CONFIDENTIAL INFORMATION

Statistical Analysis Plan (SAP)

Final V1.0
28th January 2020

EudraCT Number	2018-004648-44
Protocol Number	MedOPP253 (PATHFINDER)
Protocol Version Date	V2.0 18-May-2020
Title	A Multicenter, Open-Label, Non-Comparative, Three-Arm, Phase IIa Trial of Ipatasertib (GDC-0068) in Combination with Non-Taxane Chemotherapy Agents for Taxane-Pretreated Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Patients.
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STATISTICAL ANALYSIS PLAN (SAP)

Performed by:

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Signature Page

EudraCT Number: **2018-004648-44**
Protocol Number: **MedOPP253**

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The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

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SAP Revision History:

Version Number	Date	Changes
V1.0	28th January 2021	New

LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Advanced Breast Cancer
AE	Adverse event
ARO	Academic Research Organization
ATC	Anatomical Therapeutic Chemical
BC	Breast cancer
BPM	Beats per minute
CB	Clinical benefit
CBR	Clinical Benefit Rate
CI	Confidence interval
CNS	Central nervous system
CPMP	Committee for proprietary medicinal products
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting Toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	electronic Case Report Form
EMEA	European Medicines Agency
EOS	End of Study
ER	Endocrine receptors
EUDRACT	European Clinical Trials Database
EWP	Efficacy Working Party
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
HR	Hazard ratio
ICH	International Conference on Harmonization
ID	Identification
IMP	Investigational Medicine Products
IQR	Interquartile Range
MBC	Metastatic Breast Cancer
MEDDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression Disease
PEPI	Preoperative Endocrine Prognostic Index
PP	Per Protocol set
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred term
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases criteria
RD	Recommended Dose
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RNA	Ribonucleic acid
RR	Relative Risk
RS	Recurrence Score
SAE	Serious Adverse Event
SAIL	SAIL S.L.L.
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Steering Committee
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
STD	Standard deviation
TEAE	Treatment emergent adverse event
TLF	Tables, listings and figures
TNM	Tumor Node Metastasis
TTP	Time to progression
TTR	Time to response
WHO	World Health Organization

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1 INTRODUCTION

1.1 General

The purpose of this statistical analysis plan (SAP) is to provide a protocol specific description of the statistical analysis that will be performed to produce an integrated clinical/statistical report.

This SAP is based upon the following study documents:

- Protocol version Date: V2.0 18-May-2020
- eCRF release version date: 13-Jul-2020

1.2 Type of Study

This is a multicenter, open-label, non-comparative, three-arm, phase IIa clinical trial with safety run-in.

1.3 Study Design

1.3.1 Phase IIa

This is a multicenter, open-label, non-comparative, three-arm, phase IIa clinical trial that is designed to evaluate the safety, tolerability, and efficacy of ipatasertib (GDC-0068) in combination with eribulin, capecitabine, or carboplatin plus gemcitabine for taxane-pretreated patients with unresectable locally advanced or metastatic TNBC that is not amenable to resection with curative intent.

Patients must have received at least one, but not more than two, prior chemotherapeutic regimens for treatment of unresectable locally advanced and/or metastatic disease (at least one regimen must have contained a taxane). Earlier adjuvant or neoadjuvant therapy for more limited disease will qualify as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. Therefore, exclusive prior taxane-based therapy as adjuvant or neoadjuvant treatment is also allowed if the patient had a disease-free interval of less than 12 months after completing this treatment.

Evidence of either measurable or evaluable disease as for RECIST v.1.1 is mandatory. Patients with bone-only metastases are also eligible.

Patients will be assigned to one of the following three treatment arms based on local investigator assessment and slots availability (**maximum 18 patients per study arm**):

- **Arm A**: Ipatasertib 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus capecitabine 1000 mg/m2 tablets orally twice a day (morning and evening; equivalent to 2000 mg/m2 total daily dose), for 14 days (followed by a 7-day rest period) every 21-day cycle.
- **Arm B**: Ipatasertib 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus eribulin 1.23 mg/m2 (equivalent to eribulin mesylate at 1.4 mg/m2) administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.
- **Arm C**: Ipatasertib 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus carboplatin area under the curve (AUC) on Day 1 administered intravenously plus gemcitabine 1000 mg/m2 administered intravenously over 30 minutes on Days 1 and 8, every 21-day cycle.

1.3.2 Run-in Phase

A run-in phase for safety and tolerability of ipatasertib in combination with standard doses of capecitabine (Arm A), eribulin (Arm B), and carboplatin plus gemcitabine (Arm C) will be conducted as an initial step of the non-comparative phase IIa in this patient population.

This phase aims at evaluating and establishing the dosing schedule of ipatasertib, by analyzing the toxicity profiles of each of the combined regimens.

Up to three patients will be initially included in the first dosing level of 400 mg/day of ipatasertib. If one significant toxicity is observed during the first 2 cycles, three additional patients will be enrolled at 400 mg/day cohort to determine the number of total significant toxicities observed in six patients.

Safety Run-In Dosing Schedule:

Continuous dosing schedule	**Ipatasertib***
1 (starting dose)	400 mg/day
2	300 mg/day
3	200 mg/day**
* In the safety run-in phase of the study, ipatasertib will be administered in combination with standard doses of capecitabine (Arm A), eribulin (Arm B), and carboplatin plus gemcitabine (Arm C).	
** The evaluation of 200 mg/day can be decided if two or more significant toxicities are observed at 300 mg/day.	

If two or more significant toxicities are observed in three or six patients treated with 400 mg/day of ipatasertib, it can be decided to evaluate 300 mg/day of ipatasertib following the same procedure as described for the 400 mg/day cohort.

Patients assigned to each cohort will remain in their study cohort during the entire study period.

During the safety run-in period, the Steering Committee will meet to assess the safety and tolerability of the selected combined treatment regimens used in the study. This meeting will take place after the 3 first subjects of each Arm have completed the 2 first cycles. This data will be shared with F. Hoffmann-La Roche Ltd.

1.3.3 Interim Analysis

Once the dosing schedule of ipatasertib has been established, an early interim analysis will be performed to continue with the phase IIa.

The interim analysis will be performed independently in each arm after the last evaluable patient in the run-in phase has completed the two first cycles of study treatment to assess the toxicity profile of each regimen.

1.4 Study Flow Chart

Summary of study assessments is reported in Appendix 1 (schedule of Assessments) of the protocol.

Study Period	**Screening**			**Treatment period***			**Post-Treatment Follow-Up Period**		
Treatment Arm	**Arms A + B + C**			**Arm A**		**Arms B + C**	**Arms A + B + C**		
Day	**-28 to -1**	**-7 to -1**	**-2 to -1**	**Day 1 of each cycle (every 21 days)**	**Cycle 1 day 8**	**Day 1 of each cycle (every 21 days)**	**Day 8 of each cycle[21]**	**Within 30 days after last dose of study treatment (end of treatment)**	**Follow-up every 3 months[20] (survival period)**
Informed Consent Form[1]	X								
Local HR/HER2 status[2]	X								
Baseline signs/symptoms	X								
Check of inclusion/exclusion criteria	X								
Medical history[3]	X								
Complete physical examination and ECOG performance status	X			X		X		X	
Limited physical examination (*diarrhea, nausea, vomiting, mucositis, dyspnea/cough, skin toxicity*)					X		X		
Weight and vital signs[4]	X			X	X	X	X	X	
Body Surface Area (BSA)				X		X			
Concomitant medication reporting[5]	X			X	X	X	X	X	
Review patient diary				X		X			
Home glucose monitoring				If clinically indicated					
AE reporting[6]	X			X	X	X	X	X	
Survival status								X	X
Post-study anticancer therapy								X	X
12-lead ECG[7]	X			If clinically indicated					
ECHO or MUGA scan[8]	X			If clinically indicated					
Tumor assessments (chest, abdomen, pelvis)[9]	X			X[9]		X[9]		X[19]	
Bone scans[10]	X[10]			If clinically indicated[10]					
Brain MRI[11]				If clinically indicated[11]					
Tumor samples[12]	X							At the time of progression (if feasible)	
Blood samples[13]	X			X[13]		X[13]		At the time of progression	
	Standard Laboratory Procedures**								
Hematology[14]	X			X		X	X	X[19]	
Fasting Serum Biochemistry[15]	X			X	X	X	X	X[19]	
Glycated Hemoglobin HbA1c	X								
INR and PTT (or aPTT)	X								
Pregnancy test[16]		X		X		X		X[19]	
Viral serology[17]	X								
Prophylaxis anti-diarrheal[18]				X[18]		X[18]			
Ipatasertib dispensing and accountability				X		X			
Chemotherapy administration				X		X	X		

Abbreviations: Arm A = Ipatasertib plus capecitabine; Arm B = Ipatasertib and eribulin; Arm C = Ipatasertib plus carboplatin plus gemcitabine.
AE = Adverse events; aPTT = activated partial thromboplastin time; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor; INR = International normalized ratio; MUGA = Multiple-Gated Acquisition; PTT = Partial thromboplastin time.

***** All visits must occur within ± 2 working days (± 1 working day in Day 8 of each cycle). Assessments scheduled for Days 1 and 8 of each cycle must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up.

** Laboratory tests will be performed at the study site's local laboratory within 48 hours prior to Day 1 of each cycle following ≥ 8-hour fast. Blood test at C1D1 does not need to be repeated if it was performed at screening within 48 hours prior to start of study treatment. For patients included in Arms B or C, laboratory tests will be also performed within 24 hours prior to Day 8 of each cycle.

1. Informed Consent Form: Signed written Informed Consent Form obtained prior to any trial-specific procedure.

2. Local HR/HER2 status: Confirmation of histological diagnosis and specified estrogen receptor, progesterone receptor, and HER2 status based on local testing on the most recent analyzed biopsy.

3. Medical history: Complete medical history and demographics (including age, gender, and ethnic origin). All medications taken in the last 28 days prior to enrolment will be collected.

4. Weight and vital signs: Weight, height (only at screening), respiratory rate, blood pressure measurements (systolic and diastolic), pulse rate, and body temperature (oral, axillary, or tympanic temperature).

5. Concomitant medication reporting: Relevant concomitant medication will be recorded at screening and on an ongoing basis.

6. AE reporting: All Adverse Events occurring during the trial and until 30 days after treatment discontinuation visit (end of treatment visit) have to be recorded with grading according to the NCI-CTCAE v.5.0.

7. 12-lead ECG: One mandatory ECG at screening. Thereafter, additional ECGs should be performed if clinically indicated (symptoms, use of drugs known to prolong QTc, etc.).

8. ECHO or MUGA scan: LVEF assessment must be done within 12 weeks prior to C1D1. Afterwards, cardiac function evaluation should be repeated if clinically indicated.

9. Tumor assessments (chest, abdomen, pelvis): Baseline assessments of the chest, abdomen, and pelvis (preferably CT or MRI in case of contrast allergy) must be performed no more than 28 days before the first dose of study treatment. Post-baseline assessments will be performed every 6 weeks (± 3 days) for first 6 months of treatment and every 9 weeks (± 7 days) thereafter using the same imaging method and where possible obtained at the same institution for an individual patient as used during screening until progression disease.

10. Bone scans: Bone imaging is mandatory at baseline and thereafter will be performed every 24 weeks (± 7 days) only for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression. If a bone scan was performed > 28 days but ≤ 60 days prior to start of study treatment, the bone scan does not need to be repeated.

11. Brain imaging (MRI): Brain imaging during the trial should be performed only in subjects with known brain metastases (every 6 weeks [± 3 days] for first 6 months and thereafter every 9 weeks [± 7 days]) and those with worsening and/or new neurological symptoms.

12. Tumor samples: A tumor tissue sample from a metastatic site or the primary breast tumor must be collected at the time of study entry (mandatory), with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample from metastasis or primary breast tumor obtained at disease progression or study termination.

13. Blood samples: Blood samples are required for all patients at the time of inclusion, after two cycles of study treatment, and upon progression or study termination.

14. Hematology: Hemoglobin, hematocrit, red blood cell count, platelet count, WBC with differential count (ANC, lymphocytes, monocytes, eosinophils and basophils.

15. Fasting (≥ 8-hour fast) serum biochemistry: Renal function analysis (serum creatinine, creatinine clearance according to the Cockcroft-Gault formula), liver function [AST, ALT, ALP, gamma-glutamyl transferase (GGT), total and direct bilirubin], amylase, lipase, glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.

16. Pregnancy test: A negative serum pregnancy test must be obtained for women with childbearing potential either within 96 hours prior to C1D1 study treatment administration, or within 7 days of C1D1 (in this case, confirmed by a negative urine pregnancy test prior to C1D1 dosing). In addition, pregnancy tests (serum or urine) are to be performed within 48 hours of Day 1 of each following treatment cycle prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. In case an additional pregnancy test is indicated during the trial, a serum test should be performed.

17. Viral serology: Human Immunodeficiency Virus, Hepatitis B surface Antigen (HBsAg), total Hepatitis B core Antibody (HBcAb), Hepatitis C Virus antibody; additional tests for Hepatitis B Virus DNA or Hepatitis C Virus RNA will be required to confirm eligibility.

18. Prophylaxis anti-diarrheal: Prophylactic loperamide dose of 2 mg twice a day or 4 mg once a day will be administered daily as prophylaxis for diarrhea during at least the first initial cycle of treatment and may be extended to the next cycle if necessary and if allowed by local guidance. Refer to *Section* ***Error! Reference source not found.*** for further diarrhea management guidance.

19. These assessments do not need to be completed if they have been performed within 1 week before study withdrawal (within 4 weeks for imaging studies).

20. Follow-up every 3 months: After study treatment discontinuation, post-treatment follow-up (including survival status and post-study anticancer therapy evaluation) will be collected every 3 months (± 14 days) from the last dose of study treatment up to the EoS. Telephone contact is acceptable. If patient discontinued treatment for any reason other than progression, tumor assessment will be included in the assessment. EoS will occur at 12 months after the last patient included in the study, unless premature termination of the study.

21. Assessments scheduled for Days 1 and 8 of each cycle, must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up. If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (e.g., within a period of ± 2 working days). Day 8 visits can be omitted, at the Investigator's discretion, for patients enrolled in Arms B or C that permanently discontinue chemotherapy and continue with ipatasertib (GDC-0068) as single agent. However, laboratory assessments and clinical visits could be scheduled as needed for follow-up of ipatasertib (GDC-0068)-related adverse events. A telephone call may be also acceptable.

1.5 Sample Size

The sample size calculations were described in the protocol using the following wording:

A total sample of 54 evaluable taxane-pretreated patients (safety run-in phase + non-comparative phase) with unresectable locally advanced or metastatic TNBC will be allocated based on investigator's criteria, in accordance with previous patient's treatments and slots availability, to one of the following treatment arms:

- *Arm A: Ipatasertib (GDC-0068) plus capecitabine. The total number of patients, including safety run-in stage and final stage, will be 18.*
- *Arm B: Ipatasertib (GDC-0068) plus eribulin. The total number of patients, including safety run-in stage and final stage, will be 18.*
- *Arm C: Ipatasertib (GDC-0068) and carboplatin plus gemcitabine. The total number of patients, including safety run-in stage and final stage, will be 18.*

Justification of Total Sample Size:

This is a pilot study to determine the safety and tolerability of three different study combinations with non-taxane chemotherapy agents and ipatasertib (GDC-0068). The analysis will be exploratory without hypothesis testing. However, The Sponsor has estimated the precision for the incidence of adverse events rate in ipatasertib combinations. Based on Lotus clinical trial (59) the Sponsor assumes a 100% incidence of all grades and 50% grade≥3 adverse events, respectively.

Therefore, a sample size of 18 patients will provide the following precisions:

- *18.5% to 0% (9.25% half width of confidence interval) assuming an observed AE incidence of 100% (i.e. 95% Clopper-Pearson confidence interval of 81.5 to 100%), and*
- *24 to 24% (24% half width of confidence interval) assuming an observed AEs incidence of 50% (i.e. 95% Clopper-Pearson confidence interval of 26 to 74%).*

1.6 Statistical Plan

No hypothesis testing is planned for this study.

2 STUDY OBJECTIVES

2.1 Primary objective

To evaluate the safety and tolerability of ipatasertib in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the ITT population of patients with taxane-pretreated unresectable locally advanced or metastatic TNBC.

2.2 Secondary Objectives

To determine the efficacy of ipatasertib in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the ITT population and in each treatment arm.

2.3 Exploratory Objectives

[redacted]

3 DEFINITION OF ENDPOINTS

3.1 Primary Endpoint

- Incidence of AEs as assessed by the investigator, with severity determined through the use of National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) NCI-CTCAE v.5.0.

3.2 Secondary Endpoints

- PFS, defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined locally by the investigator by Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1.
- Time to response (TTR), defined as the time from the treatment initiation to time of the first objective tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a CR or PR, as determined locally by the investigator by RECIST v.1.1.
- ORR, defined as a CR or PR, as determined locally by the investigator by RECIST v.1.1.
- DoR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined locally by the investigator by RECIST v.1.1.
- CBR, defined as an objective response (CR or PR), or SD for at least 24 weeks, as determined locally by the investigator by RECIST v.1.1.
- OS, defined as the time from treatment initiation to death from any cause, as determined locally by the investigator by RECIST v.1.1.

- Best percentage of change from baseline in the size of target tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, as determined locally by the investigator through use of RECIST v.1.1.

3.3 Exploratory Endpoints

[redacted]

4 ANALYSIS SETS

The following sets will be analyzed:

- **Screening:** Patients who were present at the screening visit.
- **Safety run-in Set:** Patients in safety run-in phase who complete the first two cycles of treatment or who stop treatment during this time because of significant toxicities.
- **Safety and FAS (Full Analysis Set) Set:** Patients who meet selection criteria and receive at least one drug exposure. The FAS set will be considered the primary population for the analysis.

[redacted]

5 STATISTICAL METHODS

5.1 General Methodology

Definition of baseline: For each safety or efficacy parameter, the last valid assessment made before first study drug administration will be used as the baseline for all analyses of that safety or efficacy parameter unless otherwise specified.

Continuous data will be summarized in terms of the number of observations, mean, standard deviation (SD), median, minimum, maximum, and first and third quartiles, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and first and third quartiles will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n as the denominator, for frequency tables not assessed by time point the set will be used as denominator. If sample sizes are small, the data displays will show the percentages, but any textual report (e.g., clinical study report) will describe frequencies only.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. However, if a p-value is only presented to four decimal places (by SAS) it will not be rounded again but will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001".

Confidence intervals will be presented to one more decimal place than the raw data. A two-sided significance level of 5% will be used for confidence intervals.

For binary endpoints, the 95% confidence intervals (CIs) will be constructed based on an exact binary distribution.

For time to event endpoints the Kaplan-Meier method will be applied. Number and proportion of events, median survival time and survival rates, with corresponding 95%Cl will be calculated.

All scores and change from baseline will be summarized in terms of the number of observations, mean, standard deviation, 95%CI of mean, median, range and interquartile range. We will examine the residuals to assess model assumptions.

All report outputs will be produced using SAS® version 9.4 version in a secure and validated environment. All report outputs will be provided to the Sponsor in a single Microsoft Word document.

5.2 Subject Disposition

Descriptive statistics will be provided for the following:

- Overall number of subjects in the screening set, the number of patients eligible to participate in the study, and number of screen failures.
- Number and percent of subjects in each of the analysis sets.
- Number and percent of subjects excluded from each of the analysis sets along with reason for exclusion.
- Listing of subjects excluded from each of the analysis sets along with reason for exclusion.
- Study termination:
  - Number and percent of subjects who completed the study.
  - Frequency of premature termination reasons.
  - Listing of all dropouts along with reason for termination, dose level and time of termination.

No statistical tests are planned for these data.

5.3 Baseline Characteristics

Baseline characteristics will be provided by arm and overall, for the Safety/FAS set.

Descriptive statistics, including number of subjects, mean, standard deviation (SD), median and range for continuous variables and frequency and percent for categorical variables will be provided.

Baseline Characteristics:

- Demographic characteristics
- Oncological history
- Medical history
- History of Breast Cancer
- Previous early disease treatment
- Previous advanced/metastatic disease treatment
- HER2 and HR status
- Physical examination
- ECOG
- Vital Signs
- 12-lead electrocardiogram
- LVEF Evaluation
- Tumor assessment
- Prior concomitant medication

No statistical tests are planned for these data.

A by-subject listing of all demographic and other baseline characteristics will be provided.

5.4 Primary Safety Analysis

The number and the proportion of patients with significant toxicities in each arm and dosing schedule will be described. Confidence intervals (CIs) will be calculated, according to Clopper-Pearson (exact binomial intervals).

The safety run-in analysis will be developed in safety run-in set.

Table 1. Primary Safety Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Primary	Safety run-in set	Proportion of patients with significant toxicities, during the first two cycles of treatment	Start date toxicities after last day of cycle 2 will be excluded.	CI will be calculated according to Clopper-Pearson (exact binomial intervals).
Sensitivity to primary	Safety set	Proportion of patients with significant toxicities, during the first two cycles of treatment	Start date toxicities after last day of cycle 2 will be excluded.	CI will be calculated according to Clopper-Pearson (exact binomial intervals).

5.5 Efficacy Analysis

5.5.1 Response Efficacy Definitions

Overall response according RECIST v1.1 will be obtained from target lesion response, non-target lesion response and new lesions, as follows:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

We will report these results in all patients and in patients with measurable disease.

- The unconfirmed Best Overall Response, defined as the best overall response recorded from the start of the study treatment until 35 days after last dose administration date and confirmation of response is not required.
    - When CR or PR is the best response across all time points, then best overall response will be CR or PR respectively.
    - When SD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
    - When SD is the best response for < 24 weeks the best overall response will be SD < 24 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
    - When non-target disease only and Non-CR/Non-PD is the best response for < 24 weeks the best overall response will be SD < 24 w.
    - When PD is the best response across all time points, best overall response will be PD.
    - When there is no evaluable tumor assessments best overall response will be NE.
- Unconfirmed Objective Response Rate (ORR) is defined as the proportion of patients with best overall response of unconfirmed CR or unconfirmed PR.
- Unconfirmed Clinical Benefit Rate (CBR) is defined as the proportion of patients with best overall response of unconfirmed CR or unconfirmed PR or SD ≥ 24 w.
- The confirmed Best Overall Response, defined as the best overall response recorded from the start of the study treatment until 35 days after last dose administration date and confirmation of response is required.
    - When CR or PR is the best response for ≥ 4 weeks then best overall response will be CR or PR respectively.
    - When SD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
    - When SD is the best response for < 24 weeks the best overall response will be SD < 24 w.

- When non-target disease only and Non-CR/Non-PD is the best response for ≥ 24 weeks the best overall response will be SD ≥ 24 w.
- When non-target disease only and Non-CR/Non-PD is the best response for < 24 weeks the best overall response will be SD < 24 w.
- When PD is the best response across all time points, best overall response will be PD.
- When there is no evaluable tumor assessments best overall response will be NE.

- Confirmed Objective Response Rate (ORR) is defined as the proportion of patients with best overall response of confirmed CR or confirmed PR.
- Confirmed Clinical Benefit Rate (CBR) is defined as the proportion of patients with best overall response of confirmed CR or confirmed PR or SD ≥ 24 w.
- The PFS is defined as the time from randomization until death by any cause or objective tumor progression or clinical disease progression, as assessed by investigator criteria. Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. Censoring rules are specified below:

Situation	**Date of progression or censoring**	**Outcome**
Progression documented between scheduled visits	Earliest of: • Date of assessment by investigator (if progression is based on clinical criteria); or • Date of assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).	Progressed
Death before first progression disease (PD) assessment	Date of death.	Progressed
Death between adequate assessment visits	Date of death.	Progressed
No progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions.	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions.	Censored
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions.	Censored

- The Overall Survival (OS) is defined as the time from start dose until death from any cause. Patients with no death will be censored on the last available follow-up date.
- The duration of response (DoR) is defined as the time from documentation of first tumor response (either CR or PR) to disease progression or death due to any cause. The DoR will be calculated for the participants with unconfirmed CR or PR.

- The duration of Clinical Benefit (DoCB) is defined as the time from documentation of first unconfirmed clinical benefit (either CR or PR or SD ≥ 24 w) to disease progression or death due to any cause. The DoCB will be only calculated for the participants with unconfirmed clinical benefit.
- The Time to Progression (TTP) is defined as the time from randomization to objective tumor progression or clinical disease progression (TTP does not include deaths). Patients with no progression will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.
- The Time to Response (TTR) is defined as the time from randomization to unconfirmed ORR date. Patients without ORR will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.
- Maximum Tumor Shrinkage (best percentage of change from baseline in the size of target tumor lesions) is defined as the biggest percentage of tumor shrinkage from baseline (obtained from the sum of the largest diameters of the target lesions), according RECIST v1.1.

5.5.2 Secondary Efficacy Analysis

Efficacy analysis will be reported in the FAS set and separately by the three study arms.

The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.

Kaplan-Meier plots and swimmer plots for time-to-event endpoints (PFS, TTR, DoR, and OS) will be provided. Number and proportion of events, median survival time, as well as the 1- and 2-year survival rates with corresponding 95% CI, will be calculated.

Maximum tumor shrinkage will be described with the median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions according to RECIST v.1.1 criteria will be provided.

Table 2. Secondary Efficacy Estimands

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Secondary 1	Full Analysis Set	PFS	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI
Sensitivity to secondary 1	Full Analysis Set	PFS by the 3 arms	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
			- If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	
Secondary 2	Full Analysis Set	TTR	- Patients with no response will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Sensitivity to secondary 2	Full Analysis Set	TTR by the 3 arms	- Patients with no response will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date.	Kaplan-Meier plot by arm, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Secondary 3	Full Analysis Set	ORR	- Patient with missing ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 3	Full Analysis Set	ORR by the 3 arms	- Patient with missing ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to supplementary of secondary 3	Full Analysis Set	ORR in patients with measurable disease	- Patient with missing ORR outcomes will considered as no responders. - Patients without any post-baseline assessment will be considered as non-responders.	The number and proportion of patients with response with the 95% Pearson-Clopper CI will be calculated.
Secondary 4	Full Analysis Set	CBR	- Patient with missing CBR outcomes will considered as no clinical benefit. - Patients without any post-baseline assessment will be considered as no clinical benefit. - Patients with a stable disease as best response and follow-up lower than 24 weeks will be considered as no clinical benefit.	The number and proportion of patients with clinical benefit with the 95% Pearson-Clopper CI will be calculated.
Sensitivity to secondary 4	Full Analysis Set	CBR by the 3 arms	- Patient with missing CBR outcomes will considered as no clinical benefit. - Patients without any post-baseline assessment will be considered as no clinical benefit.	The number and proportion of patients with clinical benefit with the 95% Pearson-Clopper CI will be calculated.

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
			- Patients with an stable disease as best response and follow-up lower than 24 week will be considered as no clinical benefit.	
Sensitivity to supplementary of secondary 4	Full Analysis Set	CBR in patients with measurable disease	- Patient with missing CBR outcomes will considered as no clinical benefit. - Patients without any post-baseline assessment will be considered as no clinical benefit. - Patients with a stable disease as best response and follow-up lower than 24 weeks will be considered as no clinical benefit.	The number and proportion of patients with clinical benefit with the 95% Pearson-Clopper CI will be calculated.
Secondary 5	Full Analysis Set	DoR	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-response tumor assessment is available, patients will be censored at the date of treatment response + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Sensitivity to secondary 5	Full Analysis Set	DoR by the 3 arms	- Patients with no progression or death will be censored at the date of their last evaluable imaging previous 35 days after last dose administration date. - If no post-response tumor assessment is available, patients will be censored at the date of treatment response + 1 day. - Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl
Secondary 6	Full Analysis Set	OS	- Patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% Cl

Estimand	Population	Variable	Intercurrent event strategy	Summary measure
Sensitivity to secondary 6	Full Analysis Set	OS by the 3 arms	- Patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. - If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day.	Kaplan-Meier plot, number and proportion of events, median survival time, 1- and 2-year survival rates with corresponding 95% CI
Secondary 7	Full Analysis Set	Maximum Tumor Shrinkage	Only observed cases will be used	Median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions
Sensitivity to secondary 7	Full Analysis Set	Maximum Tumor Shrinkage by the 3 arms	Only observed cases will be used	Median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions

5.5.3 Handling of Missing Efficacy Data

Study variables could be missing for patients who withdrawn from the trial or for specific visits. We will report reasons for withdrawal.

Patient with missing in response outcomes (ORR and CBR) will considered as no responders. Patients without any post-baseline assessment will be considered as non-responders or without clinical benefit.

For the analysis of maximum tumor shrinkage only observed cases will be used.

The analysis of timed endpoints is based on a Kaplan-Meier method (PFS, DoR, DoCB and OS), therefore, not affected by patient withdrawals (as they are censored) provided that dropping out is unrelated to prognosis.

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of treatment initiation + 1 day.

The other variables will be managed with simple imputations methods (last observation carried forward). The effect that any missing data might have on results will be assessed via sensitivity analysis.

5.5.4 Efficacy Endpoints by Baseline Characteristics

Subgroup efficacy analyses will be analyzed in Phase II patients included FAS.

PFS, ORR, and OS will be analyzed in patients' subgroups categorized based on baseline factors of potential prognostic value. The baseline factors will include but not limited to the following: (1) sex, (2) ECOG status, (3) Number of prior lines of endocrine therapy in ABC, (4) Prior treatment with targeted therapies (PI3K, CDK4/6, and mTOR inhibitors), (5) Prior treatment with chemotherapy, (6) Number of organs involved, (7) Visceral involvement, and (8) Notch pathway activation status.

The Cox proportional hazards model will be used to test the association between prognostic factors and the outcomes if sample size is adequate. Covariate estimates, hazard ratio and corresponding 95% CIs, applicable test statistics, and P-values will be presented. We will use the Breslow method for tie handling in survival analysis. P-values and 95% CIs for hazard ratio will be based on likelihood ratio test and profile likelihood confidence intervals.

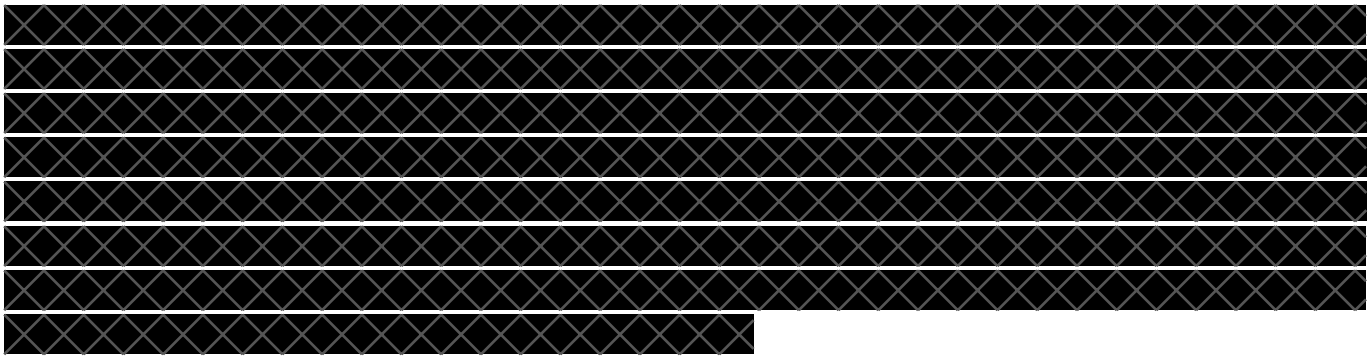
For binary outcomes we will use logistic regression for adjusting for multiple prognostic factors if sample size is adequate. Covariate estimates, odds ratios and corresponding 95% CIs and applicable test statistics, P-values will be presented. P-values and 95% CIs for odds ratio will be based on likelihood ratio test.

The MTS will be described (N, mean, median, standard deviation, minimum, and maximum) and analyzed based on Wilcoxon test. The use of multiple regression adjust by baseline factors will be deliberated.

The statistical analysis plan did not include a provision for correcting for multiplicity in tests for secondary and exploratory analyses. For all tests, we will use two-sided P-values with alpha ≤ 0.05 level of significance. The P-values emerging from these analyses will not be interpreted in a confirmative sense but will be considered of descriptive nature only.

5.6 Exploratory Analysis

These statistical analyses will be exploratory. Therefore, no pre-specified analyses are detailed in the SAP. Exploratory analyses will be performed on the exploratory analysis set.



5.7 Safety Analysis

Safety analysis will be reported in the safety set and separately by the three study arms.

5.7.1 Duration and Extent of Exposure

The study treatment period is defined as the time between the first and last dose of study combination therapy.

For ipatasertib the following parameters will be calculated:

- b: "Actual Cycle Duration" is the treatment duration for a cycle per CRF. It is the length of time (days) between actual and next cycle start date dose. At the last cycle is the difference between start and stop date dose.
- c: "Actual Cycle Dose Days" is the number of days with dose administration in the cycle, considering the interruptions.
- d: "Actual Total Dose per Cycle" is the total dose a patient took in a cycle, considering interruptions and reductions.
- e: "Intended Daily Dose per Cycle" is equal to 60 mg/m2 every 2 weeks.
- f: "Intended Cycle Duration" is equal to 14 days +/- 2 days.
- g: "Intended Cycle Dose Days" is equal to 1 day for all cycles.
- A: "Total number of cycles".
- B: "Treatment Duration" = Sum over all cycles of (b).
- C: "Days on drug" = Sum over all cycles of (c).
- D: "Total Actual Total Dose" = Sum over all cycles of (d).
- E: "Mean Intended Daily Dose" = Mean over all cycles of (e).
- F: "Total Intended Duration" = Sum over all cycles of (f).
- G: "Total Intended Dose Days" = Sum over all cycles of (g).
- H: "Intended Total Dose" = G*E
- I: "Actual Average Daily Dose on Dose Days" = D/C
- J: "Ratio for Dose Interruption" = C/G
- K: "Ratio for Cycle Duration" = F/B
- L: "Actual Average Daily Dose Intensity" = I*J*K
- M: "Relative Dose Intensity (RDI)" = L/E*100

The treatment duration (days), days on Drug and Treatment compliance (%) will be summarized in terms of the number of observations, mean, standard deviation (STD), median, minimum and maximum, to each treatment and both arms.

Extent of exposure measured as RDI will be described with median, interquartile range (IQR) and range. The RDI will be dichotomized in different cutoffs (≥50%, ≥70%, ≥80%, ≥90%, ≥100%) and described with frequencies and percentages.

5.7.2 Dose Delays, Reductions and Discontinuations

The following summaries will be provided by arm and treatment:

- Subjects with at least one dose delay.
- Subjects with at least one dose delay due to adverse event.
- Subjects with at least one dose reduction.
- Subjects with at least one dose reduction due to adverse event.
- Subjects with permanently dose discontinuation.
- Subjects with permanently dose discontinuation due to adverse event.

5.7.3 Concomitant Medications

The number and percent of unique patients taking concomitant medications will be summarized by therapeutic classification, coded term and dose level. Elective surgeries/procedures performed during the study will be presented in a listing.

The following are conventions that will be used to classify individual medications as prior and/or concomitant:

- Medications with stop dates prior to randomization will be considered prior.
- Medications with missing stop dates or stop dates the day of or after randomization will be considered concomitant, regardless of start date. Additionally, if the start date is prior to randomization or missing, the medication will also be considered prior.

Frequencies and by-subject listing of all prior and concomitant medications will be provided, containing variables listed on Prior/Concomitant Assessment eCRF, their corresponding categories (Prior or Concomitant), and WHO Anatomical Therapeutic Chemical (ATC) level 2 and preferred term if applicable.

5.7.4 Adverse Events

All AEs will be recorded on the eCRF "Adverse Events" page and will be coded using the current version of MedDRA® to give a system organ class (SOC) and preferred term (PT) for each event. All adverse event safety data will be updated to the version of MedDRA that is current at the time of the database lock and statistical analyses. Adverse events will be coded with grades defined according to CTCAE V4.0 criteria.

Treatment-emergent AEs (i.e. those events occur after the first study medication administration and were not present at baseline or worsened in severity following the start of treatment) will be tabulated. The TEAE will be tabulated according to intensity and causality. If intensity of an AE or causality of an AE to the study medication is missing, a worst-case scenario will prevail (severe in intensity or probably related will be assumed). In the summary tables the number of subjects with events and the number of events will be presented.

The onset date of an AE will be compared to the date of first dose of study drug to determine whether the AE is treatment emergent. Adverse events with an onset date on or after the date of first dose of study drug will be classified as treatment emergent.

All deaths and SAEs, regardless of cause, from treatment start until 28 days after final dose of treatment. Non-fatal AEs occurring after treatment start regardless of cause, up until 28 days after final dose of treatment or until start of new anti-cancer treatment, whichever is first. Disease progression is not

considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment. Events that are continuations of baseline abnormalities are considered treatment emergent adverse events only if there is an increase in grade over baseline, or if there is an increase following a decrease during the study.

Treatment emergent adverse events with cause possibly, probably, or definitely related to treatment as judged by the investigator. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be due to treatment.

Descriptive statistics will be used to characterize the profiles of treatment-related AEs, treatment-related deaths, SAEs, treatment-related delays, dose reductions, and/or treatment discontinuations. All AEs will be graded according to the current version of the NCI-CTCAE v.5 and the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be graded according to the NCI-CTCAE v.5. Additionally, treatment compliance, in particular dose reduction requirements, skipped doses and/or cycle delays due to AEs, will be described.

The following summaries will be provided:

- Summary of Adverse Events
    - Subjects with at least one Adverse Event (AE)
    - Subjects with at least one Treatment Emergent AE (TEAE)
    - Subjects with at least one related study drug TEAE
    - Subjects with at least one grade 3 or 4 or 5 TEAE
    - Subjects with at least one related grade 3 or 4 or 5 TEAE
    - Subjects with at least one serious TEAE
    - Subjects with at least one related serious TEAE
    - Subjects with at least one non-serious TEAE
    - Subjects with at least one Adverse Event of Special Interest (AESI)
    - Deaths due to TEAE
    - Subjects with TEAE leading to Discontinuation of Study Treatment
    - Subjects dropped out due to AE
- Summary by SOC and PT of the number and percentage of subjects reporting each:
    - Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events by Treatment and Haematologic
    - Treatment Emergent Adverse Event Related to Study Drug
    - Related Treatment Emergent Adverse Event by Treatment and Haematologic
    - AESI Treatment Emergent Adverse Events
    - Treatment Emergent Adverse Events with Grade 3 or 4 or 5
    - Related Treatment-Emergent Adverse Event with Grade 3 or 4 or 5
    - Serious Treatment Emergent Adverse Event

- Serious and Related Treatment Emergent Adverse Event
- Treatment Emergent Adverse Event by Maximum Severity
- Treatment Emergent Adverse Event Leading to Discontinuation of Study Drug

5.7.5 Clinical Laboratory Parameters

All hematology and biochemistry parameters will be presented by descriptive statistics in a tabulated summary by time point of assessment together with the respective changes from baseline. In addition, a frequency table of out-of-range values and clinically significant values will be presented by time point of assessment.

Table XX. Clinical Laboratory Parameters - Out of Range (Safety)

Parameter	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Parameter 1			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Parameter n			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table XX. Clinical Laboratory Parameters – Clinically Significant (Safety)

Parameter	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Parameter 1			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Parameter n			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table XX. Parameter n - Out of Range (Safety)

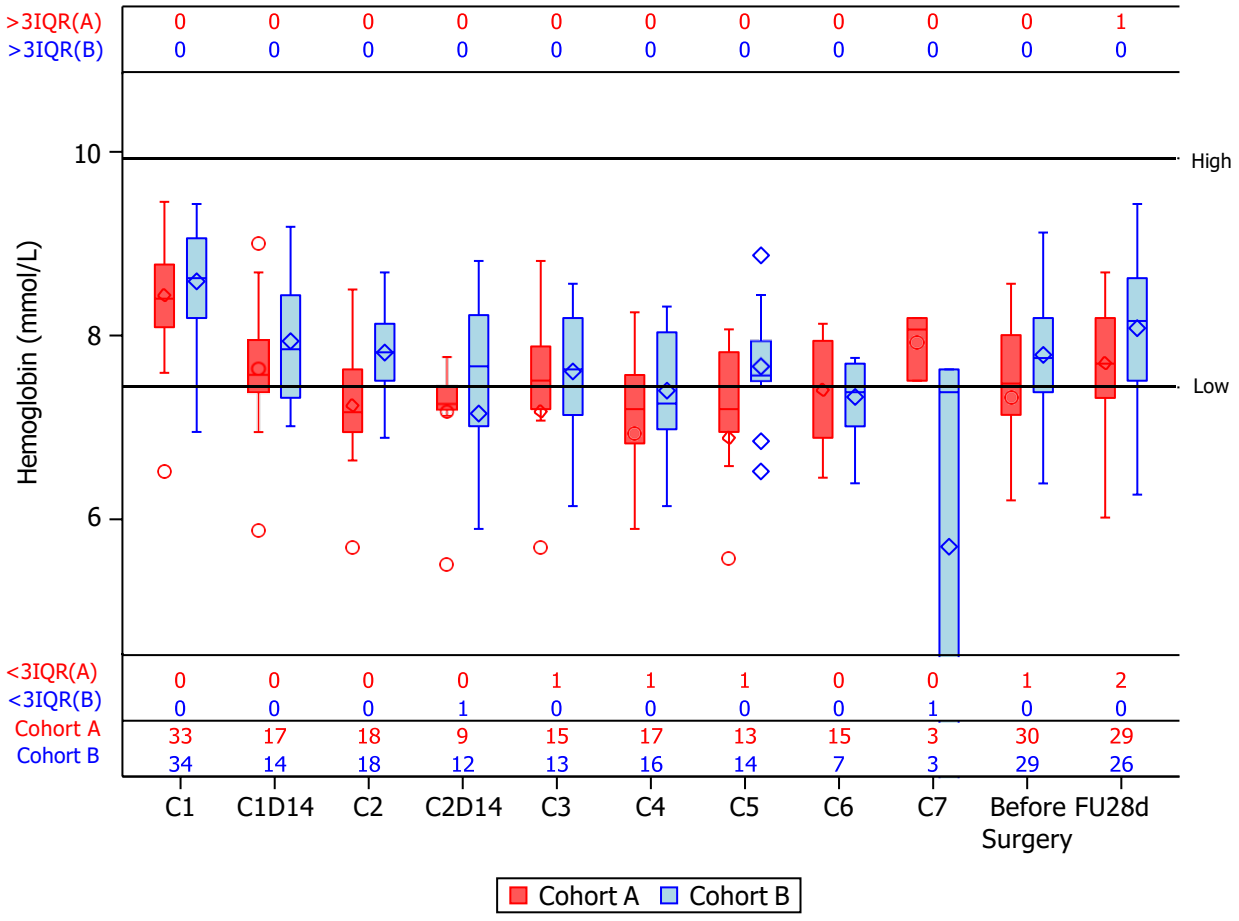
Visit	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Cycle n			n=xx	n=xx	n=xx	n=xx
	Low	Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Normal	Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	(xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		High	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	High	Low	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Normal	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		High	(xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table XX. Parameter n - Clinically Significant (Safety)

Visit	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Cycle n			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	(xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	(xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

The values of each parameter by cycle and arm will be displayed using a box plot. See example below.

Figure XX. Parameter n - Values distribution (Safety)



A by-subject listing for hematology and clinical chemistry will be provided. These listings will be presented by dose level and time point and will include center, subject identifier, laboratory parameter, parameter values (in SI units), SI unit, normal range and a flag with respect to normal range (below, within and above normal range).

5.7.6 Vital Signs

Weight, systolic and diastolic blood pressure, heart rate and respiratory rate will be presented by descriptive statistics in a tabulated summary by time point of assessment per arm group together with the respective changes from baseline.

In addition, frequency tables for the number of patients with increases or decreases from baseline in systolic/diastolic blood pressure of >20 mmHg and pulse rate of >15 bpm will be provided by time point of assessment and overall. A by-subject listing for all vital signs per dose level and time point will be provided.

5.7.7 Physical Examination

A frequency table per arm and cycle will be provided for assessment results of abnormal and clinically significant.

Table XX. Physical Examination - Abnormal (Safety)

Parameter	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Overall			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle 1			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle n			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table XX. Physical Examination - Clinically Significant (Safety)

Parameter	Baseline	Post-Baseline	Arm A (N=XX)	Arm B (N=XX)	Arm C N=XX)	Overall (N=XX)
Overall			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle 1			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Cycle n			n=xx	n=xx	n=xx	n=xx
	No	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
		Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

A by-subject listing for all body systems per dose level and time point will be provided. Only subjects with at least one abnormal finding will be included in this listing.

5.8 Run-in Phase Analysis

Run-In phase report will summarize descriptively the following results per treatment arm and dose cohort:

- Patient recruitment per site
- Subject disposition (flow chart)
- Patient characteristics
  - Age, median (range)
  - ECOG
  - Measurable or evaluable disease (Measurable, evaluable)
  - Visceral involvement (yes, no)
  - Brain metastases (yes, no)
  - Number of metastatic sites (yes, no)
  - Prior chemotherapy lines
  - Prior chemotherapy lines in advance disease
  - Previous treatment with PARP inhibitors (yes, no)
  - Previous treatment with immunotherapy (yes, no)
  - Previous treatment with androgen receptor antagonists (yes, no)
- Significant toxicities per treatment arm and dose cohort.

Treatment arm	Ipatasertib + capecitabine			Ipatasertib + eribulin			Ipatasertib + capecitabine + gemcitabine		
Significant toxicities, n(%)	**400 mg**	**(...)**	**All**	**400 mg**	**(...)**	**All**	**400 mg**	**(...)**	**All**
Yes									
No									

95% CI									

*If any significant toxicity a description of AE should be added in footnote or in other table (description, grade, duration, seriousness, relationship, and resolution).

- Adverse events of special interest (AESI) per treatment arm and dose cohort

Treatment arm	**Ipatasertib + capecitabine**			**Ipatasertib + eribulin**			**Ipatasertib + capecitabine + gemcitabine**		
Significant toxicities, n(%)	**400 mg**	**(…)**	**All**	**400 mg**	**(…)**	**All**	**400 mg**	**(…)**	**All**
Yes									
No									
95% CI									

*If any AESI is reported a description of AESI should be added in footnote or in other table (description, grade, duration, seriousness, relationship, and resolution).

- Relative dose intensity (RDI).
  - Relative dose intensity (%)
  - Total number of cycles
  - Treatment duration (days)
- Summary of TEAEs per treatment arm and dose cohort.
- TEAEs per treatment arm and dose cohort.
- TEAEs per treatment arm
- Serious TEAEs per treatment arm and dose cohort.
- Serious TEAEs per treatment arm.

5.9 Interim Analysis

Interim analysis report will summarize the following results per treatment arm:

- Subject disposition
- Baseline characteristics
- Primary safety analysis
- Duration and Extent of exposure (RDI)
- Dose Delays, Reductions and Discontinuations
- Adverse events

No statistical tests are planned for these data.

5.10 Changes of Analysis from Protocol

No changes of the statistical methods specified from protocol.

5.11 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

6 APPENDIX

6.1 Appendix 1 - SAS Codes

All report outputs will be produced using SAS® version 9.4 (TS1M5) version in a secure and validated environment.

The number and the proportion of patients with significant toxicities in each arm and dosing schedule will be described. Confidence intervals (CIs) will be calculated, according to Clopper-Pearson (exact binomial intervals).

```
proc freq data=SAFETY;
  tables TOXICITY * ARM * DOSE / binomial(exact) alpha=.05;
  title 'Incidence of Significant Toxicities (SAFETY Set)';
run;
```

6.2 Appendix 2 - List of Tables, Listings, Figures

A complete list of tables, listings and figures (TLFs) will be given in a separate document which can be updated without updating the SAP. The list will serve as a reference for both the Sponsor, the trial statistician and the statistical programmer and includes the totality of statistical output to be produced.

All output will be headed with an appropriate heading specifying the study ID and abbreviated study title.

All output will be dated and have page numbers in the form 'Page [x / y]' where x denotes the current page within an output and y the total number of pages of that output.

All statistical output will identify the underlying analysis sets and indicate the number of patients/events in this set (N) and the number of patient/events actuals contributing to the output (n). All statistical output will be presented per treatment (if applicable).

All patient listings will contain additionally to the patient identification the analysis set and the treatment.