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

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

Windows for multiple assessments

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

Time windows for laboratory assessments

Assessment	Target day of assessment	Time Interval
Baseline		*≤ Day 1*
Cycle 1 Day 8	*8*	*Day 2 to day 11*
Cycle 1 Day 15	*15*	*Day 12 to day 21*
Cycle 2 Day 1	*29*	*Day 22 to day 42*
Cycle 3 Day 1	*57*	*Day 43 to day 63*
Cycle 3 Day 15	*71*	*Day 64 to day 77*
Cycle 4 Day 1	*85*	*Day 78 to day 98*
Cycle k Day 1 (k≥5)	*d=(k-1)*28+1*	*Day d-14 to day d+13*
End of Treatment		*Assessment taken at the end of treatment visit*

Last contact date

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

Table 2-1 Last contact date data sources

Source data	Conditions
Date of Enrollment	No condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition
Tumor (RECIST) assessment date	Evaluation is marked as ‘done’.
Laboratory/PK [redacted] collection dates	Sample collection marked as ‘done’ or non-missing sample collection dates.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term
Withdrawal of informed consent date	No condition

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received one dose of study treatment. Patients will be analyzed according to the treatment they have been assigned to.

Modified full analysis set

The modified Full Analysis Set (mFAS) comprises all patients of the FAS population who have PI3KCA mutation confirmed by a Novartis designated laboratory. The mFAS will be the primary population for the analysis of efficacy endpoints.

Per protocol set (PPS)

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

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

- *Patient has received prior treatment with PI3K inhibitors.*
- *Patient does not have a PIK3CA mutation that can be confirmed by a sample that can be provided to a Novartis designated laboratory (with >10% tumor tissue (15 slides minimum from a surgical specimen, or 20 slides minimum from a biopsy) OR Patient does not have a pathology report confirming PI3KCA mutation status by a CLIA certified laboratory (Using comparable PCR Tissue Mutation Assay) and cannot provide a tumor sample (either archival or newly obtained) collected after the most recent progression or recurrence for PIK3CA mutation for confirmation by a Novartis designated laboratory.*
- *Unconfirmed diagnosis of HER2-negative aBC as defined by a negative in situ hybridization test or IHC.*
- *Patient does not have a histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ breast cancer by local laboratory.*
- *Patients are not: Diagnosed with aBC, with documented evidence of progression on or after CDK 4/ 6 inhibitor treatment. (Note: CDK 4/6 inhibitor has to be the last treatment regimen prior to study entry. Patients who received one prior chemotherapy for aBC (either in the adjuvant or metastatic setting) are allowed. Only one other prior anticancer therapy, e.g. tamoxifen, fulvestrant is allowed. The maximum number of*

prior therapies for aBC or mBC is limited to two. Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to previous therapy prior to study entry). AI treatment and received systemic chemotherapy or ET are as last treatment regimen in cohort C.

- *Patients do not have either: Measurable disease, at least one measurable lesion as per RECIST v1.1 criteria or If no measurable disease is present, then at least one predominantly lytic bone lesion must be present*
- *Patient has an ECOG performance status greater than 2 or ECOG missing*
- *Patient did not provide main study informed consent*
- *Patient enrolled in the wrong treatment cohort*
- *Patient who has been enrolled but not taken any dose of study drug*
- *Concurrent other anti-cancer therapy, or investigational therapy except palliative therapy, while on study treatment*
- *Concurrent treatment with prohibited drugs as per Protocol which puts patients under significant risk (please refer the Protocol section for Prohibhited Medication)*

Safety Set

The **Safety set** includes all patients who received at least one dose of any component of the study treatment. Patients will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

1. the assigned treatment if patients took at least one dose of that treatment.
2. the first treatment received if the assigned treatment was never received.

Safety Set in Extension Phase

The **Safety set in Extension Phase** includes all patients who received at least one dose of any component of the study treatment in Extension Phase. Patients will be analyzed according to the study treatment actually received.

The actual treatment received corresponds to:

1. the assigned treatment if patients took at least one dose of that treatment.
2. the first treatment received if the assigned treatment was never received.

Patient Classification:

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

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

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written inform consent	No dose of study treatment recieved.
mFAS	No written inform consent	PI3KCA mutation not confirmed by a Novartis designated laboratory and no dose of study treatment recieved.
Safety set	No written inform consent	No dose of study treatment
Safety set in Extension Phase	No written inform consent	No dose of study treatment in Extension Phase
Per-protocol set	Any major protocol deviation as listed in definition of per protocol set (see definition of PP set)	Patient not evaluable for mFAS

Withdrawal of Informed Consent

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

2.2.1 Subgroup of interest

The primary efficacy endpoint, progression free survival (PFS), overall response rate (ORR) and clinical benefit rate (CBR) will be summarized for the following subgroups. The subgroup analyses will be based on the mFAS:

- **Demography**
  - Age >=65 vs age <65 years
  - Gender (if more than 10 in men)
  - Ethnicity (white vs Asian vs black vs. other)
- **Prior Medication History**
  - Line of advanced anti-cancer treatment in any setting (1st line vs. 2nd line)
  - Prior chemotherapy use (adjuvant vs neoadjuvant vs. no prior use)
  - Patient population based on endocrine status and line of therapy:
    a. relapsed with documented evidence of progression more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression while on or after only one line of endocrine therapy for metastatic disease (yes vs. no)

b. relapsed with documented evidence of progression while on (neo) adjuvant endocrine therapy or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease (yes vs. no)

- **Disease Characteristics**

– Number of metastatic sites (<3 vs. >=3)
– Visceral disease (Yes vs. No)
– Bone lesions only (Yes vs. No)
– PTEN loss of expression (Loss of expression vs. No loss of expression)

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by cohort. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, Child bearing status, ECOG performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum). BMI (kg/m²) will be calculated as weight[kg] / (height[m]²) using weight and height at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to start of treatment (in months), stage at time of study entry, presence/absence of target and non-target lesions, number and type of metastatic sites involved, HER2 receptor status, estrogen receptor (ER) status, progesterone receptor (PgR) status and hormone receptor (ER and/or PgR) status.

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

Medical history and ongoing conditions

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

Other

All data collected at baseline will be listed.

2.3.1 Patient disposition

Enrollment by country will be summarized for all screened patients and also by cohort using the FAS and repeated on the mFAS as appropriate. The number (%) of treated patients included in the FAS will be presented by cohort. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented by cohort.

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

- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Phase' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the Study Evaluation Completion/ End of Post-treatment follow-up page);
- Reasons for discontinuation from the post-treatment follow-up (based on Study Evaluation Completion/ End of Post-treatment follow-up page);

Note: post-treatment follow-up for patient disposition only refers to efficacy follow-up.

2.3.2 Patient disposition in Extension Phase

Patient disposition in Extension Phase will be summarized using the Safety Set in Extension Phase. The following summaries will be provided:

- Number (%) of patients who are still on-treatment in Extension Phase (based on the 'End of Extension Treatment Phase' page not completed);
- Number (%) of patients who discontinued the Extension study treatment phase (based on the 'End of ExtensionTreatment Phase' page)
- Primary reason for Extension study treatment phase discontinuation (based on the 'End of Extension Treatment Phase' page)

Protocol deviations

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

Additional protocol deviation summaries will be provided to address the potential impact of COVID-19 pandemic in each cohort. The number and percentage of patients in the FAS with any protocol deviation with one of the following relationships will be summarized by deviation category: COVID-19 health status related, COVID-19 situation: Site issue, COVID-19 situation: Lockdown / Quarantine of patient, COVID-19 situation: Patient concern, COVID-19 situation: Drug supply issue and COVID-19 situation: Other.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.3) will be summarized by cohort.

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by cohort, separately for each component of study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval. The number (%) of patients who have dose reductions, interruptions or permanent discontinuations, and the reasons, will be summarized by cohort.

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

The safety set will be used for all summaries and listings of study treatment in Core Phase.

The safety set in Extension Phase will be used for all summaries and listings of study treatment for the patients who enter the Extension Phase.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug (alpelisib) and any combination partner, if applicable:

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

The last date of exposure to study treatment is the latest of the last dates of exposure to investigational drug or any combination partner (refer to Section 2.1.1).

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (<2 months, 2-<4 months, 4-<6 months etc.) and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

Duration of exposure to investigational drug and combination partner

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

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

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

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

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

The definition of last date of study drug exposure is defined in Section 2.1.1.

Summary of duration of exposure of investigational drug (alpelisib) will include categorical summaries based on monthly intervals (<2 months, 2-<4 months, 4-<6 months etc.) and using descriptive statistics (mean, standard deviation etc).

Cumulative dose

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

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

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

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

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.

Dose intensity and relative dose intensity

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

DI (dosing unit / unit of time) = Actual Cumulative dose (dosing unit) / Duration of exposure to study treatment (unit of time).

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

Planned dose intensity (PDI) is defined as follows:

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

Relative dose intensity (RDI) is defined as follows:

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

In this study DI, PDI and Relative dose intensity (RDI) are defined here below for the each study drugs.

Alpelisib:

- DI (mg/day) = Cumulative dose (mg) / duration of exposure (days)
- PDI is 300 mg/day
- RDI (%) = DI (mg/day) / PDI (mg/day) *100

Letrozole:

- DI (mg/day) = Cumulative dose (mg) / duration of exposure (days)
- PDI is 2.5 mg/day
- RDI (%) = DI (mg/day) / PDI (mg/day) *100

Fulvestrant, goserilin or leuprolide:

- DI (mg/day) = Cumulative dose (mg) / duration of exposure (days)

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

Dose reductions, interruptions or permanent discontinuations

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

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

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

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

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

The last zero dose of alpelisib/placebo or fulvestrant is not considered as a dose interruption.

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

For alpelisib, a dose reduction is defined as a decrease in dose from the protocol planned starting dose (e.g. from 300 mg daily to 250 mg daily) even if the dose decrease has been directly preceded by an interruption. On the other hand, if the dose decrease is followed by an interruption, with the dose resuming at the same level prior to the interruption (e.g. in the sequence 300 mg daily – 0 mg - 300 mg daily), the second dose decrease or change in dosing frequency will not be counted as dose reduction.

If, due to a dosing error, a patient receives a higher than planned starting dose and moves down to the planned starting dose then this is not considered a dose reduction. However if the dose change is from a higher than planned starting dose down to a lower than protocol planned starting dose, then this is considered a dose reduction (e.g. in the sequence: 350 mg daily, 300 mg daily, 250 mg daily; 250 mg is considered a dose reduction in the case of aplelisib).

If, due to a dosing error, a patient receives a lower than previous non-zero dose and resumes later at the protocol specified dose reduction, then the lower dose received due to dosing error and protocol specified dose reduction are dose reductions (e.g. in the sequence 300 mg daily – 200 mg daily - 250 mg daily, then 200 mg and 250 mg are considered dose reductions).

If, due to a dosing error, a patient receives a lower than previous non-zero dose and resumes later at a lower than previous non-zero dose, then 2 dose reductions will be counted (e.g. in the sequence 300 mg daily - 250 mg daily – 200 mg daily, 250 mg and 200 mg are dose reductions).

Table 2-3 Examples of Dose Reduction for alpelisib

Sequence	Reduction
With dose change	
300 mg daily - 250 mg daily – 0 mg - 250 mg daily	1 reduction (the 1st 250 mg)
300 mg daily – 300 mg daily – 0 mg - 250 mg daily	1 reduction (250 mg)
300 mg daily – 0 mg – 250 mg daily	1 reduction (250 mg)
With interruption	
300 mg daily – 0 mg - 300 mg daily	0 reductions
With dosing error	
300 mg daily – 250 mg daily – 200 mg daily*	2 reductions (250 mg, 200 mg)
300 mg daily – 200 mg daily* - 300 mg daily	1 reduction (200 mg)
300 mg daily – 200 mg daily* - 250 mg daily	2 reductions (200 mg, 250 mg)
300 mg daily – 400 mg daily* - 350 mg daily*	0 reductions since 400 mg and 350 mg are dose escalations not reduction
300 mg daily – 150 mg daily* - 300 mg daily	1 reduction (150 mg)
With dosing error at the 1st administration	
150 mg daily* - 300 mg daily	1 reduction (150 mg)

Sequence	Reduction
150 mg daily* - 0 mg – 150 mg*- 300 mg daily	1 reduction (150 mg)
150 mg daily* - 300 mg daily – 0 mg - 250 mg daily	2 reductions (150 mg and 250 mg)

*dosing error

There is no planned dose reduction for letrozole and fulvestrant; in addition the reason for fulvestrant dose reduction is not collected in the eCRF. No analysis for fulvestrant will be done on the number of, and reasons for, reductions. The established clinical dose of goserelin or leuprolide will be used in men and premenopausal women patients and no dose modification is planned in this study.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by cohort. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy etc.), setting (e.g. adjuvant, metastatic, etc.) and also by lowest ATC class, preferred term and treatment. Summaries will include total number of regimens, best response and time from last treatment to progression for the last therapy.

The medication therapy type of any combination therapy will be classified based on the following order: chemotherapy, biologic therapy, targeted therapy, hormonal therapy. For example, a combination therapy of chemotherapy and hormonal therapy will be classified as ‘chemotherapy’. For radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

In addition, number (%) of patients who received any hormonal therapy (irrespective of given in combination with chemotherapy or biologic or targeted therapy), any aromatase inhibitors, any hormonal therapy other than aromatase inhibitors in any setting and in the metastatic setting, any prior CDK4/6 inhibitors will be summarized by cohort.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.
Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS .

Post treatment anti-cancer therapy

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

Concomitant medications

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

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

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

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

According to the study protocol Table 14-2, treatment with substances which are strong CYP3A inhibitors, or inducers of CYP3Aor medications with a known risk of QT prolongation should be avoided. However, some patients may take these substances during the treatment period so these concomitant medications will be selected via programming and tabulated and listed in the Clinical Study Report. Treatment with the prohibited substances mentioned above will be identified in the database as protocol deviations.

2.5 Analysis of the primary objective

The primary objective of the study is to assess the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment per RECIST v1.1 separately in Cohorts A and C (alpelisib in combination with fulvestrant) and Cohort B (alpelisib in combination with letrozole) among patients with HR+, HER2-negative aBC harboring a PIK3CA mutation who have progressed on or after prior treatments.

2.5.1 Primary endpoint

The primary efficacy endpoint is the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment using RECIST v1.1 in each cohort.

The mFAS will be used for the primary efficacy analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

In post CDK 4/6 inhibitor progression setting a [redacted] response rate is considered as a clinically meaningful threshold in each cohort. Therefore, evidence of treatment effect will be tested using the following hypothesis:

H_0: [redacted]

H_1: [redacted]

Where p is the proportion of patients who are alive without progression at 6 months.

The primary endpoint will be presented together with two-sided 95% confidence intervals using Clopper and Pearson (1934) exact method for both cohorts separately. The null hypothesis will be rejected and evidence of treatment effect will be demonstrated if the lower bound of the 95% CI for observed proportion at 6 months is greater than [redacted] Table 2-4 displays the values of proportion of patients who are alive without any disease progression at 6 months and its 95% CI. To reject the null hypothesis [redacted] at least 44 patients need to be alive without progression at 6 months out of 112 patients in each cohort.

Table 2-4 Exact 95% Confidence Interval

Sample size (N)	Number of patients alive without PD at 6 months (k)	Proportion k/N (%)	Exact 95% Confidence Interval (CI)	
			Lower (%)	Upper (%)
112	[redacted]			

2.5.3 Handling of missing values/censoring/discontinuations

Six months is defined in this study as 24 weeks ± 1 week. Therefore tumor assessments between week 23 and 25 will be considered for the primary analysis. For primary endpoint analysis, patients who progressed, died, or discontinued study before 6 months will be counted as a "failure".

2.5.4 Supportive analyses

The primary analysis will also be performed on the FAS and may be repeated on PPS, if hypothesis on the primary endpoint for the mFAS is met.

The primary analysis will also be repeated in patients from mFAS harboring a PIK3CA mutation as determined via ctDNA. This analysis will be conducted using the same analytical conventions as the primary analysis.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

The secondary objectives in this study are to evaluate the progression free survival (PFS), progression free survival 2 (PFS2), overall response rate (ORR), clinical benefit rate (CBR), overall survival (OS), duration of response (DOR), and safety. For efficacy secondary objectives, 95% confidence intervals will be provided.

The secondary efficacy analyses will also be repeated in patients harboring a PIK3CA mutation as determined via ctDNA at baseline and conducted using the same analytical conventions.

2.7.1 Secondary endpoints

The mFAS will be used for the secondary efficacy analyses.

Progression free survival

Seconday endpoints include PFS, defined as the time from the date of start of treatement to the date of the first documented progression or death due to any cause. PFS will be based on local investigators review of tumor assessments and using RECIST 1.1 criteria (see Appendix 5 of the study protocol). If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy. Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST 1.1 will not be considered disease progression for PFS derivation. Clinical deterioration will not be considered as a qualifying event for progression.

Overall response rate

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 5 of the study protocol). ORR will be calculated based using local investigators review of tumor assessment data in patients with measurable disease at baseline. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a complete response was observed. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in the assessment of BOR.

Clinical benefit rate (CBR)

CBR is defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of stable disease (SD) lasting 24 weeks or longer or Non-CR/ Non-PD lasting 24 weeks or longer, according to RECIST 1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at 23 weeks or later from

enrollment, allowing for the +1 week visit window for tumor assessments. Patients with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if they achieve a complete response or have a 'Non-CR/Non-PD' response 23 weeks or more after start of study treatment. CBR will be calculated using the mFAS based on the investigators' tumor assessments.

Duration of response

Duration of response (DOR) only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on local investigators review of tumor assessment data. 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. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis (options A(1), C2(1), D(1), E(1), F(1-3) and G(1) from Table 3-2 in Appendix 5 of the study protocol).

Overall Survival

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

PFS after next-line of treatment (PFS2)

PFS2 is defined as time from date of start of treatment to the first documented disease progression (clinical or radiologic) on next-line therapy or death from any cause, whichever occurs first. The first documented progression on next-line treatment will be based on investigator assessment of PD (i.e. as captured on the anti-neoplastic therapy after treatment discontinuation CRF page).

1. Next-line therapy is defined as the first new (systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of EoT reason. Drugs given as part of the same regimen should be grouped as one line (i.e. part of the next-line therapy). In addition, continuation of the study treatment after the initial radiologic disease progression will not be considered as next-line therapy.
2. PFS2 will be censored if no PFS2 event (progression or death) is observed during next-line therapy before the analysis cut-off date; the censoring date will be the last contact date.
3. However, in case a second new anti-neoplastic therapy is introduced without prior PFS2 event, then PFS2 will be censored at the end date of the first new anti-neoplastic therapy (i.e. next line therapy).
4. PFS2 will be censored at last contact date if a patient is still ongoing on study treatment irrespective of the disease progression status or second progression while being on study treatment, or patient has discontinued study treatment but has not started next-line therapy and is still alive.

5. Any death prior to initiation of next-line therapy will be considered as an event for PFS2.
6. PFS and PFS2 may be identical if a patient did not experience an event (i.e. progression) prior to initiation of next-line therapy, and adequate tumor assessments continue until RECIST 1.1-documented disease progression after initiation of next-line therapy.

Extension Phase Clinical Benefit

The secondary objective related to the Extension Phase of the study is to evaluate clinical benefit as assessed by the Investigator. Proportion of patients with clinical benefit is defined by the number of patients with clinical benefit as assessed by investigator during Extension Phase (begins after the end of the Core Phase) divided by the number of patients in Extension Phase (Safety set in Extension Phase).

2.7.2 Statistical hypothesis, model, and method of analysis

PFS

The survival distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically (Kaplan-Meier curves) by cohort. The plots will display the number of patients at risk at equidistant time points. The median, 25th and 75th percentiles for PFS for each cohort will be provided with associated 95% confidence intervals (Brookmeyer and Crowley 1982). The survival probabilities at 6, 12, 18 months, and the associated 95% confidence intervals will be summarized by cohort. Kaplan-Meier estimates will be obtained using PROC LIFETEST with method=KM option in SAS. The loglog option available within PROC LIFETEST will be used to compute the confidence intervals.

ORR and CBR

ORR and CBR will be calculated based on the mFAS. ORR and CBR will be summarized using descriptive statistics (N, %) separately for each cohort along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934]. As sensitivity analysis, CBR will be calculated and summarized for patients with only measurable disease at baseline.

Duration of Response

DOR will be listed and summarized by cohort for all patients in the mFAS with confirmed BOR of CR or PR. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. A responders-only analysis will also be performed in this case.

OS

OS will be analyzed in the mFAS population. The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented for each cohort.

PFS2

PFS2 will be analyzed in the mFAS population. The PFS2 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 separately for each cohort.

Extension Phase Clinical Benefit

Proportion of patients with clinical benefit as assessed by the investigator will be summarized at scheduled visits. Clinical benefit will be summarized using the Safety Set in Extension Phase.

2.7.3 Handling of missing values/censoring/discontinuations

PFS

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

PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST 1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy.

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

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event, the event occurred after two or more missing tumor assessments. The term “missing adequate tumor assessment” is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of “UNK”. The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-5 for censoring and event date options and outcomes for PFS.

Table 2-5 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed

Situation	Date	Outcome
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Progressed

ORR

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the mFAS and will be counted as 'failures'.

PFS 2

For PFS2, refer to Table 2-6 for censoring and event date options and outcomes.

Table 2-6 Outcome and event/censor dates for PFS2 analysis

Situation	Event/Censoring Date	Outcome
No baseline assessment	Date of start of treatment	Censored
Progression or death during the next-line therapy	Date of progression (or death)	Event
Death prior to initiation of next-line therapy	Date of death	Event
No progression (or death) during the next-line therapy and no second new anti-neoplastic therapy is initiated	Last contact date	Censored
No progression (or death) during the next-line anticancer therapy and a second new anti-neoplastic therapy is initiated	End date of the next-line therapy	Censored
No next-line therapy initiated with patient known to be alive	Last contact date	Censored

2.8 Safety analyses

All safety analyses will be based on the safety set. All listings and tables will be presented for each cohort.

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., ECG, vital signs) will be considered as appropriate. All safety data will be listed.

2.8.1 Adverse events (AEs)

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

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational drug .

The following adverse event summaries will be produced by cohort: overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound BYL719. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

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

Summaries of these AESIs will be provided by cohort (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

Depending on the observed number of events, the time to first occurrence of any CTC grade > 2 AESI may be summarized using Kaplan-Meier methods for specific groupings.

Median time to onset and 95% CI will be summarized. Ascending Kaplan-Meier lots will be generated.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by cohort, system organ class and preferred term.

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

2.8.3 Laboratory data

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

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) might be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.
- In addition, HbA1c, fasting glucose and fasting C-peptide data will be summarized in tables by time point and treatment. Summary statistics include number of patients with available data, mean, standard deviation, median, minimum and maximum. Figures of mean

HbA1c/glucose/C-peptide levels with two-sided 95% confidence intervals over time by cohort may also be produced to view the trends over time.

The following listings will be produced for the laboratory data:

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

Liver function parameters

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

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those patients with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Data handling

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

Data analysis

12-lead ECGs including PR, QRS, QT, QTcF, and HR intervals will be obtained for each patient during the study. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented by cohort.

- QT, QTcF, or QTcB
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

Categorical Analysis of QT/QTc interval data based on the number of patients 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 patients will be produced by cohort.

A listing of all ECG assessments will be produced by cohort and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

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

Data handling

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

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-7 below.

Table 2-7 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase >= 10% from Baseline	decrease >= 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20

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

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

A listing of all vital sign assessments will be produced by cohort and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Cardiac imaging (MUGA / ECHO)

For left ventricular ejection fraction (LVEF) a shift table using CTC grades for 'Ejection fraction - decrease' as defined per CTCAE version v4.03 to compare baseline to the worst on-treatment value will be provided.

A listing of patients with newly occurring clinically significant abnormality will be produced by cohort.

Note: If there is any change in the methodology used throughout the study compared to baseline, the post-baseline values for which the methodology differs from baseline will be discarded in the tables presenting comparisons to baseline.

2.8.4.4 ECOG performance status

ECOG Performance status (PS) is assessed to attempt to quantify the impact of disease on daily life activities of patients.

ECOG PS scale is used to assess physical health of patients, ranging from 0 (most active) to 5 (least active) (see Table 7-4 of the study protocol for details).

Shift tables will be produced to compare baseline to the worst on-treatment value.

2.8.4.5 Additional Analyses

Time to first occurrence of any AESI with CTC grade > 2 event

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AESI grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

In the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- end date of on-treatment period (end of study treatment + 30 days).
- death date

- start date of new antineoplastic therapy before experiencing any CTC grade $\geq$ 2 event.
- data cut-off date.
- withdrawal of informed consent date

The corresponding censoring reason will be used: death, new anti cancer therapy, treatment discontinuation, ongoing at cut-off date or consent withdrawal.

Failure curves (ascending Kaplan-Meier curves) will be constructed by cohort. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented for each cohort.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

The same analysis might be repeated for events of grade 3 and grade 4.

2.8.5 Safety data for Extension Phase

Safety analyses for the Extension Phase will be performed on the Safety Set in Extension Phase. The assessment of safety will be based mainly on the duration of exposure and dosage. The following summaries will be provided since the start of Core Phase:

- Duration of exposure to study treatment;
- Dose of study treatment received;
- Dose adjustments and discontinuation of study treatment.

2.9 Pharmacokinetic endpoints

Not applicable.

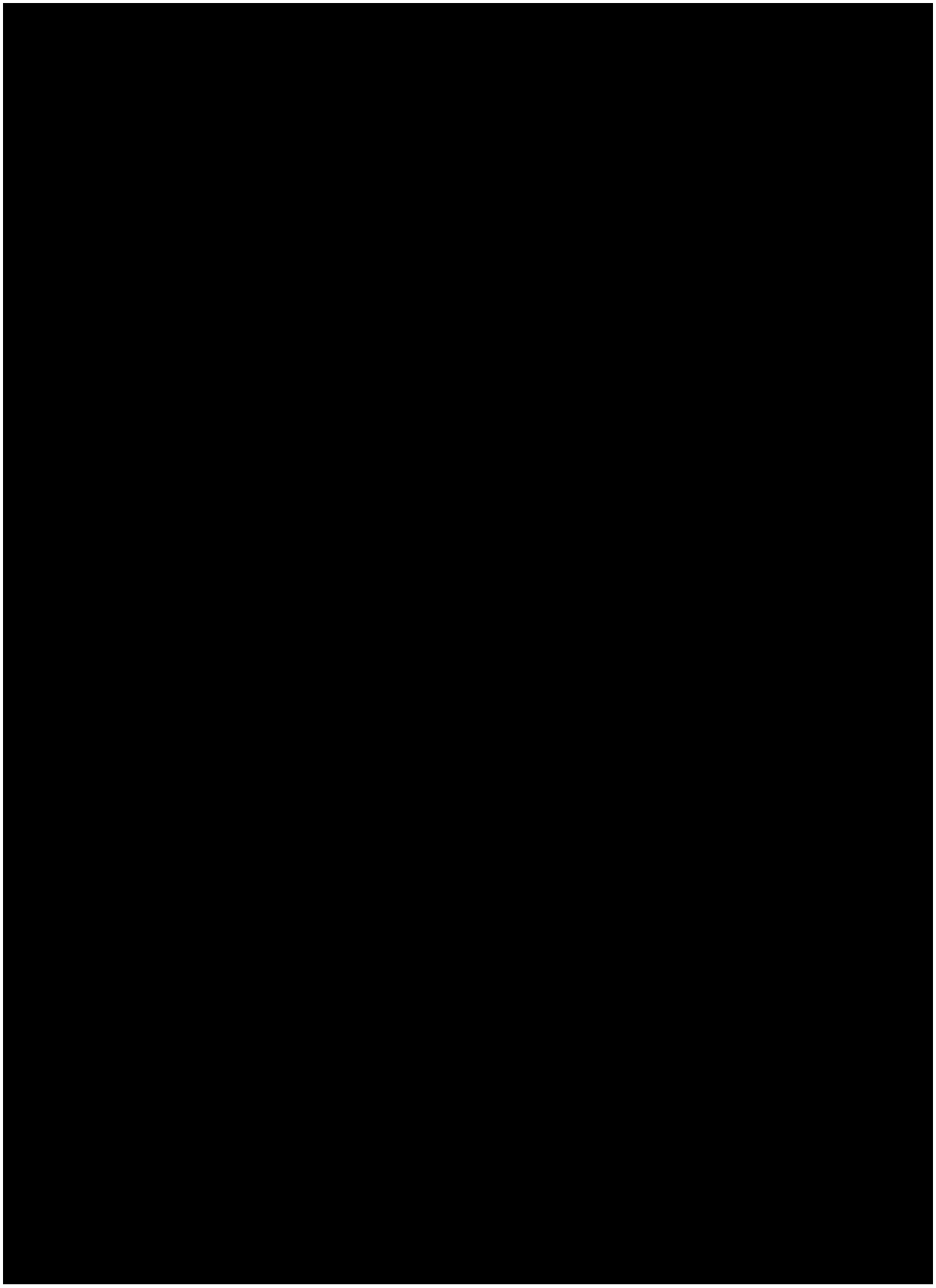
2.10 PD and PK/PD analyses

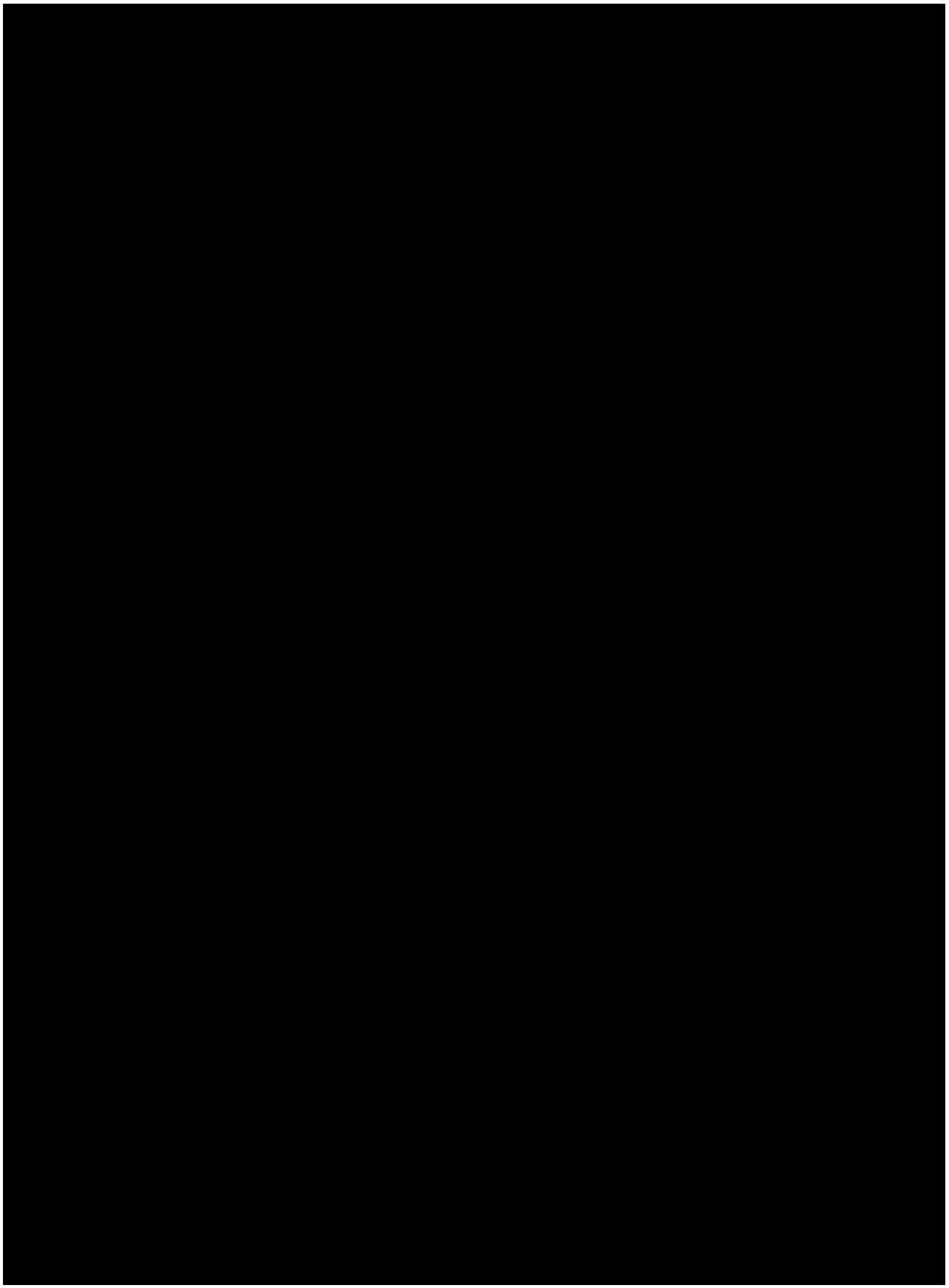
Not applicable.

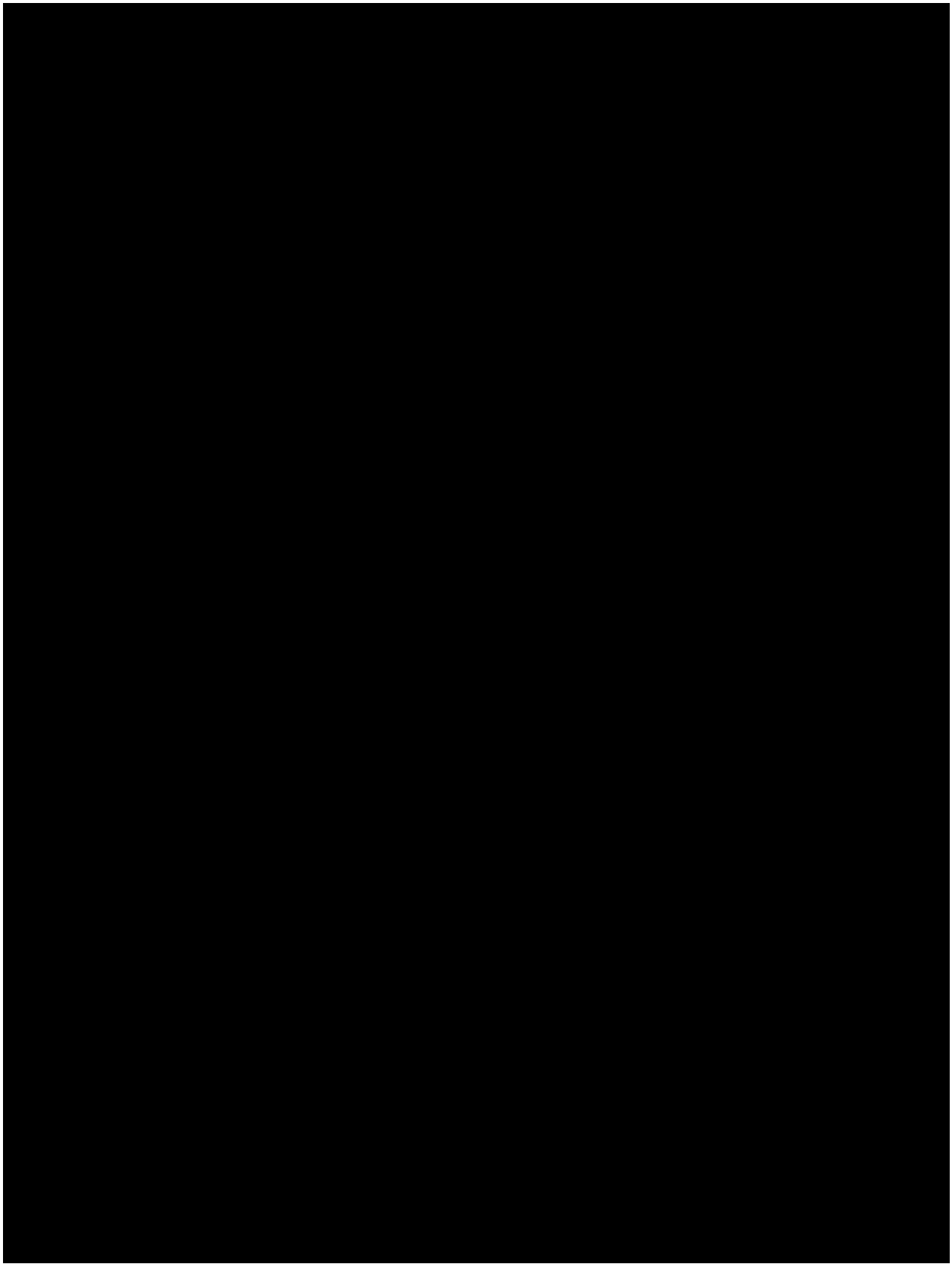
2.11 Patient-reported outcomes

Not applicable.

[redacted]







[redacted]

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

The first Interim Analysis (IA) is planned after at least [redacted] patients receiving alpelisib plus fulvestrant (cohort A) have at least 6 months of follow up. Once [redacted] patients will be recruited, the interim analysis data cutoff will be the last patients first visit plus 6 months. The second IA is planned after [redacted] patients have been treated (regardless of cohort) and have at least 6 months of follow-up on study. The third IA will be performed after the Core Phase has ended.

At the time of the first two IAs, preliminary efficacy (ORR, CBR) as well as key safety data will be analyzed in a descriptive fashion. The primary endpoint will not be analyzed and no statistical hypothesis will be tested.

The third IA will include all efficacy and safety data up to the end of the Core Phase.

Primary endpoint will not be analysed and no formal statistical hypothesis testing will be done at the time of IA and therefore no multiplicity adjustment will be made.

Preliminary efficacy as well as key safety data will be analysed in a descriptive fashion separately in each cohort.

The following endpoints will be summarized at the time of the first two IAs:

- Overall response rate (ORR)
- Clinical Benefit rate (CBR)
- Average daily dose, cumulative dose, relative dose intensity
- Duration of exposure
- Dose reduction/interupptions
- Adverse events
- Serious adverse events
- Deaths
- Adverse event of special interest (AESI)
- Laboratory parameters

3 Sample size calculation

3.1 Primary analysis

A median PFS of at least 6 months (or 50% of patients who are alive without progression after 6 months) has been observed for alpelisib 300 mg plus fulvestrant 500 mg and also for palbociclib 125 mg plus fulvestrant 500 mg in PiK3CA mutant patients previously treated with AI (without CDK4/6 inhibitor) in [CBYL719X2101] and Paloma-3 (Cristofanilli 2016) studies respectively. Currently, there is no available clinical data in post-CDK4/6 inhibitor setting in PIK3CA mutant patients. Assuming that these patients after failure to CDK4/6 inhibitor will have a lower median PFS than 6 months, a proportion of [redacted] of patients alive without progression after 6 months is considered as a clinically meaningful threshold in both cohorts for this study and was used for sample size calculation.

The sample size is based on an exact Binomial test for single proportion to test the null hypothesis H_0: [redacted] where p is the proportion of patients who are alive without progression at 6 months. With a one-sided 2.5% level of significance (two-sided 95% CI), a total sample size of 112 patients in each cohort is required in order to have a power of at least 90% when the true p ≥0.45. Table 3-1 provides the operating characteristics for N=112 and different true rates.

Table 3-1 Operating Characteristics

Sample size (N)	True rate	Prob (X≥44|True rate)
112	[redacted]	

The study will enroll a total of approximately 340 patients who have PIK3CA mutation with at least 112 patients allocated into each Cohort A (alpelisib + fulvestrant), Cohort B (alpelisib + letrozole) and Cohort C (alpelisib + fulvestrant).

At the time of the first two Interim Analysis (IA) preliminary efficacy (ORR, CBR) will be analyzed in a descriptive fashion. The primary endpoint will not be analyzed and no statistical hypothesis will be tested. Therefore no multiplicity adjustment was made.

4 Change to protocol specified analyses

4.1 Impact of COVID-19

Due to pandemic COVID in year 2020, some extra analyses will be performed outside protocol specified.

Operational impact: Specified protocol deviation categories will be assigned to important deviations related to COVID-19 (e.g., missing efficacy assessments) and these will be summarized and listed separately. A summary table of the COVID-19 related deviations by relationship category will be provided.

Safety: To help to evaluate the impact of the pandemic on safety, the incidence of COVID-19 related adverse event preferred terms will be presented incorporating COVID-19 related adverse events with an onset date in the year of 2020.

Efficacy: If there are >=10% patients with missed visits due to COVID-19, an additional sensitivity analysis for primary endpoint will be performed to address the potential impact of the COVID-19 pandemic, using local investigator assessment using RECIST v1.1 on the mFAS and considering the visit labeled by “missed visits due to COVID-19” has the same assessment value as in previous scheduled visit.

5 Appendix 1

5.1 Imputation rules

All imputation rules will be provided in full details in the PDS and the most updated rules as mentioned in the PDS will be followed.

5.1.1 Study drug

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

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

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

Scenario 1 should not applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR

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

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

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm)

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

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

Use the treatment start date

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

5.1.2 AE, ConMeds and safety assessment date imputation

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

Missing Element	**Rule**
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY • If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

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

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

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

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

5.1.2.1 Other imputations

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

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

Incomplete assessment dates for tumor assessment

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

Applying the cut-off to tumor assessment

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

5.2 AEs coding/grading

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

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

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

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of

analysis will be used. The Novartis internal CTC grading document has been added as appendix 2 to the present document. For laboratory tests where grades are not defined by CTCAE v 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

Imputation Rules

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

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

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

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

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

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

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

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

5.4 Statistical models

5.4.1 Primary analysis

The methodology is described in Section 2.5

Kaplan-Meier estimates

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

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

will be calculated using Greenwood's formula [Collett 1994].

Analysis of Binary Data

Responses will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934]

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI and exact one-sided p-value for the hypothesis test of the *null proportion* (*0.xx*).

6 Reference

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