Official Title: A Phase Ib, Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Ipatasertib in Combination With Rucaparib in Patients With Advanced Breast, Ovarian, or Prostate Cancer

NCT Number: NCT03840200

Document Date: Protocol Version 2: 09-Nov-2018

PROTOCOL

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH RUCAPARIB IN PATIENTS WITH ADVANCED BREAST, OVARIAN, OR PROSTATE CANCER**
PROTOCOL NUMBER:	BO40933
VERSION NUMBER:	2
EUDRACT NUMBER:	2018-003293-27
IND NUMBER:	130663
TEST PRODUCTS:	Ipatasertib (RO5532961); Rucaparib (CO-338)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 23 August 2018
DATE AMENDED:	Version 2: See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Nov-2018 16:10:20

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol BO40933 has been amended to modify the hyperglycemia management plan associated with ipatasertib according to fasting glucose levels. In addition, the protocol has been amended to reflect updated safety and efficacy information related to rucaparib. Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.1.1 has been updated with the rationale for including patients with ovarian clear cell carcinoma.
- Section 1.1.3 has been modified to include recent data showing the benefit of rucaparib monotherapy in selected patients with prostate cancer.
- Section 1.2.2 has been updated to include all approved indications for rucaparib in ovarian cancer and to provide updated data on rucaparib treatment in prostate cancer.
- Section 2.2.3 has been revised to remove the clinical benefit rate from the list of efficacy surrogates to be compared with PI3K pathway alterations as it does not bring additional value compared with the objective response rate. In addition, this section has been updated to reflect analysis of exploratory efficacy analysis in a subgroup of patients with prostate cancer with *BRCA1* and *BRCA2* mutations.
- Section 3.1.2 has been updated to clarify the definition of dose-limiting toxicities related to ALT and AST elevations.
- Section 3.2 has been revised to clarify the definition of the end of study.
- Section 4.1.1 has been updated to allow enrollment of patients with platinum-resistant ovarian cancer and clear cell ovarian cancer as these patients have high unmet medical need and may benefit from this novel combination. In addition, the minimum number of slides submitted for tumor tissue analysis has been increased from 10 to 12 slides to improve the yield of biomarker data and to strengthen the exploratory efficacy analyses.
- Section 4.3.2.2 has been amended to state that rucaparib may be taken with or without food which is consistent with the Rucaparib Investigator's Brochure.
- Section 4.4.1 has aligned the contraceptive language with the Rucaparib Investigator's Brochure.
- Section 4.3.1.1, Table 2, has been modified to correct the number of ipatasertib tablets supplied to all patients participating in Study BO40933.
- Section 4.3.1.2, Table 4, has been updated to include the possibility that patients receiving the 600-mg dose of rucaparib may receive three 200-mg tablets or two 300-mg tablets.
- Sections 5.1.1 and 5.1.2 were updated for consistency with the identified risks and reported adverse events in the current version of the Rucaparib Investigator's Brochure.

- Section 5.1.4.4, Table 6, has been revised to replace any reference to hyperglycemia grading according to fasting glucose levels in the recommendations for the management of hyperglycemia.
- Section 5.1.4.6 has been revised to describe photosensitivity related to rucaparib and provide recommendation for prevention consistent with guidance in the Rucaparib Investigator's Brochure.
- Section 5.1.4.8, Table 10, has been updated to be consistent with National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5, for hepatotoxicity.
- Section 5.4.3.3 has been amended regarding the reporting of spontaneous abortions and therapeutic or elective abortions performed because of an underlying maternal or embryofetal toxicity as serious adverse events.
- Section 6.6 and Appendix 2 have been updated for additional pharmacokinetic assessments to better define potential drug–drug interactions between ipatasertib and rucaparib.
- Section 10, References, has been revised.
- An error with a sampling timepoint in Appendix 2 has been corrected. The Cycle 1, Day 1 timepoint has been revised to Cycle 1, Day –7. A clarification has also been added in the footnote that the PK sample is for analysis of coproporphyrin I (CPI) and CPIII levels at baseline as described in Section 3.3.4.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH RUCAPARIB IN PATIENTS WITH ADVANCED BREAST, OVARIAN, OR PROSTATE CANCER**
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SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH RUCAPARIB IN PATIENTS WITH ADVANCED BREAST, OVARIAN, OR PROSTATE CANCER**
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IND NUMBER:	130663
TEST PRODUCT:	Ipatasertib (RO5532961); Rucaparib (CO-338)
PHASE:	Phase Ib
INDICATION:	Advanced breast, ovarian, or prostate cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, efficacy, and pharmacokinetics of ipatasertib administered in combination with rucaparib in patients with advanced breast, ovarian cancer, and prostate cancer. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol "study treatment" refers to ipatasertib, rucaparib, and the combination of both assigned to patients as part of this study.

Primary Safety Objective

The safety objective for this study is to evaluate the safety of ipatasertib administered in combination with rucaparib on the basis of the following endpoints:

- To identify a recommended Phase II dose and schedule for ipatasertib and rucaparib combination
- Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence and nature of dose-limiting toxicities (DLTs) that determine the maximum-tolerated dose (MTD) of the ipatasertib and rucaparib combination

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ipatasertib administered in combination with rucaparib in patients with prostate cancer on the basis of the following endpoint:

- Prostate-specific antigen (PSA) response, defined as the proportion of patients with a reduction in the PSA level of 50% or more

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ipatasertib administered in combination with rucaparib in patients with prostate cancer on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v.1.1)
- Duration of objective response (DOR)
- rPFS by Prostate Cancer Working Group 3 (PCWG3) criteria
- *Overall survival* (OS)

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is as follows:

- To evaluate the potential relationship between the presence of ***PI3K-AKT*** *or HR* pathway alterations (e.g., ***PTEN*** loss by immunohistochemistry [IHC], ***PIK3CA/AKT1/PTEN*** *or BRCA1/BRCA2*-altered *status* by next-generation sequencing [NGS]) and the anti-tumor activity of ipatasertib in combination with rucaparib in patients with prostate cancer on the basis of the following endpoints:
  - PSA response rate
  - ORR
  - DOR
  - rPFS
  - OS

Pharmacokinetic Objectives

The *pharmacokinetic* (PK) objective for this study is as follows:

- To characterize the *PK* profile of ipatasertib, its metabolite G-037720, and rucaparib, when administered in combination, on the basis of the plasma concentration of ipatasertib and rucaparib at specified timepoints

Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To evaluate possible predictive and prognostic biomarkers in the tissue and plasma based on the following endpoint:
  - Exploration of possible relationships between the tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., rPFS)
- To evaluate pharmacodynamic effects of ipatasertib and the combination of ipatasertib with rucaparib in the tissue based on the following endpoint:
  - Changes in molecular biomarkers in pretreatment and on-treatment tumor tissues
- To identify possible mechanisms of resistance to the study treatments through the comparative analysis of potential biomarkers in the blood based on the following endpoint:
  - Changes in molecular biomarkers in pretreatment and post-progression plasma and blood samples

Study Design

Description of Study

This is a Phase Ib, open-label, non-randomized study in patients with advanced breast, ovarian, or prostate cancer to investigate the dose, safety, pharmacokinetics, and preliminary efficacy of ipatasertib in combination with rucaparib.

The study consists of two parts: a Dose-Escalation Phase (Part 1) in patients with previously treated advanced breast cancer, ovarian cancer, or prostate cancer and a Dose-Expansion Phase (Part 2) in patients with advanced prostate cancer who have had at least one line of prior therapy with second-generation androgen-receptor (AR)-targeted agents (e.g., abiraterone, enzalutamide, apalutamide).

Patients must have fresh or archival tumor tissue samples available for submission for biomarker analyses for IHC (e.g., ***PTEN*** loss) and NGS methodologies (e.g., ***PIK3CA/AKT1***/PTEN *or BRCA1/BRCA2*-altered status).

Dose-Escalation Phase (Part 1)

The Dose-Escalation Phase, Part 1, will determine the recommended dose of ipatasertib in combination with rucaparib in patients with advanced breast, ovarian, or prostate cancers. There will be a 7-day run-in period with ipatasertib alone prior to Cycle 1, Day 1 *to allow for PK assessment of ipatasertib monotherapy versus that in combination with rucaparib.* After the completion of the ipatasertib run-in period, patients will begin Cycle 1, Day 1 of the ipatasertib and rucaparib combination treatment.

Two dose levels of rucaparib administered orally (PO) BID will be evaluated with two dose levels of ipatasertib in 28-day cycles. There will be approximately 6 patients per dose level. The highest dose level of each agent with an acceptable safety profile and with a minimum of 6 patients, at which, less than one-third of patients experience a DLT, will be declared the recommended Phase II dose (RP2D). Preliminary assessment of the anti-tumor activity and biomarkers of response or resistance to combined ipatasertib and rucaparib will also be conducted in Part 1.

All patients will continue to receive study treatment until disease progression (according to RECIST v1.1 *for breast and ovarian cancer* or PCWG3 criteria *for prostate cancer*), unacceptable toxicity, death, or patient or investigator decision to withdraw, whichever occurs first.

Dose-Expansion Phase (Part 2)

In the Dose-Expansion Phase, Part 2, the potential RP2D of combined ipatasertib and rucaparib *identified* in Part 1 will be further evaluated for safety, pharmacokinetics, and preliminary efficacy in patients with advanced prostate cancer who have been treated with at least one line of second-generation androgen-receptor targeted therapy. There will be no run-in phase for the ipatasertib monotherapy. Approximately 30 patients will be enrolled, of *whom* approximately 70% are expected to have HR-intact tumors, and approximately 50% are expected to have *PTEN*-loss tumors based on the prevalence previously described in castration-resistant prostate cancer (CRPC). Enrollment may be extended to ensure at least 15 patients with HR-intact features are enrolled. A patient with a homologous recombination (HR)-deficient tumor is considered a patient with one of the following molecular features defined by the FoundationOne NGS assay:

- *Deleterious* alteration in *at least* one of the following genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*

Mandatory archival or fresh tissue will be collected at the time of enrollment and optional fresh tumor biopsies on study treatment will be collected. *In addition, plasma and blood samples may be analyzed for deleterious alterations and further classification of mutational status.*

All patients will continue to receive study treatment until disease progression (according to RECIST v1.1 or PCWG3 criteria), unacceptable toxicity, death, or patient or investigator decision to withdraw, whichever occurs first.

Number of Patients

Approximately 54 patients will be enrolled in this study: approximately 24 patients will be enrolled in Part 1 (Dose-Escalation Phase) and approximately 30 patients will be enrolled in Part 2 (Dose-Expansion Phase).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- A life expectancy of at least 3 months
- Ability to swallow oral study drug
- Have adequate organ and marrow function as confirmed by the laboratory values listed below, obtained within 28 days prior to the first dose of study treatment

Bone marrow function assessments (without transfusion within 28 days prior to receipt of study treatment)

- ANC $\geq$ 1500 cells/μL (1.5×10^9/L) without granulocyte-colony stimulating factor support
- Platelet count $\geq 100.0 \times 10^9$/L
- Hemoglobin $\geq$ 9 g/dL (or 5.6 mmol/L)

Chemistry panel assessments

- AST and ALT $\leq 1.5 \times$ upper limit of normal (ULN); if liver metastases, $\leq 2.5 \times$ ULN
- Bilirubin $\leq 1.5 \times$ ULN ($\leq 3 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome)
- Serum albumin $\geq$ 3.0 g/dL
- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min
- Fasting glucose $\leq$ 150 mg/dL and hemoglobin $A_{1c} \leq$ 7.5%

- Resolved or stabilized toxicities resulting from previous therapy to Grade 1 (except for alopecia and neuropathy).

  An ongoing, Grade 2, non-hematologic toxicity related to the most recent treatment regimen may be permitted with approval from the Medical Monitor

Cancer-Related Inclusion Criteria

- Have a histologically confirmed diagnosis of ovarian (Part 1 only), breast (Part 1 only) or prostate cancer (Part 1 and Part 2)
- Disease must be either metastatic or locally advanced disease that cannot be treated with curative intent
- For patients with ovarian cancer (Part 1 only):
  - High-grade (2 or 3) serous or endometrioid *or clear cell* epithelial ovarian, fallopian tube, or primary peritoneal cancer (PPC)

    If the tumor is of mixed histology, $>$ 50% of the primary tumor must be confirmed to be high-grade serous, endometrioid, *or clear cell*.
  - Must have received at least one prior platinum-based therapy and *may* have platinum-sensitive disease (i.e., documented radiologic disease progression $\geq$ 6 months following the last dose of the platinum treatment administered) *or platinum-resistant disease*
  - Have a CA-125 level that is $> 2 \times$ ULN
  - Must have measurable disease by RECIST v1.1
- For patients with breast cancer (Part 1 only): must be human epidermal growth factor receptor 2 negative (HER2–) (estrogen receptor [ER]/progesterone positive or negative)
  - ER/progesterone-positive patients must have received and progressed on at least one endocrine therapy (adjuvant or metastatic)
  - ER/progesterone-negative/HER2– (triple-negative breast cancer [TNBC]) patients must have received at least one prior line of chemotherapy for metastatic breast cancer
  - Must not have received more than two prior lines of chemotherapy for metastatic breast cancer
  - Must have measurable disease by RECIST v1.1
- For patients with prostate cancer:
  - Adenocarcinoma of the prostate without small cell or neuroendocrine features
  - Surgical or medical castration with testosterone $<$ 50 ng/dL (1.7 nM)
  - Patients treated with luteinizing hormone-releasing hormone *analogs* must have initiated therapy at least 4 weeks prior to the first dose of study treatment and continue throughout the study treatment

- Progression of prostate cancer either via PSA progression (two rising PSA levels measured ≥ 1 week apart, with second result ≥ 1 ng/mL) or radiographic progression with or without PSA progression
- Must have received at least one prior line of second-generation androgen receptor targeted therapy (e.g., abiraterone, enzalutamide, apalutamide)
- Patients with prostate cancer must have either measurable disease by RECIST v1.1 or bone lesions by bone scan, or both.

- Submission of a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of *12* freshly cut, unstained, serial tumor slides from the most recently collected tumor tissue for central molecular analysis (retrospective NGS testing for HR and *PI3K-AKT* pathway status and for other protocol-mandated secondary and exploratory assessments). Cytologic or fine needle aspirate samples are not acceptable. Tumor tissue from bone metastases is not acceptable.
  - If the specimen is either insufficient or unavailable, the patient may still be eligible if the patient is willing to consent to and undergo an additional pretreatment core or excisional biopsy of the non-target lesion (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.
- For women of childbearing potential: *be* abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must *be* abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the final dose of ipatasertib or 6 months after the last dose of rucaparib, whichever occurs later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of progesterone-only injectable or implantable contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: *be* abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must *be* abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 28 days after the last dose of ipatasertib or for 6 months after last dose of rucaparib whichever occurs later. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must *be* abstinent or use a condom during the treatment period and for 28 days after the last dose of ipatasertib or rucaparib to avoid exposing the embryo.

  Examples of contraceptive methods with a failure rate of < 1% per year, when used consistently and correctly, include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone releasing system, and sexual abstinence.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of ipatasertib or 6 months after the final dose of rucaparib

  Women of childbearing potential must have a negative serum pregnancy test result within 3 days prior to initiation of study drug.
- Prior treatment with a PARP inhibitor, *AKT* inhibitor, or *PI3K* inhibitor
- Treatment with investigational therapy within 14 days prior to initiation of study drug
- Symptomatic and/or untreated CNS metastases

  Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.

  Patients with leptomeningeal carcinomatosis will be excluded.
- Uncontrolled tumor-related pain

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization. Patients should be recovered (e.g., to Grade 1 or resolved) from the effects of radiation prior to study enrollment. There is no required minimum recovery period beyond the 7 days required for radiation therapy.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization.
- Non–study-related minor surgical procedures $\leq$ 5 days or major (invasive) surgical procedure $\leq$ 14 days prior to first dose of study treatment

  Patient must be sufficiently recovered from surgery and stable, and wound healing must have occurred.
- Patients with active hepatitis C virus (HCV)

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test or a positive quantitative HBV DNA test

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test, a quantitative HBV DNA test must be performed.

  Patients receiving anti-viral therapy for HBV are not eligible.
- Known HIV infection
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Serious infection requiring antibiotics within 14 days of first dose of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Need for chronic corticosteroid therapy of $\geq$ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

- History of another malignancy within 5 years prior to randomization, except for either adequately treated non-melanomatous carcinoma of the skin, adequately treated melanoma in situ, adequately treated non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta, and low-grade T1 tumors), or other malignancies where the patient has undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to have a recurrence rate of $<5\%$ at 5 years.
- History of clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to enrollment
  - History of myocardial infarction within 6 months prior to first dose of study drug
  - New York Heart Association Class III or IV cardiac disease
  - Unstable arrhythmias or unstable angina
- Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study

Ipatasertib-Specific Exclusion Criteria

Patients who meet any of the following criteria specific to ipatasertib will be excluded from study entry:

- Type 1 or Type 2 diabetes mellitus requiring insulin at study entry

  However, patients who are on a stable dose of oral diabetes medication ≥ 4 weeks prior to initiation of study treatment may be eligible for enrollment. Patients must meet the laboratory eligibility criteria for fasting blood glucose and hemoglobin A_{1c} as outlined in the inclusion criteria.
- History of inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis), active bowel inflammation (e.g., diverticulitis)
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 4 weeks or five elimination half-live of the inhibitors, whichever is longer, prior to initiation of study drug

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical *efficacy* analysis or safety follow-up is received from the last patient, whichever occurs later.

For an individual patient, the last visit is defined as the end of treatment visit or the time of disease progression whichever occurs the last.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 36 months.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are ipatasertib (RO5532961) and rucaparib (CO-338). The dose levels of ipatasertib and rucaparib to be used in this study are as follows:

- Dose Level 1: 300 mg ipatasertib once daily (QD) + 400 mg rucaparib twice daily (BID)
- Dose Level 2a: 300 mg ipatasertib QD + 600 mg rucaparib BID
- Dose Level 2b: 400 mg ipatasertib QD + 400 mg rucaparib BID
- Dose Level 3: 400 mg ipatasertib QD + 600 mg rucaparib BID

Both IMPs will be administered orally (tablets).

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Primary Analysis

The safety analyses will include all patients who received at least one dose of any study drug, and will be analyzed and summarized separately for the Part 1 and Part 2; data will not be combined across phases.

Adverse events, deaths, change in laboratory test results, change in vital signs, and exposure to components of study treatment will be assessed to determine the safety of treatment regimen.

For safety-evaluable patients, study drug administration data will be tabulated or listed by arm, and any dose modifications will be flagged. Descriptive statistics will be used to summarize the total dose of ipatasertib and rucaparib received.

Verbatim descriptions of adverse events will be mapped to appropriate thesaurus terms. All adverse events occurring on or after treatment Day 1 will be summarized by the mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade. In addition, adverse events leading to treatment withdrawal or death, and serious adverse events will be listed with more detailed information, such as the day of onset of an adverse event, duration of adverse event, toxicity grade, and so on.

Relevant laboratory and vital signs (heart rate, blood pressure, and temperature) and ECG data will be displayed by time post-dose, with NCI CTCAE Grade 3 and 4 values identified where appropriate. Additionally, changes in laboratory data will be summarized by grade using the NCI CTCAE toxicity grade. Selected vital signs and selected laboratory data will be summarized by visit.

The extent of study drug exposure (dose and duration) will be examined to determine the degree of treatment tolerability. In addition to study treatment duration and total dose received, any dose modification of study drugs will also be summarized.

Determination of Sample Size

There is no formal hypothesis testing planned. The determination of sample size for each part is described below.

For Part 1 (Dose-Escalation Phase), approximately 24 patients are planned to be enrolled based on the dose-escalation rules.

For Part 2 (Dose-Expansion Phase), approximately 30 patients with advanced prostate cancer who have had at least one line of prior therapy with second-generation AR-receptor targeted agents (e.g., abiraterone, enzalutamide, apalutamide) are planned to be enrolled. No formal statistical hypothesis testing is planned. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary endpoint of PSA response rate, the analyses will be based on patients enrolled in Part 2. Thirty patients provide reasonably reliable estimates for hypothesis generation.

Interim Analyses

An interim analysis for safety (including DLTs) will be performed by the Sponsor prior to dose expansion (Part 2)

Given the hypothesis-generating nature of this study, the Sponsor may conduct an interim analysis of efficacy in Part 2. The decision to conduct such an interim analysis and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The Clinical Study Report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed and interpreted by members of Roche's study team and management.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
aCGH	array comparative genome hybridization
ADP	adenosine diphosphate
AKT	*protein kinase B*
AR	androgen receptor
AUC_{0-t}	area under the concentration–time curve from Time 0 to Time t
BID	twice daily
BRCA1 (2)	*breast cancer gene 1 (2)*
C_{max}	maximum plasma concentration
CP I (III)	*coproporphyrin I (III)*
CR	complete response
CRO	contract research organization
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOC	epithelial ovarian cancer
ER	estrogen receptor
ET	endocrine therapy
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FMI	Foundation Medicine, Inc.
g	germline
GCIG	Gynecologic Cancer InterGroup
HbA_{1c}	*hemoglobin* A_{1c}
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2 negative
HIPAA	Health Insurance Portability and Accountability Act
HR+	hormone receptor positive
HR	homologous recombination
ICH	International Council for Harmonisation
ICR	Immunologic Constant of Rejection
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
LFT	liver function test
mCRPC	metastatic castration-resistant prostate cancer
mPFS	median progressive-free survival
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NGS	next-generation sequencing
OATP	organic-anion-transporting polypeptide
ORR	objective response rate
OS	overall survival
PARP	poly (adenosine diphosphate ribose) polymerase
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD-L1	programmed death–ligand 1
PFT	pulmonary function test
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PO	orally
popPK	population pharmacokinetic
PPC	primary peritoneal cancer
PR	partial response

Abbreviation	Definition
PSA	prostate-specific antigen
PTEN	phosphatase and tensin homolog
QD	once daily
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
rPFS	radiographic progression-free survival
s	somatic
SD	stable disease
T_{max}	time to maximum concentration
TNBC	triple-negative breast cancer
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON OVARIAN, BREAST, AND PROSTATE CANCER

1.1.1 Background on Ovarian Cancer

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer (Morgan et al. 2011; U.S. Cancer Statistics Working Group 2013). Globally, epithelial ovarian cancer (EOC) affects 238,719 women annually and results in 140,200 cancer-related deaths, with an annual incidence of 65,584. EOC, fallopian tube cancer, and primary peritoneal cancer comprise tumors of Müllerian origin. They share common clinical and biological behavior and are typically grouped together in treatment paradigms and clinical investigations (Levanon et al. 2008; Salvador et al. 2008; Flesken-Nikitin et al. 2013).

The standard of care for ovarian cancer at initial diagnosis includes primary tumor reduction surgery, followed by platinum (carboplatin) and taxane (paclitaxel) systemic chemotherapy and bevacizumab (McGuire et al. 1996; Piccart et al. 2000; Ozols et al. 2003; Ledermann et al. 2013; Burger et al. 2018). After initial therapy, most women with advanced disease will have a progression-free interval of approximately 1.5–2 years, depending on the extent of post-operative residual disease and response to chemotherapy (Cannistra 2004). Relapse following initial treatment is common and only 10%–30% of women experience long-term survival (Cannistra 2004).

The choice of treatment for relapsed disease is based on the treatment-free interval relative to the last therapy administered and chemotherapy agents used. As many patients experience multiple relapses, prognosis and response to therapy decrease as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free interval, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to platinum-based therapy.

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor monotherapy has elicited objective responses in patients with platinum-sensitive disease, as well as in patients with platinum-resistant disease. However, response rates are higher in the former population (Gelmon et al. 2011; Kaye et al. 2012; Sandhu et al. 2013). Although initially PARP inhibitors were thought to be active only in *BRCA-mutated* tumors, more recent studies have shown that their efficacy can be extended to include a larger group of ovarian cancer *patients with BRCA wild-type tumors* (Mirza et al. 2016; Coleman et al. 2017; Swisher et al. 2017).

The phosphoinositide 3-kinase (*PI3K*)-*AKT* pathway is frequently deregulated in ovarian cancer. Array comparative genomic hybridization (aCGH) studies have identified this pathway as the most frequently altered in ovarian cancer (Huang et al. 2011). *In particular, this pathway is dysregulated in 30%–40% of ovarian clear cell carcinoma, which is an*

aggressive subtype. Inhibitors of this pathway continue to be evaluated in ovarian cancer although currently none are approved for this indication (Gasparri et al. 2017).

1.1.2 Background on Breast Cancer

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 1.67 million new cases reported in 2012 (Ferlay et al. 2013). It accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths. Breast cancer is a genetically heterogeneous and biologically diverse disease that can be clinically subdivided into subgroups that guide therapeutic intervention, which is based on the expression of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2). Triple-negative breast cancer (TNBC) accounts for about 20% of breast cancers diagnosed worldwide. Patients with metastatic TNBC exhibit a particularly poor clinical outcome, generally with rapid progression and a median overall survival (OS) rate of approximately 16 months (Rodler et al. 2010). Although TNBC may respond to chemotherapy, including taxanes, there are no approved first-line regimens for patients with this specific subtype of breast cancer. While olaparib is the first targeted-therapy approved for this subtype, it is limited to patients with germline mutations in *BRCA*. Hormone receptor positive (HR+)/HER2-negative (HER2−) breast cancer (hereafter referred to as HR+ breast cancer) accounts for over 70% of all breast cancer subtypes. Patients with metastatic HR+ breast cancer may be treated with endocrine therapy (ET), either alone or in combination with a targeted therapy such as CDK4/6 inhibitor or mammalian target of rapamycin (mTOR inhibitor), or with chemotherapy.

Approximately 5% of unselected patients with breast cancer carry a germline *BRCA* mutation (Kurian et al. 2009) and such mutations are more likely to be present in patients with a strong family history of breast cancer and patients who have TNBC (Mavaddat et al. 2012). In a recent study of olaparib versus chemotherapy in HER2− patients with germline *BRCA* mutations, median progression-free survival (mPFS) was significantly longer in the olaparib group than in the chemotherapy group (Robson et al. 2017). Activity in patients without germline mutations is still being evaluated.

Overall, *PIK3CA/AKT1/PTEN*-altered tumors are frequently observed in breast cancer, and are reported in approximately 35% of TNBC patients and in approximately 50% of HR+/HER2− breast cancers (Cancer Genome Atlas Network 2012). To date, the relationship between *PI3K-AKT* pathway activation and prognosis in early breast cancer is mixed, with some data demonstrating association with favorable outcomes, some data with poor prognosis, and a number of studies showing insignificant results (Yang et al. 2016). Information demonstrating significant differences in the prevalence of these gene alterations between primary and metastatic tumor tissues is limited, while enrichment in metastatic patients is probable (Millis et al. 2015). For patients with metastatic HR+/HER2− breast cancer, everolimus (a mTOR inhibitor) in combination with exemestane is an approved therapy during the endocrine-sensitive phase of disease

(Baselga et al. 2012). Other inhibitors of this pathway are being actively explored in both HR+/HER2− breast cancer and TNBC (Dey et al. 2017).

1.1.3 Background on Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of death in men in the Western world (Ferlay et al. 2015). Although most men are diagnosed with localized disease, progression to metastatic disease of the bones and visceral organs leads to significant morbidity and mortality (Logothetis et al. 2012; Basch et al. 2014). In the United States, prostate cancer is the most common non-skin cancer diagnosed, with over 180,890 new cases and 26,120 deaths (American Cancer Society 2016). Likewise, in Europe, prostate cancer leads male cancer diagnoses with approximately 417,000 new cases, and 92,000 deaths (Ferlay et al. 2013).

Androgen deprivation therapy constitutes the mainstay of treatment for advanced prostate cancer. Two novel androgen-receptor (AR) targeting agents, abiraterone, and enzalutamide have had a significant impact in changing the treatment landscape of prostate cancer. Both agents initially showed overall survival benefit in men with castration-resistant prostate cancer (CRPC) following progression on docetaxel chemotherapy (de Bono et al. 2011; Scher et al. 2012). Subsequently both agents demonstrated improvement in radiographic progression free survival (rPFS) and OS when used as front-line therapy for males with metastatic CRPC (mCRPC) and who had minimal or no symptoms and no prior chemotherapy (Ryan et al. 2013; Beer et al. 2014). Abiraterone has also demonstrated survival benefit in an earlier disease state, hormone sensitive prostate cancer (Fizazi et al. 2017), and enzalutamide and apalutamide have demonstrated metastasis-free survival benefit in nonmetastatic CRPC (Smith et al. 2018; Hussain et al. 2018).

As these agents are being used in earlier disease states, there is a high unmet need in patients who have disease progression on novel AR-targeting agents. Cross-resistance occurs between the abiraterone and enzalutamide; the rate of response to abiraterone therapy after treatment with enzalutamide is less than 10%, whereas the response rate for enzalutamide after abiraterone is 15-30% (Smith et al. 2017; Noonan et al. 2013; Schrader et al. 2014). The benefit of taxanes appears to be diminished after treatment with abiraterone or enzalutamide, as compared with benefit in patients who have not received such treatments, although taxanes remain active (de Bono et al. 2017). Novel therapies for these patients are needed.

Olaparib has demonstrated strong signal for anti-tumor activity in patients with somatic and germline homologous recombination (HR) repair defects (HR-deficient) (Mateo et al. 2015). Patients without homologous HR defects (HR-intact) had minimal benefit from olaparib monotherapy. Early data from a combination of olaparib and durvalumab similarly showed benefit largely limited to patients with HR-deficient tumors (Karzai abstract GU ASCO 2018). Olaparib in combination with abiraterone has also been reported showing potential benefit in an all-comer population although tumor was

evaluable for HR-status in only 27% of patients (Clarke et al. 2018). *Rucaparib has received breakthrough designation by the U.S. Food and Drug Administration (FDA) in 2018 based on results from the TRITON2 study, which showed significant single-agent disease activity of rucaparib in patients with metastatic CRPC with BRCA1 and BRCA2 germline or somatic mutations (Abida et al. 2018).*

Other treatments with novel mechanisms of action, such as *PI3K* inhibitors, may also have a role in the future treatment landscape of prostate cancer. The *PI3K-AKT* pathway is one of the most frequently activated pathways in prostate cancer, with genomic alterations occurring in approximately 50% of cases with genetic loss of phosphatase and tensin homolog (*PTEN*) as the most common cause (Robinson et al. 2015). Deregulation of this pathway results in activation of downstream targets (e.g., PRAS40, mTOR, GSK3b, FOXO, etc.) involved in survival, proliferation, cell-cycle progression, growth, migration, and angiogenesis (Yuan and Cantley 2008). Activation of the *PI3K-AKT* pathway is physiologically relevant as it compensates for AR downregulation and provides a means for receptor blockade escape; in a similarly reciprocal manner, blockade of the *PI3K-AKT* pathway leads to increased stability and activity of the AR, demonstrating the cooperative action of both pathways to enable prostate cancer progression (Carver et al. 2011; Mulholland et al. 2011).

Clinical studies have consistently demonstrated that low *PTEN* expression and *PTEN* loss (together referred to as *PTEN* loss hereafter) are associated with worse prognosis (Yoshimoto et al. 2007; Reid et al. 2010; Antonarakis et al. 2012; Chaux et al. 2012; Zafarana et al. 2012; Cuzick et al. 2013; Barnett et al. 2014; Ferraldeschi et al. 2015; Kim et al. 2015), regardless of whether patients are newly diagnosed, receiving treatment for localized disease, or have late-line advanced metastatic castration-resistant disease. Collectively, these results suggest that activation of the *PI3K-AKT* pathway is an important driver for prostate cancer and that the pathway is a relevant target for treatment.

1.2 BACKGROUND ON IPATASERTIB AND RUCAPARIB

1.2.1 Background on Ipatasertib

Ipatasertib is a potent, highly selective, small-molecule inhibitor of all three isoforms of the serine/threonine kinase *AKT*. Ipatasertib is being developed by Genentech/Roche as a single agent and in combination with other therapies for the treatment of cancers in which activation of the *PI3K-AKT*-mTOR pathway may be relevant for tumor growth or therapeutic resistance.

In nonclinical models with high levels of phosphorylated *AKT* or *PI3K-AKT* pathway activity (i.e., *PIK3CA* mutation, *PTEN* alterations), sensitivity to ipatasertib has been observed across different tumor models, including ovarian, breast, and prostate cancers (Lin et al. 2013). In vivo efficacy studies support the use of ipatasertib as a single agent

or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors.

Clinical studies in a variety of tumor types have been conducted with ipatasertib both as monotherapy and in combination. Combination partners have included hormonal therapies (i.e., abiraterone and enzalutamide), MEK inhibitor, chemotherapy, and immunotherapy. Randomized studies with ipatasertib have been conducted in breast, prostate, and gastric cancer.

The randomized Phase Ib/II study GO27983 was conducted in patients with mCRPC post-docetaxel. Ipatasertib (400-mg dose) when added to abiraterone and prednisone/prednisolone showed improved rPFS benefit compared with abiraterone and prednisone/prednisolone in the all-comer population and in patients with *PTEN*-loss tumors (hazard ratio = 0.75 for all-comer; hazard ratio = 0.39 for *PTEN*-loss by Immunologic Constant of Rejection [ICR] immunohistochemistry [IHC] assay). There is an ongoing randomized Phase III study CO39303 evaluating 400 mg ipatasertib when added to abiraterone and prednisone/prednisolone compared to abiraterone and prednisone/prednisolone in front-line mCRPC.

The randomized Phase II study, GO29227, evaluated the addition of ipatasertib to paclitaxel in front-line metastatic TNBC patients and those with a *PTEN* loss (by IHC) and separately, patients with *PIK3CA/AKT1/PTEN*-altered tumors. Results from this study showed improvement in median PFS in the intent-to-treat (ITT) population (hazard ratio = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm); and more pronouncedly in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio = 0.44; 9 months vs. 4.9 months). There is an ongoing randomized Phase III study CO40016 evaluating 400 mg ipatasertib when added to paclitaxel compared to paclitaxel in first-line TNBC and HR+/HER2– breast cancer for patients with *PIK3CA/AKT1/PTEN*-altered tumors.

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 Background on Rucaparib

Rucaparib is a PARP inhibitor approved *for the treatment of* women with *BRCA*-mutated ovarian cancer *who have been treated with* two *or more lines of chemotherapy and as maintenance therapy for women with ovarian cancer (regardless of BRCA-mutational status) who have either a complete or partial response to platinum-based therapy*. Nonclinical evaluation has demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous mutant cell lines to rucaparib, which is attributed to PARP inhibition alone, and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary (germline [g]) and acquired (somatic [s]) deficiencies of *BRCA1* and *BRCA2*. Clinical data indicate that benefit from treatment with a PARP inhibitor includes patients with a *gBRCA* or *sBRCA* mutation, and may extend to patients with other HR-deficient

alterations. *Rucaparib received breakthrough designation by the FDA in 2018 based on results from the TRITON2 study, which showed significant single-agent disease activity of rucaparib in patients with metastatic CRPC with BRCA1 and BRCA2 germline or somatic mutations (Abida et al. 2018).* This supports the investigation of PARP inhibitors, such as rucaparib, in a broader group of tumors with HR-deficiency (inclusive of *sBRCA* and *BRCA*-like, as well as other non-*BRCA* mutations involved in HR-deficiency). *Additional* Phase II and Phase III clinical studies with oral rucaparib *monotherapy are ongoing* in patients with *ovarian, prostate, or bladder cancer. Clinical trials investigating oral rucaparib in combination with other anti-cancer therapies are also planned or ongoing*.

Refer to the Rucaparib Investigator's Brochure for details on nonclinical and clinical studies of rucaparib.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

HR-deficient tumors are dependent on PARP-mediated DNA repair and have profound sensitivity to PARP inhibitor (Tutt et al. 2010; Fong et al. 2009; McCabe et al. 2006). In contrast, the clinical activity of PARP inhibitor in HR-intact tumors has been limited (Esteller et al. 2000). Preclinical data suggests that *PI3K-AKT* pathway inhibition can be exploited to induce HR deficiency in HR-intact cells and promote sensitization to PARP inhibition (Ibrahim et al. 2012). Combining a *PI3K* inhibitor with a PARP inhibitor has also demonstrated synergistic activity in a genetically engineered *BRCA1*-deficient mouse model as well as in humans for *BRCA1*-mutated breast cancer patient-derived xenograft tumors suggesting potential relevance of the combination even in HR-deficient tumors (Juvekar et al. 2012). PARP inhibitor can promote *PI3K-AKT* pathway activation, which can cause resistance to cytostatic agents (Szanto et al. 2009), and concurrent inhibition of both pathways can prevent this salvage pathway.

A Phase I study has evaluated the combination of a PARP inhibitor with an AKT inhibitor in breast, ovarian, and endometrial cancer (Westin et al. 2017). The combination was well tolerated and there was preliminary evidence of durable tumor activity all three tumor types. Response was independent of *BRCA1/2* status, but possibly associated with *PI3K-AKT* activation. Patients with prostate cancer were not included in the study population but high prevalence of *PTEN*-loss and HR deficiency in mCRPC provides strong rationale for extending exploration of this combination in prostate cancer.

Despite recent advances, metastatic ovarian, breast, and prostate cancer remain incurable diseases, and there is a need to develop improved anti-cancer therapies. *PI3K* inhibitors have demonstrated activity in later-line settings for patients in all three tumor types but activity has largely been limited to HR-deficient tumors. There is strong preclinical and early clinical data to support combining ipatasertib and rucaparib to expand disease activity to tumors regardless of HR status. In prostate cancer, the combination has high relevance as novel mechanisms of action are needed following progression on AR-targeted therapies due to mechanisms of cross-resistance with other AR-targeted therapies and with docetaxel. Patients with HR-deficient tumors that were

previously treated with AR-targeted therapies have shown response to *PI3K* inhibitors suggesting that this pathway remains an active and relevant target. Combining with ipatasertib can potentially bring this benefit to HR-intact patients and enhance the benefit in HR-deficient patients.

The study design including dose-escalation and dose-expansion intends to minimize risk to patients by allowing for thorough safety review. There are limited overlapping toxicities between ipatasertib and rucaparib. Dose-expansion in prostate cancer will provide an opportunity to assess early signals for disease activity in a patient population of high unmet need. The Sponsor has assessed that the potential benefit-risk profile of ipatasertib in combination with rucaparib justifies the initiation of the proposed clinical study with the initial Dose-Escalation Phase.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of ipatasertib administered in combination with rucaparib in patients with advanced breast, ovarian cancer, and prostate cancer. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol "study treatment" refers to ipatasertib, rucaparib, and the combination of both assigned to patients as part of this study.

2.1 PRIMARY SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of ipatasertib administered in combination with rucaparib on the basis of the following endpoints:

- To identify a RP2D and schedule for ipatasertib and rucaparib combination
- Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Incidence and nature of dose-limiting toxicities (DLTs) that determine the MTD of the ipatasertib and rucaparib combination

2.2 EFFICACY OBJECTIVES

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ipatasertib administered in combination with rucaparib in patients with prostate cancer on the basis of the following endpoint:

- Prostate-specific antigen (PSA) response, defined as the proportion of patients with a reduction in the PSA level of 50% or more

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ipatasertib administered in combination with rucaparib in patients with prostate cancer on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1)
- Duration of objective response (DOR)
- rPFS by Prostate Cancer Working Group 3 (PCWG3) criteria
- OS

2.2.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is as follows:

- To evaluate the potential relationship between the presence of *PI3K-AKT or HR* pathway alterations (e.g., *PTEN* loss by IHC, *PIK3CA/AKT1/PTEN- or BRCA1/BRCA2*-altered *status* by next-generation sequencing [NGS]) and the anti-tumor activity of ipatasertib in combination with rucaparib in patients with prostate cancer on the basis of the following endpoints:
  - PSA response rate
  - ORR
  - DOR
  - rPFS
  - OS

2.3 PHARMACOKINETIC OBJECTIVES

The *pharmacokinetic* (PK) objective for this study is as follows:

- To characterize the *PK* profile of ipatasertib, its metabolite G-037720, and rucaparib, when administered in combination, on the basis of the plasma concentration of ipatasertib and rucaparib at specified timepoints as listed in Appendix 2

2.4 BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To evaluate possible predictive and prognostic biomarkers in the tissue and plasma based on the following endpoint:
  - Exploration of possible relationships between the tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., rPFS)
- To evaluate pharmacodynamic effects of ipatasertib and the combination of ipatasertib with rucaparib in the tissue based on the following endpoint:

  - Changes in molecular biomarkers in pretreatment and on-treatment tumor tissues
- To identify possible mechanisms of resistance to the study treatments through the comparative analysis of potential biomarkers in the blood based on the following endpoint:
  - Changes in molecular biomarkers in pretreatment and post-progression plasma and blood samples

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study

This is a Phase Ib, open-label, non-randomized study in patients with advanced breast, ovarian, or prostate cancer to investigate the dose, safety, pharmacokinetics, and preliminary efficacy of ipatasertib in combination with rucaparib.

The study consists of two parts: a Dose-Escalation Phase (Part 1) in patients with previously treated advanced breast cancer, ovarian cancer, or prostate cancer and a Dose-Expansion Phase (Part 2) in patients with advanced prostate cancer who have had at least one line of prior therapy with second-generation AR-targeted agents (e.g., abiraterone, enzalutamide, apalutamide).

Approximately 24 patients will be enrolled in Part 1 (Dose-Escalation Phase) and approximately 30 patients will be enrolled in Part 2 (Dose-Expansion Phase). Patients must have fresh or archival tumor tissue samples available for submission for biomarker analyses for IHC (e.g., *PTEN* loss) and NGS methodologies (e.g., *PIK3CA/AKT1/PTEN or BRCA1/BRCA2*-altered status).

3.1.1.1 Dose-Escalation Phase (Part 1)

The Dose-Escalation Phase, Part 1, will determine the recommended dose of ipatasertib in combination with rucaparib in patients with advanced breast, ovarian, or prostate cancers. There will be a 7-day run-in period with ipatasertib alone prior to Cycle 1, Day 1. After the completion of the ipatasertib run-in period, patients will begin Cycle 1, Day 1 of the ipatasertib and rucaparib combination treatment. The study schema for Part 1 is presented in Figure 1, and the study flow for Part 1 is presented in Figure 2.

Two dose levels of rucaparib administered orally (PO) BID will be evaluated with two dose levels of ipatasertib in 28-day cycles. There will be approximately 6 patients per dose level. The highest dose level of each agent with an acceptable safety profile and with a minimum of 6 patients, at which, less than one-third of patients experience a DLT, will be declared the RP2D. Preliminary assessment of the anti-tumor activity and biomarkers of response or resistance to combined ipatasertib and rucaparib will also be conducted in Part 1. The dose levels of ipatasertib and rucaparib to be used in this study are listed in Table 1.

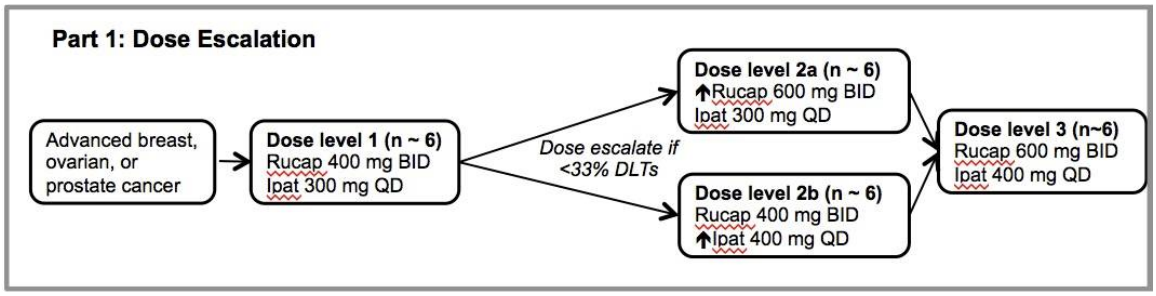
All patients will continue to receive study treatment until disease progression (according to RECIST v1.1 *for breast and ovarian cancer* or PCWG3 criteria *for prostate cancer*), unacceptable toxicity, death, or patient or investigator decision to withdraw, whichever occurs first.

Table 1 Dose Levels of Ipatasertib and Rucaparib

Dose Level	Ipatasertib (mg)	Rucaparib (mg)
1	300 mg QD	400 mg BID
2a	300 mg QD	600 mg BID
2b	400 mg QD	400 mg BID
3	400 mg QD	600 mg BID

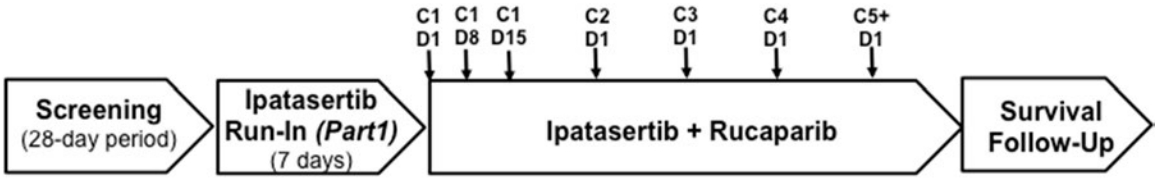
BID = twice daily; QD = once daily.

Figure 1 Study Schema Part 1



BID = twice daily; DLTs = dose-limiting toxicities; Ipat = ipatasertib; Rucap = rucaparib; QD = once daily.

Figure 2 Study Flow for Part 1



C = Cycle; D = Day.

3.1.1.2 Dose-Expansion Phase (Part 2)

In the Dose-Expansion Phase, Part 2, the potential RP2D of combined ipatasertib and rucaparib *identified* in Part 1 will be further evaluated for safety, pharmacokinetics, and preliminary efficacy in patients with advanced prostate cancer who have been treated with at least one line of second-generation AR-targeted therapy. There will be no run-in phase for the ipatasertib monotherapy. Approximately 30 patients will be enrolled, of *whom* approximately 70% are expected to have HR-intact tumors, and approximately

50% are expected to have *PTEN*-loss tumors based on the prevalence previously described in CRPC (Robinson et al. 2015). Enrollment may be extended to ensure at least 15 patients with HR-intact features are enrolled. A patient with a HR-deficient tumor is considered a patient with one of the following molecular features defined by the FoundationOne NGS assay:

- *Deleterious* alteration in *at least* one of the following genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L*

Mandatory archival or fresh tissue will be collected at the time of enrollment and optional fresh tumor biopsies on study treatment will be collected. *In addition, plasma and blood samples may be analyzed for deleterious alterations and further classification of mutational status.*

All patients will continue to receive study treatment until disease progression (according to RECIST v1.1 or PCWG3 criteria), unacceptable toxicity, death, or patient or investigator decision to withdraw, whichever occurs first.

3.1.2 Definition of Dose-Limiting Toxicity

A DLT will be defined as any of the following adverse events related to study treatments occurring during the DLT reporting period, which corresponds to the first cycle of study treatment (i.e., from Cycle 1, Day –7 to Day 28; Cycle 1 has 35 days):

- Any death related to study treatment
- Grade 4 neutropenia lasting for ≥7 days
- Grade ≥3 neutropenia complicated by fever ≥38°C or infection
- Grade 4 thrombocytopenia lasting for ≥7 days
- Grade ≥3 thrombocytopenia complicated by hemorrhage or that requires transfusion
- Study treatment-related Grade ≥3 non-hematologic toxicity (graded according to the NCI CTCAE, v5.0) except for the following:
  - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
  - Grade 3 nausea, vomiting, or diarrhea that responds to maximal supportive care within 72 hours
  - Grade 3 rash that resolves to Grade 1 within 7 days with maximal supportive care
  - Grade 3 hyperglycemia that is controlled with subcutaneous insulin
  - *Grade 3 ALT or AST elevation that is not accompanied by a concurrent increase in bilirubin (i.e., greater than the upper limit of normal [ULN])*
  - *Any other* Grade 3 laboratory abnormality that is asymptomatic and is deemed not to be clinically significant by the investigator

Patients who miss seven or more doses of either ipatasertib or rucaparib during the DLT-evaluation period for reasons other than a DLT will be replaced. In addition, patients who are discontinued from the study prior to completing the DLT-evaluation period for reasons other than a DLT (e.g., disease progression, consent withdrawn) will also be replaced. If a patient experiences a DLT, study treatment will be interrupted immediately for that individual and a safety assessment will be conducted.

The NCI CTCAE v5.0 will be used to characterize the toxicity profile of the study treatments for all patients.

An interim analysis for safety (including DLTs) will be performed by the Sponsor prior to the Dose-Expansion Phase (Part 2) to assess data from all patients in the Dose-Escalation Phase (Part 1). The interim analysis will be completed after the last evaluable patient in Part 1 has competed the first cycle of treatment. The combination dose levels demonstrating acceptable safety will be carried forward to the Dose-Expansion Phase (Part 2) of the study.

3.1.3 Tumor-Response Assessment

For all patients with breast and ovarian cancer, tumor response will be evaluated according to RECIST v1.1. For patients with ovarian cancer, CA-125 response will be assessed according to Gynecologic Cancer InterGroup (GCIG) criteria. For patients with prostate cancer, tumor response and PSA response will be evaluated according to PCWG3 criteria.

3.1.4 Internal Safety Monitoring

The Study Team, including the Study Medical Monitor and Safety Scientist, will monitor patient safety throughout the study. In addition to the ongoing assessments of the incidence, nature, and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigators and the Medical Monitor, the Study Team will review all necessary cumulative data at regular intervals during the study. Assessment of safety and all available PK data for the Dose-Escalation Phase (Part 1) will be performed by the Study Team prior to opening enrollment for Dose-Expansion Phase (Part 2).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical *efficacy* analysis or safety follow-up is received from the last patient, whichever occurs later.

For an individual patient, the last visit is defined as the end of treatment visit or the time of disease progression, whichever occurs later.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 36 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for *Study Treatment* Dose and Schedule

Based on preclinical and limited clinical studies, the combination of ipatasertib and rucaparib may have synergistic anti-tumor activity. This study is designed to assess the safety and preliminary efficacy of the two drugs in combination.

The starting dose for ipatasertib in Part 1 will be 300 mg PO QD, and the starting dose for rucaparib in Part 1 will be 400 mg PO BID. The highest potential dose for ipatasertib is 400 mg QD, which is the current dose of ipatasertib being studied in combination with abiraterone in prostate cancer and with paclitaxel in breast cancer. Ipatasertib is given continuously with abiraterone; it is given for 21 days of every 28-day cycle with paclitaxel. The highest potential dose for rucaparib is 600 mg BID *given continuously*, which is the approved dose for rucaparib monotherapy. Since ipatasertib has not been administered with rucaparib before, the Dose-Escalation Phase includes different dose combinations in cohorts of approximately 6 patients each. Additional dose de-escalation levels for ipatasertib or rucaparib (or both) may be explored during Part 1 if the frequency of DLT is $>$33%.

In Part 1, there is a 7-day run-in period for ipatasertib alone prior to Cycle 1. The rationale for the run-in is to allow for PK *assessment* of ipatasertib monotherapy *after the run-in phase for comparison with the pharmacokinetics* in combination with rucaparib. Based on available information to date, there could be a potential for increased exposure to ipatasertib when given in combination with rucaparib *due to CYP3A inhibition by rucaparib*. PK sampling of ipatasertib monotherapy at steady-state and following addition of rucaparib at steady state will add to PK data for drug–drug interaction evaluation and aid in determining the RP2D for both agents when administered in combination. *Trough rucaparib concentrations will also be evaluated and compared with published single-agent data*.

Based on prior Phase I data with an AKT inhibitor combined with a PARP inhibitor (Westin et al. 2017), the overlapping toxicities are expected to be limited. Given the available clinical safety data, ipatasertib 300 mg QD and rucaparib 400 mg BID are considered appropriate starting doses to evaluate the combination.

3.3.2 Rationale for Patient Population

The combination will be evaluated in Part 1 in patients with advanced breast, ovarian, and prostate cancer. PARP inhibitors have previously demonstrated single-agent activity in these tumor types (see Section 1.1), but activity has been *most pronounced in* patients with HR-deficient tumors. There remains potential to expand and extend clinical benefit of PARP inhibitors to patients with HR-intact tumors with the addition of ipatasertib. This study is designed to explore the simultaneous inhibition of PARP and AKT, thereby targeting the tumor in a multifactorial fashion that may enhance the efficacy of PARP and *PI3K-AKT* inhibition by inducing an HR-deficient phenotype regardless of tumor HR-status by germline/somatic mutation. Based on the distribution

of genetic alterations in HR and *PI3K-AKT* pathways in prostate cancer, this tumor type provides a unique opportunity to explore the combined activity of two different biomarker segments. In addition, there exists a high unmet need in patients who have previously received AR-targeted therapies and this population is expected to grow as these therapies are moving up in use to earlier lines of therapy.

3.3.3 Rationale for Biomarker Assessments

An exploratory objective of this study is to evaluate biomarkers (including the HR and *PI3K* pathway, and immune-related biomarkers) in tumor tissue and in plasma that will be used to help understand the response or resistance in patients treated with ipatasertib plus rucaparib. In addition, tissue and blood-based samples will be assessed for additional biomarkers in an effort to identify factors that may correlate with the safety and efficacy of the study treatments, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology through the use of NGS, whole genome sequencing (WGS), and/or other methods.

3.3.3.1 Rationale for the Collection of Tumor Tissue for Examining Alterations in the HR and *PI3K-AKT* Signaling Pathway

Activation of *PI3K-AKT* signaling frequently occurs in prostate cancer primarily through loss of *PTEN* expression, which occurs in approximately 45% of patients with prostate cancer and is associated with worse outcomes (Ferraldeschi et al. 2015). In the Phase II study GO27983, a pre-specified patient population with *PTEN*-loss tumors, as identified using archival or newly obtained biopsy tissue, demonstrated an improved mPFS benefit from ipatasertib treatment (de Bono et al. 2017). In addition, patients with prostate cancer who had defects in their DNA-repair genes experienced a high-response rate to the PARP inhibitor, olaparib (Mateo et al. 2015).

These considerations support the use of archival tissue (i.e., sample from primary prostate tumor) or a newly obtained biopsy to determine the *PI3K-AKT* pathway alterations and HR status of the disease, thus evaluating for a patient population with a higher probability of having a clinically meaningful response to ipatasertib combined with rucaparib. In the current study, PTEN-tumor status will be determined using an IHC assay and HR pathway status will be determined using an NGS assay (e.g., Foundation Medicine, Inc. [FMI]). Additional alterations in the *PI3K–AKT*-signaling pathway will also be assessed using NGS assay. Review of *PI3K–AKT*-pathway alterations and HR status in tumor tissue and response measures will be performed on an ongoing basis. In addition, in the cohorts in the Dose-Expansion Phase, enrollment may be restricted to patients with tumors demonstrating an intact HR pathway.

To obtain the most accurate reflection of the patient's current disease while minimizing burden, a specimen from the most recently obtained tumor tissue will be requested.

3.3.3.2 Rationale for Collection of Blood Samples for Non-Invasive Disease Monitoring

Circulating-tumor DNA (ctDNA) can be detected in the blood of patients with epithelial cancers and may have diagnostic and therapeutic significance (Schwarzenbach et al. 2011). For example, the mutational status of tumor cells may be obtained through the isolation of ctDNA (Maheswaran et al. 2008), and ctDNA has been used to monitor treatment effectiveness in melanoma (Shinozaki et al. 2007). In the current study, blood samples will be collected at screening, at the time of first tumor assessment, and at the study completion/early termination visit in order to evaluate oncogenic genetic alterations at baseline and to assess for the possible emergence of new alteration after treatment with ipatasertib and rucaparib. Genetic alterations will be evaluated in relevant genes in the HR and *PI3K* pathway. Identifying potential discordances in the HR and *PI3K*-pathway status between tumor samples and ctDNA may help generate hypotheses regarding the prognostic and predictive significance of these alterations in the enrolled patients that can be further tested in a future pivotal study.

3.3.3.3 Rationale for Collection of DNA (Blood) for Exploratory Whole Genome Sequencing

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in the identification of important pathways, guiding the development of new targeted agents.

Genetic variants of drug-metabolizing enzymes and transporters can alter the pharmacokinetics of drugs, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding UGT1A1, which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse events associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies suggest that ipatasertib is primarily metabolized by the CYP450 enzyme CYP3A, with a minor contribution by CYP2D6. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, including differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics of ipatasertib and its metabolite G-037720. The decision to analyze the samples will be based on a review of the PK data. For example, if a patient in a given cohort has substantially higher ipatasertib plasma levels than other patients in that cohort, he or she may carry a defective allele of a gene important in the metabolism or transport of ipatasertib. The

genotyping efforts would be guided by results from in vitro metabolism studies and by results from ongoing clinical studies with ipatasertib.

The pharmacogenetic analysis, if needed, will be performed on identifiable (referring to the blinded clinical trial number assigned to the patient at the time of enrollment and not to the actual name or other protected health information of the patient) DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis will be restricted to the evaluation of genes that may be involved in the pharmacokinetics of ipatasertib and its metabolite G-037720 (e.g., drug metabolism, disposition, or elimination genes, or genes influencing these processes).

In addition, tumor DNA can contain both reported and unreported chromosomal alterations resulting from the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, the blood sample will help determine whether an observed alteration identified in the tumor tissue is somatic throughout the evaluation of the DNA isolated in peripheral blood *using WGS or similar assay techniques*.

This sample for WGS will be collected if approved locally.

3.3.3.4 Rationale for Optional Collection of Tumor Biopsies for Exploratory Purposes

Pre- and during-treatment tumor tissue may be collected from patients for DNA and/or RNA extraction for exploratory NGS or other research on non-inherited biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular and biological pathways). These tumor tissue samples will be collected from patients who sign an Optional Research Biosample Repository Informed Consent Form, and whose tumor biopsies can be obtained on study as described in Appendix 1 with minimal risk and discomfort. These samples will be used to assess pharmacodynamic biomarkers in order to evaluate evidence of biologic activity of the study treatments. In addition these biopsies may provide insights into the tumor immunobiology, stromal markers, and critical signaling targets of HR and *PI3K* signaling cascades.

3.3.4 Rationale for the Pharmacokinetic Evaluation Schedule

Plasma samples for PK characterization of ipatasertib, its metabolite G-037720, and rucaparib, will be collected as outlined in Appendix 2. The sampling schedule is designed to enable characterization of ipatasertib PK using non-compartmental analysis and/or population PK (popPK) methodology. In addition, the PK data will allow comparison of ipatasertib exposure with single-agent ipatasertib data from the Phase I clinical trial (Study PAM4743g) and with ipatasertib data from other trials to evaluate whether ipatasertib exposures are altered in combination with rucaparib, which is a mild CYP3A4 inhibitor.

Rucaparib is metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Given that ipatasertib is a mild-to-moderate inhibitor of CYP3A4 (see the Ipatasertib Investigator's Brochure) and is not an inhibitor of CYP2D6 and CYP1A2, ipatasertib is not expected to alter rucaparib exposure in a clinically significant manner. Therefore, only trough concentrations of rucaparib will be evaluated in this study and compared to historical data in the literature.

Prior to start of any drug treatment in Part 1, a PK biomarker sample may be collected to measure baseline levels of coproporphyrin *(CP)* I and III, which are putatively transported into the liver by uptake transporters OATP1B1 and OATP1B3.

The levels of these endogenous substrates of organic-anion-transporting polypeptide (OATP) transporters, if warranted, will be measured in an exploratory way prior to and on ipatasertib treatment to understand the impact of ipatasertib on OATP functionality. If the analysis is conducted, remaining plasma samples from PK analysis will be used for assessing on-treatment effect on CPI and CPIII levels.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 54 patients will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- A life expectancy of at least 3 months
- Ability to swallow oral study drug
- Have adequate organ and marrow function as confirmed by the laboratory values listed below, obtained within 28 days prior to the first dose of study treatment

  Bone marrow function assessments (without transfusion within 28 days prior to receipt of study treatment)

  – ANC ≥ 1500 cells/μL (1.5×10^9/L) without granulocyte-colony stimulating factor support

  – Platelet count $\geq 100.0 \times 10^9$/L

  – Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L)

  Chemistry panel assessments

  – AST and ALT $\leq 1.5 \times$ ULN; if liver metastases, $\leq 2.5 \times$ ULN

- Bilirubin $\leq 1.5 \times$ ULN ($\leq 3 \times$ ULN if hyperbilirubinemia is due to Gilbert's syndrome)
- Serum albumin ≥ 3.0 g/dL
- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min
- Fasting glucose ≤ 150 mg/dL and hemoglobin A_{1c} *(HbA_{1c})* $\leq 7.5\%$

- Resolved or stabilized toxicities resulting from previous therapy to Grade 1 (except for alopecia and neuropathy).

  An ongoing, Grade 2, non-hematologic toxicity related to the most recent treatment regimen may be permitted with approval from the Medical Monitor

Cancer-Related Inclusion Criteria

- Have a histologically confirmed diagnosis of ovarian (Part 1 only), breast (Part 1 only) or prostate cancer (Part 1 and Part 2)
- Disease must be either metastatic or locally advanced disease that cannot be treated with curative intent
- For patients with ovarian cancer (Part 1 only):
  - High-grade (2 or 3) serous or endometrioid *or clear cell* epithelial ovarian, fallopian tube, or primary peritoneal cancer (PPC)

    If the tumor is of mixed histology, $>50\%$ of the primary tumor must be confirmed to be high-grade serous, endometrioid, *or clear cell*.
  - Must have received at least one prior platinum-based therapy and *may* have platinum-sensitive disease (i.e., documented radiologic disease progression ≥ 6 months following the last dose of the platinum treatment administered) *or platinum-resistant disease*
  - Have a CA-125 level that is $>2 \times$ ULN
  - Must have measurable disease by RECIST v1.1
- For patients with breast cancer (Part 1 only): must be HER2-(ER/progesterone positive or negative)
  - ER/progesterone-positive patients must have received and progressed on at least one endocrine therapy (adjuvant or metastatic)
  - ER/progesterone-negative/HER2– (TNBC) patients must have received at least one prior line of chemotherapy for metastatic breast cancer
  - Must not have received more than two prior lines of chemotherapy for metastatic breast cancer
  - Must have measurable disease by RECIST v1.1
- For patients with prostate cancer:
  - Adenocarcinoma of the prostate without small cell or neuroendocrine features
  - Surgical or medical castration with testosterone <50 ng/dL (1.7 nM)

  - Patients treated with luteinizing hormone-releasing hormone *analogs* must have initiated therapy at least 4 weeks prior to the first dose of study treatment and continue throughout the study treatment
  - Progression of prostate cancer either via PSA progression (two rising PSA levels measured ≥ 1 week apart, with second result ≥ 1 ng/mL) or radiographic progression with or without PSA progression *(see Appendix 5 for guidance)*
  - Must have received at least one prior line of second-generation androgen receptor targeted therapy (e.g., abiraterone, enzalutamide, apalutamide)
  - Patients with prostate cancer must have either measurable disease by RECIST v1.1 or bone lesions by bone scan, or both.
- Submission of a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of *12* freshly cut, unstained, serial tumor slides from the most recently collected tumor tissue for central molecular analysis (retrospective NGS testing for HR and *PI3K-AKT* pathway status and for other protocol-mandated secondary and exploratory assessments). Cytologic or fine needle aspirate samples are not acceptable. Tumor tissue from bone metastases is not acceptable.
  - If the specimen is either insufficient or unavailable, the patient may still be eligible if the patient is willing to consent to and undergo an additional pretreatment core or excisional biopsy of the non-target lesion (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.
- For women of childbearing potential: *be abstinent* (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must *be* abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the final dose of ipatasertib or 6 months after the last dose of rucaparib, whichever occurs later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and established proper use of progesterone-only injectable or implantable contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method plus spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: *be* abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must *be* abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 28 days after the last dose of ipatasertib or for 6 months after last dose of rucaparib whichever occurs later. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must *be* abstinent or use a condom during the treatment period and for 28 days after the last dose of ipatasertib or rucaparib to avoid exposing the embryo.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year, when used consistently and correctly, include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone releasing system, and sexual abstinence.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of ipatasertib or 6 months after the final dose of rucaparib

  Women of childbearing potential must have a negative serum pregnancy test result within *3* days prior to initiation of study drug.

- Prior treatment with a PARP inhibitor, *AKT* inhibitor, or *PI3K* inhibitor
- Treatment with investigational therapy within 14 days prior to initiation of study drug
- Symptomatic and/or untreated CNS metastases

  Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.

  Patients with leptomeningeal carcinomatosis will be excluded.

- Uncontrolled tumor-related pain

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization. Patients should be recovered (e.g., to Grade 1 or resolved)

from the effects of radiation prior to study enrollment. There is no required minimum recovery period beyond the 7 days required for radiation therapy.

Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization.

- Non–study-related minor surgical procedures $\leq$5 days or major (invasive) surgical procedure $\leq$14 days prior to first dose of study treatment

  Patient must be sufficiently recovered from surgery and stable, and wound healing must have occurred.

- Patients with active hepatitis C virus (HCV)

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test or a positive quantitative HBV DNA test

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test, a quantitative HBV DNA test must be performed.

  Patients receiving anti-viral therapy for HBV are not eligible.

- Known HIV infection
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Serious infection requiring antibiotics within 14 days of first dose of study treatment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Need for chronic corticosteroid therapy of $\geq$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- History of another malignancy within 5 years prior to randomization, except for either adequately treated non-melanomatous carcinoma of the skin, adequately treated melanoma in situ, adequately treated non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta, and low-grade T1 tumors), or other malignancies where the patient has undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to have a recurrence rate of $<$5% at 5 years.
- History of clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to enrollment
  - History of myocardial infarction within 6 months prior to first dose of study drug

- New York Heart Association Class III or IV cardiac disease
- Unstable arrhythmias or unstable angina

- Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.

Ipatasertib-Specific Exclusion Criteria

Patients who meet any of the following criteria specific to ipatasertib will be excluded from study entry:

- Type 1 or Type 2 diabetes mellitus requiring insulin at study entry

  However, patients who are on a stable dose of oral diabetes medication $\geq$4 weeks prior to initiation of study treatment may be eligible for enrollment. Patients must meet the laboratory eligibility criteria for fasting blood glucose and HbA_{1C} as outlined in the inclusion criteria.
- History of inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis), active bowel inflammation (e.g., diverticulitis)
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 4 weeks or five elimination half-live of the inhibitors, whichever is longer, prior to initiation of study drug

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study; the investigational products will not be blinded or masked. All patients enrolled will receive oral rucaparib and oral ipatasertib.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ipatasertib (RO5532961) and rucaparib (CO-338).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets in packaged bottles. For information on the formulation and handling of ipatasertib, see the Ipatasertib Investigator's Brochure. A brief description of the investigational product is provided in Table 2.

Table 2 Description of Ipatasertib

Drug Name:	GDC-0068, RO5532961
INN:	Ipatasertib
Formulation:	Tablet; film coated 200 mg–oval, brownish pink, embossed with ROCHE on one side 100 mg–oval, light or pale or grayish yellow, embossed with ROCHE on one side
How Supplied:	200 mg and/or 100 mg (as hydrochloride salt) strength, 30 count in high-density polyethylene bottles with desiccant and child-resistant screw cap
Storage Conditions:	Do not store above 25°C; protect from moisture

INN = International Nonproprietary Name.

4.3.1.2 Rucaparib

Rucaparib will be supplied by the Sponsor as 200-mg and 300-mg tablets in packaged bottles. For information on the formulation and handling of rucaparib, see the Rucaparib Investigator's Brochure. A brief description of the investigational product is provided in Table 3.

Table 3 Description of Rucaparib

Drug Name:	CO-338
INN:	Rucaparib
Formulation:	Tablet; film coated 200 mg–blue, round, embossed with C2 300 mg–yellow, oval, embossed with C3
How Supplied:	200 and/or 300 mg (as free base) strength, 60-count each, in high-density polyethylene bottles or equivalent with child-resistant caps
Storage Conditions:	15°C–30°C (59°F–86°F)

INN = International Nonproprietary Name.

All potential doses of rucaparib and the tablets that will be assigned for each dose level are described in Table 4.

Table 4 Doses and Tablets of Rucaparib

Rucaparib Dose [a]	Tablet	Number of Tablets
600 mg	*300-mg tablet* *Or* 200-mg tablet	*2* 3
500 mg	300-mg tablet 200-mg tablet	1 1
400 mg	200-mg tablet	2
300 mg	300-mg tablet	1

BID = twice a day.

[a] All rucaparib doses are to be prescribed BID. The number of tablets listed above is for one single dose of a BID dosing schedule.

The study drug container for rucaparib will be labeled according to national regulations for investigational products and will detail the applicable expiry date.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.

4.3.2.1 Ipatasertib

Patients will self-administer oral ipatasertib QD (approximately 24 hours apart) at the cohort-assigned dose throughout the treatment period unless dose reduction is required for adverse event management. Ipatasertib may be taken with or without food. *It may be taken concurrently with rucaparib on days when the patient is taking both.* If a dose is missed (i.e., not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

On PK sampling days, patients will be instructed not to administer ipatasertib study drug at home but to bring their bottles of ipatasertib and their dosing diaries to the clinic. Patients will be instructed when to take their doses of ipatasertib in the clinic in the context of the schedule of activities for the given visit. Time of dose administration will be collected on the PK sampling day and for prior dose administered *the day* before a PK sampling visit. Any incidence of vomiting within 3 hours after drug administration should also be recorded for the day of PK sampling. A sufficient amount of ipatasertib should

be provided to the patient to last one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib and their medication diaries to each study visit.

4.3.2.2 Rucaparib

Patients will self-administer oral rucaparib BID (approximately 12 hours apart) at the cohort-assigned dose throughout the treatment period unless dose reduction is required for adverse event management. *In Part 1 only, patients will start rucaparib on the evening of Day 1 of Cycle 1 following all PK sampling of ipatasertib on that day*. Patients should take rucaparib as directed by the treating physician. Patients may take *rucaparib* with *or* without food. *Rucaparib may be taken concurrently with ipatasertib on days when the patient is taking both.* Each dose should be taken with at least 8 ounces (240 mL) of water. Tablets should be swallowed whole. Missed doses (i.e., patient does not take dose within 6 hours of the scheduled time) or vomited doses will not be made up; the patient should resume rucaparib dosing with the next scheduled dose.

On PK sampling days, patients will be instructed not to administer rucaparib study drug at home but to bring their bottles of rucaparib and their dosing diaries to the clinic. Patients will be instructed when to take their doses of rucaparib in the clinic in the context of the schedule of activities for the given visit. Time of dose administration will be collected on the PK sampling day and for prior doses administered *the day* before a PK sampling visit. Any incidence of vomiting within 3 hours after drug administration should also be recorded for the day of PK sampling. A sufficient amount of rucaparib should be provided to the patient to last one treatment cycle. Patients will be instructed to bring their bottles of rucaparib and their medication diaries to each study visit.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (ipatasertib and rucaparib) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Ipatasertib *or Rucaparib*

Currently, the Sponsor does not have any plans to provide the Roche IMP ipatasertib or any other study treatments or interventions to patients who have completed the study.

The Sponsor may evaluate whether to continue providing ipatasertib *and/or rucaparib* in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- *Progesterone only injectable or implantable contraceptives*

  Of note, a decrease in glucose tolerance has been observed in some patients treated with medroxyprogesterone acetate contraceptive injection treatment. Medroxyprogesterone acetate injection contraception should be used with caution, given the potential risk of worsening glycemic control.
- Prophylactic anti-emetic and antidiarrheal medications
- Prophylactic or therapeutic anticoagulation therapy

  Caution should be exercised in patients receiving warfarin (Coumadin®) as rucaparib can be an inhibitor of CYP2C9. Patients taking warfarin should have their INR monitored regularly per standard clinical practice.
- Inactivated vaccinations
- Bisphosphonates or denosumab
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  After Cycle 2, palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease). Rucaparib may be continued during palliative radiotherapy. Treatment with ipatasertib should be suspended for at least 7 days before and after the procedure. For single-day radiotherapy, the ipatasertib hold may be shorter, if approved in advance by the Medical Monitor.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Cautionary Therapy

Use of concomitant corticosteroids with ipatasertib can increase risk of hyperglycemia. Patients who require use of systemic corticosteroids ≥ 10 mg of prednisone (or an equivalent dose of other corticosteroid) should hold ipatasertib during that time period to reduce risk of hyperglycemia.

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, which may increase the risk of toxicity of these drugs. Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing the frequency of INR monitoring.

In vitro data suggest that ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A4. A clinical drug-drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state ipatasertib dosed at 600 mg QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug-drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A.

Data from a clinical study showed that ipatasertib exposures were reduced by approximately 50% when co-administered with enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures. Therefore, the following drugs should be avoided while taking ipatasertib:

- Strong CYP3A4/5 inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and/or voriconazole
- Strong CYP3A4/5 inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4/5 substrates with a narrow therapeutic index.

Note: Chronic use of strong CYP3A inhibitors or inducers, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor are prohibited (see Section 4.4.3)

Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 5 half-lives or 7 days, whichever is shorter, after the last dose of these drugs.

Patients are permitted to take moderate inhibitors of CYP3A4/5 with caution. Patients should be closely monitored. Refer to the following information for further guidance on CYP450-drug interactions and a list of common substrates, inhibitors, and inducers:

Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers (U.S. FDA):

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above lists of medications are not comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

For additional information on rucaparib pharmacokinetics and drug interactions please refer to Rucaparib Package Insert or Summary of Product Characteristics.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator. Herbal therapies that require caution or are prohibited due to CYP interactions, such as St. John's wort, are described in Section 4.4.2.1.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 14 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- Quinidine or other anti-arrhythmic agents with a narrow therapeutic index
- Chronic use of strong CYP3A inhibitors or inducers, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor (refer to the guidance in Section 4.4.2)

4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 10 days after the final dose of study treatment.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patient re-screening may be considered under exceptional circumstances, after approval by the Medical Monitor.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity will be captured to assess if any differences in safety exist based on this entry.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height will be recorded at screening only. Weight will be recorded at screening and on Day 1 of each cycle.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, while the patient is in a seated position, and temperature.

4.5.5 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status scale (see Appendix 4) and recorded on the eCRF.

4.5.6 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Disease progression should be determined by radiographic means (including computed tomography [CT] scans, magnetic resonance imaging [MRI] scans, and bone scans). The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

For patients with breast and ovarian cancer, overall response at a single timepoint will be assessed by the investigator using RECIST v1.1. For patients with prostate cancer, response assessments will be per PCWG3 guidelines (bone lesions will be assessed per PCWG3 criteria and soft tissue lesions will be assessed per RECIST v1.1). An objective response should be confirmed by repeat assessments $\geq$4 weeks after initial documentation. For symptomatic deterioration attributed to disease progression, every effort should be made to document progression through use of objective criteria per RECIST v1.1.

Baseline CT/MRI assessments should be performed $\leq$28 days before starting study treatment. Baseline bone scans (technetium bone scan) should be performed within 6 weeks of starting study treatment.

- CT scans are the preferred imaging modality for tumor assessments in patients with breast and ovarian cancer and soft tissue tumor assessments for patients with prostate cancer. Tumor assessments should include a diagnostic quality, contrast-enhanced CT scan of the chest, abdomen, and pelvis at baseline. CT scans of the neck should be included if clinically indicated. To be suitable for RECIST assessments, CT scans should have a maximum thickness of 5 mm and no gaps. Subsequent tumor assessments should include CT scans of the chest, abdomen, and pelvis, and other known sites of disease

- In patients for whom a CT scan is contraindicated because of an allergy to intravenous (IV) radiographic contrast, both a CT scan of the chest without contrast and an MRI scan of the abdomen and pelvis with contrast are recommended.
- MRI scans may be performed in lieu of CT scans. However, an MRI scan of the chest may be performed only with the approval of the Medical Monitor. At screening, tumor assessments should include a diagnostic quality, contrast-enhanced MRI scan of the chest (if approved), abdomen, and pelvis. MRI scans of the neck should be included if clinically indicated. To be suitable for RECIST assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps. Subsequent tumor assessments should include MRI scans of the chest (if approved), abdomen, and pelvis as well as other known sites of disease.
- For patients with prostate cancer, bone lesions should be assessed by bone scans and evaluated by PCWG3 criteria. For adequate assessment of bone lesions, it is expected that the radiologist will adjust window leveling accordingly. If progressive disease is suspected only on the basis of new lesions detected by bone scan, a confirmatory bone scan must be performed at least 6 weeks after the initial scan which showed disease progression. Bone scans conducted prior to Week 12 of study treatment may show a false positive due to “flare” phenomenon and should not be considered a confirmatory scan for disease progression (see Appendix 5 for guidance).
- For patients with breast and ovarian cancer, a bone scan will be conducted at screening. For patients with known or suspected bone metastases, follow-up bone scans should be conducted at the time of tumor assessments and at the study treatment discontinuation visit (unless followed by other imaging modalities).

The frequency of tumor assessments for all patients will be approximately every 8 weeks (or 2 cycles) $\pm$2 weeks after initiation of study treatment for the first 6 months and then every 12 weeks (or 3 cycles) thereafter and as clinically indicated. At the investigator's discretion, imaging may be repeated at any time if progressive disease is suspected. The frequency of tumor assessments may be further reduced after 1 year with approval of the Medical Monitor. Tumor assessments at the end of treatment visit are not required if radiographic disease progression per RECIST v1.1 or PCWG3 criteria (if applicable) has been documented previously or if the last tumor assessments were performed $<$4 weeks prior to the end of treatment visit. If an initial CR or PR is noted, confirmatory scans should be performed $\geq$4 weeks later. In the case of stable disease (SD), follow-up measurements should have met the SD criteria at least once after study entry at a minimum interval of no less than 4 weeks.

For patients with prostate cancer, tumor assessments should continue per above schedule until radiographically assessed disease progression even if study treatment has been discontinued for other reasons. For patients with breast and ovarian cancer, continuation of tumor assessments is preferred but not required.

4.5.7 Other Disease-Specific Assessments

For patients with prostate cancer:

- PSA samples collected will be tested at a central laboratory obtained on Day 1 of each cycle starting with Cycle 1. If medically indicated, additional PSA samples may be collected and tested locally. Early increases in PSA levels (before 12 weeks) should be disregarded in determining PSA responses per PCWG3. Treatment should be continued in the case of an isolated increase in PSA without radiographic or clinical progression.

For patients with ovarian cancer:

- CA-125 measurements will be obtained on Day 1 of each cycle starting with Cycle 1. All CA-125 measurements will be performed by a local laboratory. See Appendix 7 for GCIG guidelines for response using CA-125. If there is an indication of disease progression based on CA-125 elevation, further evaluation by an unscheduled radiographic assessment may be required. Treatment should be continued in the case of an isolated increase in CA-125 without radiographic or clinical progression.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1 and Appendix 2). Results of the following assessments should be available for review at the Day 1 visit every cycle to inform dosing decision: hemoglobin, absolute neutrophil count, platelet count, fasting glucose, AST, ALT, and pregnancy test. Fasting glucose level results should also be available for review at each visit.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, BUN or urea, creatinine, total protein, albumin, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, LDH, amylase, and lipase
- Coagulation: INR, aPTT, and PT
- Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides) performed following a $\geq$8-hour fast
- Fasting and non-fasting blood glucose (fasting defined as following $\geq$8 hour fast)
- Glycosylated hemoglobin (HbA_{1c})
- Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening and monthly thereafter, and as clinically indicated. A final pregnancy test will be performed at the study treatment discontinuation visit.

- Home glucose monitoring: for any patients who initiate home glucose monitoring (see Table 6 for management guidelines of fasting hyperglycemia), a glucose log will be made available for capturing these results
- For patients with prostate cancer: PSA may be done by local laboratory assessment at screening if needed for eligibility
- For patients with prostate cancer: serum testosterone
- For patients with ovarian cancer: CA-125

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- For patients with prostate cancer: PSA samples on Day 1 of every cycle and at study treatment discontinuation to be tested at a central laboratory.

The following samples will be sent to the Sponsor or designee for analysis:

- Plasma samples for PK analysis of ipatasertib, G-037720, and rucaparib (see Appendix 2)
- Blood sample (pharmacogenomic sample) for DNA extraction to enable analysis via WGS and NGS (if approved by local regulatory authorities)
- Biomarker samples (blood, plasma, and tissue) for mandatory exploratory biomarker research include, but not limited to, the following assays and assay platforms:
  - Single-nucleotide polymorphisms that may impact exposure or other responses, or NGS results interpretation
  - Mutation and copy-number variations by NGS or PCR-based methods in tumor tissue and ctDNA
  - Expression analysis (e.g., RNASeq) of genes related to the HR and *PI3K-AKT* pathway, immune infiltration/activation, DNA damage repair pathway, apoptosis, and cancer biology
  - IHC-based analysis or quantitative digital IHC of tumor suppressors, such as *PTEN*, and markers of immune infiltration and activation, such as CD8 and programmed death–ligand 1 (PD-L1)
- Archival or newly collected tumor tissue sample obtained at baseline for determination of alterations in the HR and *PI3K* pathway and for exploratory biomarker research

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least *12* slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If fewer slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores,

embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, evaluation of cytokines, chemokines, and potential protein markers of PARP and AKT inhibition. Research may involve extraction of DNA, ctDNA, or RNA, analysis of mutations, and genomic profiling through use of NGS of a comprehensive panel of genes. Research may aim to distinguish germline mutations from somatic mutations. NGS methods may also include WGS, but only at participating sites (see Section 4.5.11).

NGS may be performed by FMI. If performed by FMI, the investigator may obtain results from these analyses by requesting an NGS report directly from FMI. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet criteria for testing.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and serum samples collected for PK may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and tumor tissue samples collected for study-related procedures and biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the

samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from FMI). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Post-Treatment Follow-Up

After treatment discontinuation, all patients will be followed for survival information unless the patient requests to be withdrawn from study survival follow-up; this request must be documented in the source file and signed by the investigator.

Post-treatment follow-up information will be collected via telephone calls and/or clinic visits, or patients' medical records, approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor.

Patients with prostate cancer who discontinue study treatment in the absence of disease progression, per RECIST v1.1 or PCWG3, will return to the clinic for tumor assessment follow up visits approximately every 3 months from last tumor assessment (CT or MRI scan and bone scan) until radiographically assessed disease progression (see Appendix 1).

4.5.11 Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS to identify mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research may aim to distinguish germline mutations from somatic mutations. The samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Patient medical information associated with WGS samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the WGS analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.12 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at baseline or after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.8. Refer to Section 4.5.13.3 for details on sample storage, use of samples after patient withdrawal (Section 4.5.13.6), confidentiality standards for data (Section 4.5.13.4), and availability of data from biomarker analyses (Section 4.5.13.4).

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition

- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ipatasertib, rucaparib, the HR and *PI3K* pathway, immune infiltration/activation, apoptosis, and the biology of breast, ovarian, and prostate cancer, or drug safety:

- **Left over blood, serum, plasma, and tumor tissue samples** (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.13.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.13.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR patient's death or loss of competence, the patient's samples and data will continue to be used as part of the RBR research.

4.5.13.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR

samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.13.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Unacceptable toxicity related to study treatment (see Section 5)
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of another non-protocol-specified anti-cancer therapy
- Disease progression per investigator assessment according to RECIST v1.1 or PCWG3
  - Rise in CA-125 or rise in PSA without radiographic disease progression does not require treatment discontinuation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced, with the exception of patients enrolled in Part 1 (Dose-Escalation Phase) who are not considered DLT-evaluable (see Section 3.1.2).

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study drug (see Appendix 1 for additional details).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). Patients with prostate cancer who discontinue prior to radiographic progression should continue tumor assessments until radiographically assessed disease progression.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced except for patients in Part 1 who are not considered DLT-evaluable (see Section 3.1.2).

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence

- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with ipatasertib and rucaparib in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1 and Section 5.1.2). Ipatasertib is not approved, and clinical development is ongoing. Refer to the Ipatasertib Investigator's Brochure for a complete summary of safety information. Refer to the Rucaparib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash.

Refer to the Ipatasertib Investigator's Brochure for a detailed description of the anticipated safety risks for Ipatasertib.

5.1.2 Risks Associated with Rucaparib

Rucaparib has been associated with risks such as the following: anemia, thrombocytopenia, *febrile neutropenia,* nausea, constipation, vomiting, diarrhea, asthenia/fatigue, *pyrexia, increased blood creatinine, decreased neutrophil count, and* dyspnea.

Note: AST or ALT elevation is not considered an identified risk in the Rucaparib Investigator's Brochure but has been reported with rucaparib.

Refer to the Rucaparib Investigator's Brochure for a detailed description of the anticipated safety risks for Rucaparib.

5.1.3 Risks Associated with Ipatasertib and Rucaparib

Ipatasertib and rucaparib have both been associated with *the following* risks: nausea, vomiting, diarrhea, *and* asthenia/fatigue.

Note: AST or ALT elevation is a potential risk in the Ipatasertib Investigator's Brochure. AST or ALT elevation is not considered as a potential or identified risk in the Rucaparib Investigator's Brochure but has been reported with rucaparib.

Refer to the Ipatasertib and Rucaparib Investigator's Brochure for a detailed description of the anticipated safety risks for rucaparib.

5.1.4 Management of Patients Who Experience Adverse Events

Guidelines for managing selected adverse events are provided in this section to improve safety and tolerability; however, patients may be treated per institutional practices as appropriate. If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug may not require modification. The reasons for dose modifications (e.g., interruptions, reduction, and withdrawal) or delays, supportive measure taken, and the outcome will be recorded in the eCRF.

5.1.4.1 General Management of Rucaparib-Related Adverse Events

Treatment with rucaparib should be held if any of the following are observed:

- Grade 3 or 4 hematologic toxicity
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines, and Grade 3 ALT/AST elevations not accompanied by bilirubin $>$ ULN or other signs of liver dysfunction)
- In addition, at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity that is attributed to rucaparib and not adequately controlled by concomitant medications and/or supportive care.

Rucaparib should be held until the toxicity resolves to Grade $\leq$2. BID dosing may then be resumed at either the same dose or a lower dose per investigator discretion. If treatment is resumed at the same dose and the patient soon experiences the same toxicity, the dose should be reduced following resolution of the repeated event to Grade $\leq$2. If the patient continues to experience the same toxicity, additional dose reduction steps are permitted down to a minimum dose of 300 mg BID (see Table 11).

Unless otherwise specified, rucaparib dose re-escalation upon resolution of toxicity to Grade $\leq$1 is permitted upon agreement between the investigator and Sponsor.

If a patient continues to experience the same toxicity despite multiple dose reduction steps to the lowest allowed dose or if dosing with rucaparib is interrupted for

$>$28 consecutive days due to the toxicity, treatment should be discontinued unless otherwise agreed between the investigator and the Sponsor.

5.1.4.2 Management of Rucaparib Treatment-Emergent Creatinine Elevations

Rucaparib is a potent inhibitor of MATE1 and MATE2-K transporters, which are involved in active secretion of creatinine. Rucaparib-mediated creatinine elevation occurs early in treatment and then stabilizes. Creatinine elevation is not typically accompanied by elevations in urea (BUN). Creatinine elevation resolves with *treatment interruption* of rucaparib and recurs with re-challenge. Creatinine elevation has not been associated with evidence or reports of permanent renal impairment. The following are guidelines for rucaparib dose modifications in the events of Grade $\geq$3 creatinine elevations:

- For Grade 4 isolated creatinine elevations (BUN $\leq$ ULN), hold rucaparib and investigate with ultrasound, urinalysis, and so on for potential alternative etiologies. When other reversible causes are treated or ruled out and the event has resolved to Grade 1 or better, then resume rucaparib at a reduced dose.
- For Grade 3 isolated creatinine elevations (BUN $\leq$ ULN), investigate with ultrasound, urinalysis, and so on for potential alternative etiologies. In the absence of another reversible cause (e.g., obstructions or infections) or evidence of renal injury, continue rucaparib at the same dose. Hold rucaparib for other reversible causes until the patient is treated and the event has resolved to Grade 1 or better, and then resume rucaparib at the same dose.

5.1.4.3 Management of Treatment-Emergent Diarrhea

Diarrhea has been associated with both ipatasertib and rucaparib administration.

For diarrhea occurring after Cycle 2 that persists for more than 5 days, despite treatment with an anti-diarrheal agent, a stool culture for infectious workup (i.e., *Clostridium difficile*, enteric bacteria, cytomegalovirus) will be obtained, and diarrhea should be treated with the appropriate antibiotic.

Table 5 Diarrhea Management Guidelines

Severity of Diarrhea	Management Guideline
Grade 1	Continue study drugs at the current dose level. Manage with loperamide 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea-free interval. Dietary modifications such as avoiding any lactose-containing foods. Hydration with 8–10 glasses of clear liquid such as broth and low-calorie electrolyte-enhanced drinks per day.
Grade 2	Manage with loperamide as early as possible 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea-free interval. Dietary modifications such as avoiding any lactose-containing foods. Hydration with 8–10 glasses of clear liquid, such as broth and low-calorie electrolyte-enhanced drinks, per day. For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. Interrupt ipatasertib. Rucaparib may be continued at the investigator's discretion. If diarrhea persists for >3 days following interruption of ipatasertib, rucaparib should also be interrupted. Ipatasertib and rucaparib can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to Grade 1 *or better*. Reduce ipatasertib and rucaparib by one additional dose level (see Table 3) for recurrent Grade 2 diarrhea.
Grade 3	Rule out infectious etiology. Treatment per Grade 2 management guidelines and supportive care. Interrupt ipatasertib and rucaparib until diarrhea improves to Grade 1 *or better*. Ipatasertib and recaparib should be reduced by one dose level (see Table 3 and Table 4) when treatment is restarted. For recurrent Grade 3 diarrhea, reduce ipatasertib and rucaparib dose by one additional dose level (see Table 3), or permanently discontinue ipatasertib and rucaparib per investigator discretion.
Grade 4	Management as per Grade 3 guidelines. Permanently discontinue ipatasertib and rucaparib.

If both study drugs are interrupted, step-wise reintroduction of one agent at a time (e.g., ipatasertib monotherapy for several days followed by reintroduction of rucaparib if diarrhea remains Grade ≤ 1) may be pursued.

5.1.4.4 Fasting Hyperglycemia

Hyperglycemia has been associated with ipatasertib and other agents targeting the *PI3K/AKT/mTOR* pathway but not associated with rucaparib or other PARP inhibitors. For this reason, management guidelines will address ipatasertib, only.

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined in Table 6 and are intended to provide guidance for fasting glucose measurements assessed in the clinic. This table is not meant to inform grading of adverse events, which should be conducted per NCI CTCAE v5.0. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and the investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, a blood glucose log should be reviewed at each clinic visit (and source data retained); entry of results into the patient's eCRF will be limited to values which result in intervention.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgment) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Table 6 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value >ULN to 160 mg/dL *(8.9 mmol/L)*	• Monitor fasting glucose per protocol. • Consider home glucose monitoring.
Fasting glucose value >160 to 250 mg/dL *(>8.9–13.9 mmol/L)*	• Interrupt ipatasertib until *the* fasting *glucose value decreases to ≤160 mg/dL*. • Initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin). • If the patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table 3). • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Fasting glucose value 250 to 500 mg/dL *(>13.9–27.8 mmol/L)*	• Interrupt ipatasertib until *fasting glucose value decreases to ≤160 mg/dL*. • Initiate home glucose monitoring. • Treat hyperglycemia as per standard of care. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • If the patient is already on an oral anti-diabetic mediation, ipatasertib should be reduced by one dose level when treatment is restarted. • If previously the patient has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If *fasting glucose value between 250 and 500 mg/dL* recurs, the dose of ipatasertib should be reduced by one dose level when treatment is restarted.
Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value >500 mg/dL *(>27.8 mmol/L)*	• Interrupt until *fasting glucose value decreases to ≤160 mg/dL*. • Treat hyperglycemia per standard of care. • Initiate home glucose monitoring. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduced ipatasertib by one dose level when treatment is restarted. • If *fasting glucose value >500 mg/dL* recurs, permanently discontinue ipatasertib.

ULN = upper limit of normal.
Note: For all grades, the patient should receive education on a diabetic diet.

5.1.4.5 Nausea and/or Vomiting

Nausea and/or vomiting has been associated with both ipatasertib and rucaparib administration.

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron (or equivalent anti-emetic *treatment*; see Table 7).

For persistent nausea and/or vomiting attributable to ipatasertib, dosage-modification guidelines are outlined in Table 7.

Table 7 Nausea and Vomiting Management Guidelines

Severity of Nausea and Vomiting	Management Guideline
Grade 1	• Provide maximum supportive care as needed.
Grade 2	• Provide maximum supportive care as needed. • Provide ondansetron (or equivalent anti-emetic medication) as needed.
Grade ≥ 3	• Interrupt ipatasertib and rucaparib until nausea or vomiting resolves to Grade ≤2. • Provide maximum supportive care as needed. • Provide ondansetron (or equivalent anti-emetic) as needed. • If Grade ≥ 3 nausea or vomiting recurs, ipatasertib and rucaparib should be reduced by one dose level (refer to Table 3) when treatment is restarted.

If both study drugs are interrupted, step-wise reintroduction of one agent at a time (e.g., ipatasertib monotherapy for several days followed by reintroduction of rucaparib if nausea/vomiting remains Grade ≤ 2) may be pursued.

5.1.4.6 Rash

Rash has been associated with ipatasertib administration *and skin photosensitivity has been associated with rucaparib treatment*.

Ipatasertib should be permanently discontinued for rash associated with erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown below (see Table 8). *With respect to skin photosensitivity being related to rucaparib, patients should always protect themselves appropriately when exposed to the sun.*

Table 8 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib and rucaparib treatment until resolution to Grade 1 *or better* or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids • Follow above guidance and reduce ipatasertib by one dose level for recurrent Grade 2 rash.
Grade 3	• Interrupt ipatasertib and rucaparib treatment until resolution to Grade 1 *or better* or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 *or better* or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib and rucaparib may be resumed at one dose level below the previous dose (refer to Table 3). • If recovery of the skin toxicity to Grade 1 *or better* does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib and rucaparib.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib and rucaparib should be permanently discontinued.

If both study drugs are interrupted, step-wise reintroduction of one agent at a time (e.g., ipatasertib monotherapy for several days followed by reintroduction of rucaparib if rash remains Grade $\leq$ 1) may be pursued.

5.1.4.7 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib.
As pneumonitis has not been observed with rucaparib, the management guidance will address ipatasertib, only. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 9).

Table 9 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and pulmonary function tests. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• Prescribe corticosteroids if there are clinical symptoms and infectious etiology is ruled out. Interrupt ipatasertib treatment as long as corticosteroids are being given. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • If pneumonitis resolves to Grade 1 *or better* after completion of the steroid taper, ipatasertib may be resumed at either the previous dose or one dose level below the previous dose (see Table 3) per investigator assessment. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose. • Discontinue ipatasertib if recovery to Grade 1 *or better* is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment as long as corticosteroids are being given. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • If pneumonitis resolves to Grade 1 *or better*, following completion of the steroid taper, continue ipatasertib at one dose level below the previous dose (see Table 3). Discontinue ipatasertib if recovery to Grade 1 *or better* is not evident within 28 days. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued
Grade 4	• If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

5.1.4.8 Hepatotoxicity

Liver enzyme elevations have been associated with both ipatasertib and rucaparib administration.

Permanently discontinue rucaparib and ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × baseline and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other

causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria (see Section 5.3.5.6).

Table 10 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 *AST or ALT >ULN–3.0 × ULN if baseline was normal; 1.5–3.0 ×baseline if baseline was abnormal or total bilirubin >ULN–1.5 ×ULN if baseline was normal; >1.0–1.5 ×baseline if baseline was abnormal*	• Continue study drugs. • Monitor LFTs until values resolve to baseline values.
Grade 2 *AST or ALT >3.0–5.0 ×ULN if baseline was normal; >3.0–5.0 × baseline if baseline was abnormal or total bilirubin >1.5–3.0 × ULN if baseline was normal; >1.5–3.0 × baseline if baseline was abnormal*	• Continue study drugs. • The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 *AST or ALT >5.0–20.0 ×ULN if baseline was normal; >5.0–20.0 ×baseline if baseline was abnormal or total bilirubin >3.0–10.0× ULN if baseline was normal; >3.0–10.0× baseline if baseline was abnormal*	• Interrupt ipatasertib until improvement of AST/ALT to Grade ≤2. Treatment may be resumed at previous dose level. • Continuation of rucaparib with elevation of AST/ALT up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 × ULN. If levels do not decline within 2 weeks or they continue to rise, treatment interruption and improvement to Grade ≤2 will be required before rucaparib can be resumed with reduction by one dose level. • Consider hepatology consult. • Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. • If another Grade 3 event occurs, interrupt rucaparib and ipatasertib. On return of LFTs to Grade ≤2, resume ipatasertib, reducing the dose by one level and rucaparib, reducing the dose by one level. • Further Grade 3 occurrences must result in permanent discontinuation of rucaparib and ipatasertib.
Grade 4 *AST or ALT >20.0 ×ULN if baseline was normal; >20.0× baseline if baseline was abnormal or total bilirubin >10.0× ULN if baseline was normal; >10.0× baseline if baseline was abnormal*	• Permanently discontinue treatment with ipatasertib and rucaparib.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

If both study drugs are interrupted, step-wise reintroduction of one agent at a time (e.g., ipatasertib monotherapy for several days followed by reintroduction of rucaparib if liver enzymes remain Grade ≤ 2) may be pursued.

5.1.4.9 Dose Modifications

Rucaparib Dose Modifications

Potential dose reduction steps for rucaparib based on different current doses of rucaparib are shown in Table 11. In Part 1, during the DLT evaluation period (Cycle 1), dose reductions of rucaparib are not allowed for reasons other than a DLT or a decision by the Sponsor based on emerging safety data.

In Part 1, during the DLT evaluation period (Cycle 1), dose interruptions of rucaparib are not allowed for reasons other than toxicity. Patients are eligible for safety and DLT evaluation of the dose cohort if they receive at least 70% of the planned total dose of each study drug within Cycle 1 or they experience a DLT at any time during Cycle 1. During the remainder of the study, treatment with rucaparib may be interrupted for up to 28 days (1 cycle) for toxicity or reasons unrelated to toxicity. If rucaparib is withheld because of adverse events for > 28 days, the patient will be discontinued from rucaparib. If, however, in the judgment of the investigator, the patient is likely to derive clinical benefit from rucaparib after a hold of > 28 days, study drug may be restarted with the approval of the Medical Monitor.

Once a RP2D has been established at the end of Part 1, those patients in Part 1 who are treated at a dose below the RP2D and are tolerating study drugs may be escalated to the RP2D at the discretion of the investigator with approval from the Medical Monitor.

Table 11 Dose Reductions for Rucaparib

Current Dosage	Dose Reduction
600 mg BID	500 mg BID
500 mg BID	400 mg BID
400 mg BID	300 mg BID
300 mg BID	No further dose reductions allowed

BID = twice daily.

Ipatasertib Dose Modifications

The ipatasertib dose reduction instructions provided in Table 12 are intended to serve as recommended guidelines to allow ongoing treatment for patients without signs or symptoms of disease progression while monitoring patient safety. Guidelines for implementing dosage modifications and treatment interruption or discontinuation for patients who experience specific adverse events are provided in Section 5.1.1.

In Part 1, during the DLT evaluation period (Cycle 1), dose reductions of ipatasertib are not allowed for reasons other than a DLT or a decision by the Sponsor based on emerging safety data.

In Part 1, during the DLT evaluation period (Cycle 1), dose interruptions of ipatasertib are not allowed for reasons other than toxicity. Patients are eligible for safety and DLT evaluation of the dose cohort if they receive at least 70% of the planned total dose of each study drug within Cycle 1 or they experience a DLT at any time during Cycle 1.

During the remainder of the study, treatment with ipatasertib may be interrupted for up to 28 days (1 cycle) for toxicity or reasons unrelated to toxicity. If ipatasertib is withheld because of adverse events for > 28 days, the patient will be discontinued from ipatasertib. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from ipatasertib after a hold of > 28 days, study drug may be restarted with the approval of the Medical Monitor.

Once a RP2D has been established at the end of Part 1, those patients in Part 1 who are treated at a dose below the RP2D and are tolerating study drugs may be escalated to the RP2D at the discretion of the investigator with approval from the Medical Monitor.

Table 12 Dose Reductions for Ipatasertib

Current Dosage	Dose Reduction
400 mg QD	300 mg QD
300 mg QD	200 mg QD
200 mg QD	No further dose reductions allowed

QD = once daily.

No more than two dose reductions are allowed, and dose re-escalation is not permitted.

Summary of Study Drug Modifications for Both Treatments

A summary of dose modification allowances is shown in Table 13.

Table 13 Part 1 and Part 2 Dose Modification

	Part 1, Cycle 1	Part 1, Cycle 2+ and Part 2
Dose reduction	Only for DLT or Sponsor decision	For toxicity (see Table 11 and Table 12 for dose reductions)
Dose hold	For toxicity; must receive >70% doses to be evaluable for DLT	For up to 28 days[a] for toxicity or reasons unrelated to toxicity

DLT = dose-limiting toxicity.

[a] If a longer hold is required for slowly resolving toxicity, Sponsor approval is required.

5.1.4.10 Treatment Interruption

Ipatasertib and/or rucaparib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug(s). If either drug has been withheld for >28 days because of toxicity, the patient should be discontinued from that drug, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Patients discontinuing ipatasertib because of treatment-related toxicity may continue on rucaparib monotherapy as per investigator's discretion. Patients discontinuing on rucaparib because of treatment-related toxicity may continue on ipatasertib monotherapy at the discretion of the investigator. Ipatasertib and/or rucaparib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Myelodysplastic syndrome
- Acute myeloid leukemia
- Grade ≥3 diarrhea
- Grade ≥3 hyperglycemia
- Grade ≥3 rash
- Grade ≥ 2 colitis/enterocolitis
- Grade ≥2 pneumonitis

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 14 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 14 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 15):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 15 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events that are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ *baseline value*) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- *Treatment-emergent ALT or AST $>3\times$baseline value in combination with total bilirubin $>2\times$ULN (of which $\geq$35% is direct bilirubin)*
- Treatment-emergent ALT or AST $>3\times$ *baseline value* in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 or PCWG3 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible: [redacted], M.D. (Primary)

Telephone No.: [redacted]

Email: [redacted]

Medical Monitor:	[redacted], M.D. (Secondary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted], M.D. (Tertiary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events that Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events that Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of ipatasertib or within 6 months after the last dose of rucaparib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the final dose of ipatasertib or within 6 months after the last dose of rucaparib. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For

ipatasertib, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with ipatasertib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Ipatasertib Investigator's Brochure
- Rucaparib Investigator’s Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis will be based on patients data collected through study discontinuation or at the end of study. All analyses will be conducted using the safety-evaluable population, defined as all patients who receive any amount of study treatment.

No formal hypothesis testing is planned. The safety, tolerability, clinical activity, and pharmacokinetics of ipatasertib, and its metabolite G-037720, with rucaparib will be described and summarized.

Data will be described and summarized as warranted by sample size. That is, listings may be used in lieu of tables in the event of small sample size.

Descriptive statistics will be used to summarize the safety and clinical activity of treatment regimens. Continuous variables will be summarized using means, standard

deviation, median, and range; categorical variables will be summarized using count and percentage.

6.1 DETERMINATION OF SAMPLE SIZE

There is no formal hypothesis testing planned. The determination of sample size for each part is described below.

For Part 1 (Dose-Escalation Phase), approximately 24 patients are planned to be enrolled based on the dose-escalation rules.

For Part 2 (Dose-Expansion Phase), approximately 30 patients with advanced prostate cancer who have had at least one line of prior therapy with second-generation AR-receptor targeted agents (e.g., abiraterone, enzalutamide, apalutamide) are planned to be enrolled. No formal statistical hypothesis testing is planned. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary endpoint of PSA response rate, the analyses will be based on patients enrolled in Part 2. Table 16 shows estimated PSA response rate and its 95% CI based on the Clopper-Pearson method given various observed numbers of responders among the 30 patients. Thirty patients provide reasonably reliable estimates for hypothesis generation.

Table 16 Estimated PSA Response Rate and Its 95% CI for 30 Patients

Number of Responders	Response Rate (%)	95% CI (%)
6	20	7.71, 38.57
9	30	14.73, 49.40
12	40	22.66, 59.40
15	50	31.30, 68.70
18	60	40.60, 70.34
21	70	50.60, 85.27
24	80	61.43, 92.29

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for patient discontinuations from the study treatment and from the study will be listed and summarized. Enrollment, study treatment administration, and major protocol deviations will be described, listed, or summarized and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex race/ethnicity, weight, type of malignancy, and baseline ECOG performance status will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Concomitant medications received during the treatment period will be summarized.

6.4 EFFICACY ANALYSES

Efficacy analyses will include all evaluable patients, defined as all patients who receive any amount of study treatment.

6.4.1 Primary Efficacy Endpoint for Patients with Prostate Cancer

For patients with prostate cancer, PSA response rate is defined as the proportion of patients achieving a PSA decline $\geq$50% from baseline. Patients without a post-baseline PSA assessment will be considered non-responders. The PSA response rate will be calculated, and the 95% CI will be estimated using the Clopper-Pearson method.

6.4.2 Secondary Efficacy Endpoints for Patients with Prostate Cancer

For patients with prostate cancer, an objective response is defined as a CR or PR on two consecutive occasions $\geq$4 weeks apart, according to RECIST v1.1 and PCWG3 criteria, in patients with measurable disease at baseline. Patients without a post-baseline tumor assessment will be considered non-responders. ORR is defined as the proportion of patients who have an objective response in patients with measurable disease at baseline. ORR will be calculated, and the 95% CI will be estimated using the Clopper-Pearson method.

Among patients with an objective response (responders), DOR will be defined as the time from first occurrence of a documented objective response until the time of documented disease progression or death from any cause during the study, whichever occurs first. For patients who do not have documented disease progression or death during the study, DOR will be censored at the day of the last evaluable tumor assessment.

rPFS is defined as the time from study treatment initiation to the first occurrence of documented disease progression, as assessed by the investigator with use of the PCWG3 criteria (soft tissue by CT or MRI scans according to RECIST v1.1, and bone metastasis by bone scan according to the PCWG3 criteria) or death from any cause, whichever occurs first. For patients who do not have documented disease progression or death during the study, rPFS will be censored at the day of the last evaluable tumor assessment.

OS will be defined as the time from study treatment initiation to the time of death due to any cause. For patients who do not have death during the study, OS will be censored at the last known alive date.

Kaplan-Meier methodology will be used to estimate the median rPFS, DOR, and OS, and the Kaplan-Meier curves will be provided. The Brookmeyer-Crowley method will be used to construct the 95% CI for each median.

6.4.3 Exploratory Efficacy Endpoints

Additional exploratory analyses will evaluate treatment effect in additional biomarker-defined segments (e.g., *PTEN*-loss) within prostate cancer in Part 2.

6.5 SAFETY ANALYSES

The safety analyses will include all patients who received at least one dose of any study drug, and will be analyzed and summarized separately for the Part 1 and Part 2; data will not be combined across phases.

Adverse events, deaths, change in laboratory test results, change in vital signs, and exposure to components of study treatment will be assessed to determine the safety of treatment regimen.

For safety-evaluable patients, study drug administration data will be tabulated or listed by arm, and any dose modifications will be flagged. Descriptive statistics will be used to summarize the total dose of ipatasertib and rucaparib received.

Verbatim descriptions of adverse events will be mapped to appropriate thesaurus terms. All adverse events occurring on or after treatment Day 1 will be summarized by the mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 toxicity grade. In addition, adverse events leading to treatment withdrawal or death, and serious adverse events will be listed with more detailed information, such as the day of onset of an adverse event, duration of adverse event, toxicity grade, and so on.

Relevant laboratory and vital signs (heart rate, blood pressure, and temperature) and ECG data will be displayed by time post-dose, with NCI CTCAE Grade 3 and 4 values identified where appropriate. Additionally, changes in laboratory data will be summarized by grade using the NCI CTCAE toxicity grade. Selected vital signs and selected laboratory data will be summarized by visit.

The extent of study drug exposure (dose and duration) will be examined to determine the degree of treatment tolerability. In addition to study treatment duration and total dose received, any dose modification of study drugs will also be summarized.

6.6 PHARMACOKINETIC ANALYSES

For Part 1, plasma samples for PK characterization of ipatasertib, its metabolite G-037720, and rucaparib will be collected on Day 1 of Cycle 1 for ipatasertib and G-037720, Day 15 *of* Cycle 1, *and Days 1 and 15 of Cycle 2* (ipatasertib, G-037720, and rucaparib). For ipatasertib, the sampling will allow for determination of the total exposure (area under the concentration–time curve from Time 0 to Time t [AUC_{0-t}]) and the time to achieve maximum concentration (T_{max}), and maximum concentration (C_{max}) at steady state as a single agent (baseline) and in the presence of rucaparib. For rucaparib, the sampling will allow for determination of predose trough concentrations. Any effect of rucaparib on ipatasertib, or its metabolite G-037720, will be evaluated by comparing the *pharmacokinetics of ipatasertib in combination with rucaparib* on Day 15 of Cycle 1 to *monotherapy pharmacokinetics with* Day 1 of Cycle 1 *after the single-agent run-in phase*. Mean and individual concentration–versus-time graphs will be plotted, and PK parameters will be tabulated and summary statistics reported for all analytes. Other PK parameters may be determined as data allow. Potential correlations of relevant PK parameters with dose, safety or efficacy outcomes, and other covariates may be explored.

For Part 2, trough samples of ipatasertib, G-037720, and rucaparib will be collected on Day 15 *of* Cycle 1 *and on Days 1 and 15 of Cycle 2* to confirm comparability to Part 1 trough and/or historical data in a descriptive manner.

Any remaining PK samples after evaluation of ipatasertib, G-037720, and rucaparib may be used for exploratory evaluation of other analytes related to the administered drugs or biomarkers, enzymes, and transporters affecting their disposition *or safety profile*.

Additional PK analyses will be conducted as appropriate.

6.7 BIOMARKER ANALYSES

Exploratory biomarker analyses (in tumor tissues and plasma, whole blood, or serum) will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. Results will be presented in a separate report.

WGS data will be analyzed in the context of this study and may be explored in aggregate with data from other studies to increase researchers' understanding of disease pathobiology and guide the development of new therapeutic approaches.

6.8 INTERIM ANALYSES

An interim analysis for safety (including DLTs) will be performed by the Sponsor prior to dose expansion (Part 2)

Given the hypothesis-generating nature of this study, the Sponsor may conduct an interim analysis of efficacy in Part 2. The decision to conduct such an interim analysis

and its timing will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The Clinical Study Report will also document that such an interim analysis occurred. The interim analysis, should it occur, will be performed and interpreted by members of Roche's study team and management.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes,

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by F. Hoffmann-La Roche Ltd (Roche) and will be managed by Roche and a contract research organization (CRO). The Sponsor will provide clinical operations oversight, data management, and medical monitoring.

Approximately 20 sites globally will participate to enroll approximately 54 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

The Study Medical Monitor and the Study Team (see Internal Safety Monitoring, Section 3.1.4) will monitor and evaluate patient safety throughout the study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment/Procedure (Window)	Screening [a]	Ipatasertib single-agent PK Run-In **(PART 1 only)**		Cycle 1			Cycle 2		Cycle 3		Cycles ≥ 4	Treatment Discontinuation [b]	Post-Tx FU [c]
	≤28 days of first dose	Day −7	Day −1	Day 1	Day 8 (±2)	Day 15 [d] (±2)	Day 1	Day 15	Day 1	Day 15 [d]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months
Informed consent(s)	x [e]												
Demographic data (age, sex, and self-reported race/ethnicity)	x												
Medical history and baseline conditions [f]	x												
Archival FFPE tumor tissue	x [g]												
Concomitant medications [h]	x			x	x	x	x	x	x	x	x	x	
Adverse events [i]	x			x	x	x	x	x	x	x	x	x	x
Complete physical examination [j]	x [a]											x	
Limited physical examination [k]				x	x	x	x	x	x	x	x		
ECOG performance status	x [a]			x			x		x		x	x	
Vital signs [l]	x			x	x	x	x	x	x	x	x	x	
Weight and height (height at screening only)	x			x			x		x		x	x	
Electrocardiogram [m]	x [m]			As clinically indicated								x [m]	
PSA (prostate cancer only) [n]	x [n]			x			x		x		x	x	x
Serum testosterone (prostate cancer only) [o]	x											x	
CA-125 (ovarian cancer only)				x			x		x		x	x	

Appendix 1: Schedule of Activities

Assessment/Procedure (Window)	Screening [a] ≤28 days of first dose	Ipatasertib single-agent PK Run-In **(PART 1 only)** Day −7	Day −1	Cycle 1 Day 1	Day 8 (±2)	Day 15 [d] (±2)	Cycle 2 Day 1	Day 15	Cycle 3 Day 1	Day 15 [d]	Cycles ≥ 4 Day 1	Treatment Discontinuation [b] Within 30 days of the Last Study Treatment	Post-Tx FU [c] Every 3 (±1) Months
Hematology [p]	x			x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x	
Fasting blood glucose [r]	x	x		x	x	x	x	x	x	x	x	x	
Nonfasting blood glucose, serum (Part 1 only)				x [s]		x [s]							
Chemistry panel [t]	x			x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x [q]	x	
Pregnancy test (females only) [u]	x												
Urinalysis [v]	x			As clinically indicated									
Coagulation: aPTT, PT, and INR	x			As clinically indicated									
Amylase and lipase	x						x				Day 1 of Cycles 4, 6, 9, 12, and every 3 cycles thereafter	x	
Fasting lipid profile	x						x					x	
Hemoglobin A_{1c}	x						x						
Tumor assessment of soft tissue per RECIST v1.1 [w, x]	x [a]						End of Cycles 2, 4, 6, and every 3 cycles thereafter [z]					x	x
Tumor assessment: bone scan [y]	x [a]											x	x
Ipatasertib administration [z]		Daily QD ipatasertib		Daily QD administration of ipatasertib									
Rucaparib administration [z]				Daily BID administration of rucaparib									
Drug accountability							x		x		x	x	

Appendix 1: Schedule of Activities

Assessment/Procedure (Window)	Screening [a]	Ipatasertib single-agent PK Run-In **(PART 1 only)**		Cycle 1			Cycle 2		Cycle 3		Cycles ≥ 4	Treatment Discontinuation [b]	Post-Tx FU [c]
	≤28 days of first dose	Day −7	Day −1	Day 1	Day 8 (±2)	Day 15 [d] (±2)	Day 1	Day 15	Day 1	Day 15 [d]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months
Plasma PK sample [aa]		See Appendix 2											
Blood sample for WGS control [bb]		See Appendix 3											
Blood sample for pharmacogenomics [bb]		See Appendix 3											
Plasma sample for somatic tumor mutations [bb]		See Appendix 3											
Plasma sample for exploratory biomarkers [bb]		See Appendix 3											
Blood sample for RBR (for DNA extraction; optional) [cc]		See Appendix 3											
Optional tumor biopsy – dose escalation (Part 1) [dd]		See Appendix 3											
Optional tumor biopsy – cohort expansion (Part 2) [ee]		See Appendix 3											
Survival follow-up													x

CR = complete response; CT = computed tomography; Discont. = Discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; FU = Follow-up; IHC = immunohistochemistry; IxRS = interactive voice- or Web-based response system; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PK = pharmacokinetic; PCWG3 = Prostate Cancer Working Group 3; PR = partial response; PSA = prostate-specific antigen; QD = once daily; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease; Tx = Treatment; WGS = whole genome sequencing.

Notes: All visits should occur within ±3 days of the scheduled visit, unless otherwise specified. On treatment visit days, all assessments should be performed prior to dosing, unless otherwise specified. Unplanned visits not specified by the protocol or unscheduled assessments (possibly including PK sample collection) may be performed as clinically indicated at discretion of the investigator; the associated data should be recorded on the relevant eCRF in support of an adverse event diagnosis or tumor assessments.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening. Bone scans within 42 days prior to Cycle 1, Day 1 may be used. If eligibility assessments were not completed within 28 days from the original date of the screening visit, the patient will need to be rescreened for eligibility (see Section 4.5.1 for details).

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 (±3) days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit, provided that all tests required at the treatment discontinuation visit are performed. Tumor assessments at the treatment discontinuation visit may be omitted if the most recent prior assessment was performed less than 28 days ago or the patient has already had confirmation of radiographic disease progression.

[c] After treatment discontinuation, patients with prostate cancer who discontinue study treatment in the absence of disease progression will return to the clinic for tumor assessment follow up visits approximately every 3 months from last tumor assessment (CT or MRI scan and bone scan) until radiographically assessed disease progression. For all patients, unless the patient requests to be withdrawn from survival follow-up, the required information will be collected via telephone calls and/or clinic visits, or patients' medical records, approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[d] Day 15 clinical visit and assessments up to Cycle 3 only. During subsequent cycles, site personnel may contact the patient by telephone to assess the occurrence of adverse events as described in footnote j. The rationale for the telephone call is to allow proactive medical management of adverse events and to minimize delayed reporting by patient, owing to the monthly clinic visit schedule.

[e] Informed consent, including optional consent, must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Medical history includes clinically significant diseases within the previous 5 years, surgeries, complete cancer history (including prior cancer therapies and procedures), complete cardiovascular history, reproductive status, and smoking history (see Section 4.5.2).

[g] A FFPE tumor tissue block or a minimum of 10 freshly cut, unstained, serial slides from patients will be submitted at screening. Cytologic or fine-needle aspiration samples are not acceptable. Tumor tissue from bone metastases is not acceptable. If archival tissue is insufficient, a fresh tumor biopsy meeting the minimum requirement may be obtained with if the patient's consent.

[h] Concomitant medications include any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 14 days prior to prior to initiation of study treatment until 28 days after the last dose of study treatment.

[i] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed by the investigator as stable and no further changes are expected, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered by the investigator to be related to study treatment or trial-related procedures until a final outcome can be reported.

[j] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At study discontinuation visit, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Perform a limited, symptom-directed physical examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Vital signs include respiratory rate, pulse (heart) rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] ECG recordings will be obtained as part of the screening assessment, as clinically indicated during study treatment, and at the end of treatment visit.

[n] If the progression disease will be based on PSA at screening, at least two PSA samples (obtained at least 1 week apart) will be assessed locally at screening for confirmation of eligibility (if no data are available prior to screening). Central testing required for Day 1 of each cycle and at study treatment discontinuation. Patients who discontinue study treatment prior to 12 weeks of treatment should have an assessment of PSA in post-treatment follow-up period that is at least 12 weeks following the start of study treatment if they have not yet started another systemic treatment.

[o] For patients with prostate cancer, serum testosterone samples will be assessed locally at screening for determination of eligibility and at study treatment discontinuation to confirm testosterone remains at castration level.

[p] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[q] Test may be performed ≤ 96 hours prior to dosing for each clinic visit during study treatment; screening assessments performed ≤ 96 hours prior to dosing on Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1.

[r] For all clinic visits during study treatment, the glucose level of the patient must be performed ≤96 hours prior to dosing and must be reviewed prior to further ipatasertib administration and prior to discharge from the clinic. Blood glucose may be obtained by a glucometer (fingerstick). For fasting blood glucose, patients should fast ≥ 8 hours prior to testing.

[s] Nonfasting blood glucose samples are to be collected on PK collection days at the same timepoints listed for ipatasertib PK sample in Appendix 3. Patients will be required to eat a meal approximately 30 minutes postdose on Day 1 *of* Cycle 1 and Day 15 *of* Cycle 1. The exact date may be shifted by ±7 days or more to match the PK collection per Appendix 3.

[t] Chemistry panel includes sodium, potassium, chloride, magnesium, bicarbonate, BUN (or urea), creatinine, total protein, albumin, calcium, and liver function test panel (total and direct bilirubin, alkaline phosphatase, ALT, AST, and LDH.

[u] Women of childbearing potential must have a negative serum pregnancy test result within *3* days prior to initiation of study drug.

[v] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood).

[w] Tumor assessments should include the chest, abdomen, and pelvis (and other body regions if clinically indicated) at screening and at subsequent tumor assessments, even if there are no detectable lesions at baseline. CT scans are the preferred imaging modality for tumor assessments. MRI scans may be substituted for CT scans and the same imaging method used at screening should be used throughout the study. Responses will be assessed according to RECIST v1.1. For patients with prostate cancer, CT or MRI assessments for soft tissue lesions should continue per Section 4.5.6 until radiographically assessed disease progression regardless of study treatment discontinuation.

[x] Tumor assessments should be performed ± 2 weeks of the scheduled cycles for the first 6 months and then every 12 weeks (or 3 cycles), thereafter, and as clinically indicated. At the investigator's discretion, imaging may be repeated at any time if progressive disease is suspected. The frequency of tumor assessments may be further reduced after 1 year with approval of the Medical Monitor. Tumor assessments at the end of treatment visit are not required if radiographic disease progression per RECIST v1.1 or PCWG3 criteria (if applicable) has been documented previously or if the last tumor assessments were performed <4 weeks prior to the end of treatment visit. If an initial CR or PR is noted, confirmatory scans should be performed ≥4 weeks later. In the case of SD, follow-up measurements should have met the SD criteria at least once after study entry at a minimum interval of no less than 4 weeks. For patients with prostate cancer, tumor assessments should continue per above schedule until radiographically assessed disease progression even if study treatment has been discontinued for other reasons. For patients with breast and ovarian cancer, continuation of tumor assessments is preferred but not required.

[y] A technetium bone scan will be performed at screening (within 42 days before starting study treatment) to evaluate for the presence of bone metastases. For patients with prostate cancer, bone scans must continue per Section 4.5.6 until radiographically assessed disease progression regardless of study treatment discontinuation. For patients with breast and ovarian cancer, a bone scan is needed for screening assessment. For patients with known or suspected bone metastases, follow up bone scans should be done at time of tumor assessments and at the study treatment discontinuation visit (unless followed by other imaging modalities).

[z] If dosing of study treatment is withheld for any reason, study day count should continue and the omitted dose will not be made up and will be reported on the eCRF as "not administered" for that day. *For patients enrolled in Part 1, rucaparib should be started in the evening of Day 1 of Cycle 1 following collection of all ipatasertib PK samples.*

[aa] See Appendix 2 for PK sample collection.

[bb] Samples will be collected only at sites with local regulatory authority approval. See Appendix 3 for further details

[cc] The optional RBR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study. See Appendix 3 for further details.

[dd] The optional predose tumor biopsy specimen will be obtained after eligibility criteria have been fulfilled and prior to Day −7 of Cycle 1. A subsequent biopsy will be performed on either Day −1 or *Day* 1 of Cycle 1, prior to the administration of rucaparib. An additional biopsy will be collected on Day 15 of Cycle 2. See the laboratory manual for details.

[ee] The optional predose tumor biopsy specimen will be obtained after eligibility criteria have been fulfilled and prior to Day 1 of Cycle 1. An additional biopsy will be collected on Day 15 of Cycle 2. See the laboratory manual for details.

Appendix 2
Schedule of Pharmacokinetic Samples (Parts 1 *and* 2)

Table 1 Schedule of Pharmacokinetic Samples in Dose-Escalation Phase (Part 1)

Visit	Timepoint	Sample Type
Cycle 1, Day –7 [a]	Prior to first ipatasertib administration	Ipatasertib PK (Plasma)
Cycle 1, Day 1 [b]	1 hour (±10 min) post-ipatasertib dose	Ipatasertib PK (Plasma)
	2 hour (±10 min) ipatasertib post-dose	Ipatasertib PK (Plasma)
	3 hour (±30 min) ipatasertib post-dose	Ipatasertib PK (Plasma)
	5 hour (±30 min) ipatasertib post dose	Ipatasertib PK (Plasma)
Cycle 1, Day 15 [c]	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)
	1 hour (±10 min) post-ipatasertib dose	Ipatasertib PK (Plasma)
	2 hour (±10 min) post-ipatasertib dose	Ipatasertib PK (Plasma)
	3 hour (±30 min) post-ipatasertib dose	Ipatasertib PK (Plasma)
	5 hour (±30 min) post-ipatasertib dose	Ipatasertib PK (Plasma)
Cycle 2, Day 1 [c]	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)
Cycle 2, Day 15 [c]	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)

CPI =coproporphyrin I; CPIII =coproporphyrin III; PK = pharmacokinetic.

Note: Ipatasertib PK samples will be collected for analysis of both ipatasertib and its metabolite G-037720.

[a] The Cycle 1, Day –7 assessment should be done prior to start of ipatasertib and rucaparib administration. *The sample will be used for measurement of baseline CPI and CPIII levels prior to treatment initiation.*

[b] PK sampling on Day 1 of Cycle 1 should be completed before initiation of rucaparib therapy.

[c] If a patient's ipatasertib or rucaparib treatment has been interrupted for ≥1 day immediately before the Cycle 1, Day 15 and Cycle 2 visits, PK samples may be rescheduled to another day when both study treatments have been given for at least 5 consecutive days. Cycle 1, Day 15 and Cycle 2 visit assessments during the treatment period should be performed within ±7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Table 2 Schedule of Pharmacokinetic Samples in Dose-Expansion Phase (Part 2)

Visit	Timepoint	Sample Type
Cycle 1, Day 15	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)
Cycle 2, Day 1 [a]	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)
Cycle 2, Day 15 [a]	Prior to ipatasertib and rucaparib administration	Ipatasertib PK (Plasma) Rucaparib PK (Plasma)

PK = pharmacokinetic.

Notes: Except for Cycle 1, Day 1, all other study visits and assessments during the treatment period should be performed within ±7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Ipatasertib PK samples will be collected for analysis of both ipatasertib and its metabolite G-037720.

[a] If a patient's ipatasertib or rucaparib treatment has been interrupted for ≥1 day immediately before the visit, PK samples may be rescheduled to another day when both study treatments have been given for at least 5 consecutive days.

Appendix 3
Schedule of Biomarker Samples (Parts 1 *and* 2)

Table 1 Schedule of Biomarker Samples in Dose-Escalation Phase (Part 1)

Visit	Timepoint	Sample Type
Cycle 1, Day −7 (Part 1)	Prior to first ipatasertib administration	Blood sample for WGS control
		Blood sample for pharmacogenomics
		Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers
		Blood sample for RBR (for DNA extraction; optional)
Cycle 2, Day 1	Prior to ipatasertib and rucaparib administration	Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers
Treatment discontinuation		Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers

RBR = *Research* Biosample Repository; WGS = whole genome sequencing.

Table 2 Schedule of Biomarker Samples in Dose- Expansion Phase (Part 2)

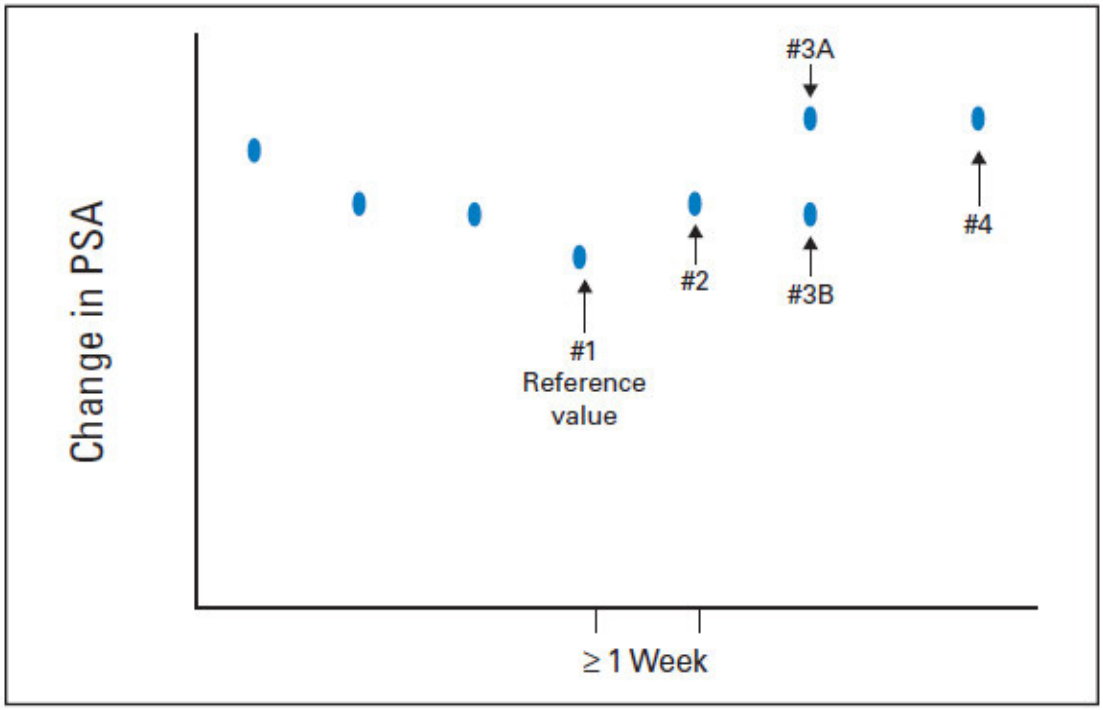
Visit	Timepoint	Sample Type
Cycle 1, Day 1	Prior to first ipatasertib administration	Blood sample for WGS control
		Blood sample for pharmacogenomics
		Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers
		Blood sample for RBR (for DNA extraction; optional)
Cycle 2, Day 1	Prior to ipatasertib and rucaparib administration	Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers
Treatment discontinuation		Plasma sample for somatic tumor mutations
		Plasma sample for exploratory biomarkers

RBR = *Research* Biosample Repository; WGS = whole genome sequencing.

Appendix 4
Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix 5
PSA Progression Eligibility Criteria



PSA=prostate-specific antigen.

Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 1 ng/mL or higher.

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Appendix 6
Criteria for Radiographic Progression per Prostate Cancer Working Group 3

Date Progression Detected (Visit) [a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 8	Bone lesions: Two or more new lesions compared to **baseline** bone scan by PCWG3.	Timing: at least 6 weeks after progression identified or at Week 16 visit. [c]	Two or more new bone lesions on bone scan (compared to Week 8 scan).
	Soft tissue lesions: Progressive disease on CT or MRI scan by RECIST v1.1 [b]	No confirmatory scan required for soft tissue disease progression.	NA
Week 16 or later	Bone lesions: Two or more new lesions on bone scan compared **to Week 8** bone scan.	Timing: at least 6 weeks after progression identified; required for bone lesions observed on bone scan [c]	Persistent [d] or increased number of bone lesions on bone scan compared to prior scan.
	Soft tissue lesions: Progressive disease on CT or MRI scan by RECIST v1.1. [b]	No confirmatory scan required for soft tissue disease progression.	NA

CT = computed tomography; MRI = magnetic resonance imaging; NA = not applicable; PCWG3= Prostate Cancer Working Group 3, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Adapted from Scher et al. 2016.

[a] Progression detected by bone scan at an unscheduled visit will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan. Progression detected by bone scan at an unscheduled visit prior to Week 12 will require a confirmatory scan at least 6 weeks later showing two or more new bone lesions on bone scan.

[b] For RECIST v1.1, see Appendix 8. Up to five lesions (with a maximum of 2 lesions per organ) will be recorded as target lesions (e.g., lung, liver, adrenal, nodal).

[c] Confirmation must occur at the next available scan regardless of whether the patient will continue study treatment.

[d] For confirmation, at least two of the lesions first identified as new must be present at the next available scan.

Appendix 7
Modified Gynecologic Cancer InterGroup (GCIG) Guidelines

GCIG GUIDELINES FOR RESPONSE USING CA-125 (ADAPTED FOR USE IN THIS TRIAL)

Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125) definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires at least one pre-treatment sample $> 2 \times$ upper limit of normal (ULN) and two post-treatment samples confirming a response.

A response to CA-125 has occurred if there is at least a 50% decrease as the result of the treatment. The pre- or post-treatment samples must satisfy the following criteria:

1. There must be at least one sample that is $> 2 \times$ ULN prior to initiation of treatment.
2. The second sample (post-treatment) must be $\leq 50\%$ of the pre-treatment sample.
3. The confirmatory third sample must be ≥ 21 days after the second sample and $\leq 110\%$ of the second sample.
4. Any intervening samples between samples 2 and 3 must be $\leq 110\%$ of the previous sample unless considered to be increasing because of tumor lysis.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

REFERENCE:

Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA-125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21(2):419–23.

Appendix 8
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph

nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the study, all lesions (nodal and non-nodal) that are recorded at baseline should be recorded as actual measurements at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- **Non-CR/Non-PD**: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease (PD) for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion

should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (With or Without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave

a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.