| | |
|---|---|
| **Official Protocol Title:** | A Phase 2 Study of Olaparib Monotherapy in Participants with Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer |
| **NCT Number:** | NCT03742895 |
| **Document Date:** | 12-Aug-2025 |

# Title Page

**THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).**

**Protocol Title:** A Phase 2 Study of Olaparib Monotherapy in Participants with Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer

**Protocol Number:** 002-04

**Compound Number:** MK-7339

**Sponsor Name:**

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

**Legal Registered Address:**

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

**Regulatory Agency Identifying Number(s):**

| | |
|---|---|
| NCT | NCT03742895 |
| IND | 139,696 |
| EudraCT | 2018-003007-19 |
| EU CT | 2022-500797-34 |
| WHO/UTN | U1111-1278-1505 |

**Approval Date:** 12 August 2025

## Sponsor Signatory

Typed Name:
Title:

Date

**Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).**

## Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| Amendment 04 | 12-AUG-2025 | As the protocol-specified analyses, other than exploratory biomarker analyses, have been completed, the study has been amended to discontinue efficacy and survival follow-up for all participants. Additionally, imaging scans will no longer undergo central review, and central laboratory assessments will be removed for participants receiving study intervention. |
| Amendment 03 | 02-JUN-2022 | To allow *BRCA* testing to be performed at both local and central levels for enrollment; and to add an optional prescreening visit for obtaining samples for *BRCA* testing. |
| Amendment 02 | 23-SEP-2020 | To add Cohort 3 (participants with somatic breast cancer susceptibility gene 1/2 mutated [*BRCA*m] breast cancer) and to add language to allow an increase in sample size for Cohort 1 (*BRCA*m) and Cohort 2 (homologous recombination repair [HRR] mutated [HRRm] or homologous recombination deficiency positive [*BRCA1/2* non-mutated, HRR-non-mutated]) as the study progresses. |
| Amendment 01 | 28-JAN-2019 | To define the loss of heterozygosity (LOH) cutoff that will be used to determine a positive versus a negative score. |
| Original Protocol | 07-SEP-2018 | Not applicable |

# PROTOCOL AMENDMENT SUMMARY OF CHANGES

## Amendment: 04

## Overall Rationale for the Amendment:

As the protocol-specified analyses, other than exploratory biomarker analyses, have been completed, the study has been amended to discontinue efficacy and survival follow-up for all participants. Additionally, imaging scans will no longer undergo central review, and central laboratory assessments will be removed for participants receiving study intervention.

## Summary of Changes Table

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Primary Reason for Amendment** | | |
| Section 1.1, Synopsis | Duration of Participation: Imaging scans will no longer undergo central review. Participants on study intervention should continue local tumor imaging as per investigator discretion and SOC. | To address a change in strategy. The protocol-specified analyses, other than exploratory biomarker analyses, have been completed. Consequently, additional tumor scans and response assessments are no longer necessary. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Additional Changes** | | |
| Title Page | Added NCT and WHO/UTN numbers. | To include current trial registry information. |
| Section 1.1, Synopsis | Overall Design: Updated estimated duration of study from 7 years to 8 years. | Based on the current estimated time from FPE to LPLV of over 7.5 years. |
| | Duration of Participation: As of Amendment 04, participants currently on treatment can stay on treatment until one of the conditions from the discontinuation criteria is met, and participants who discontinue study intervention for any reason will be discontinued from the study without further follow-up. | Refer to Section 1.1 rationale about strategic shift. |
| | Duration of Participation: Pharmacokinetics/pharmacodynamics and biomarker samples will no longer be collected (but local safety laboratory assessments should continue as per institutional standards), and PROs will be discontinued. | Refer to Section 1.1 rationale about strategic shift. |
| | Duration of Participation: Described the final study visit for participants discontinuing from study intervention, and referred to Section 8.4.1 for safety reporting. | Refer to Section 1.1 rationale about strategic shift. |
| | Duration of Participation: Participants on efficacy or survival follow-up are considered to have completed the study. | Refer to Section 1.1 rationale about strategic shift. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Duration of Participation: Added a statement to indicate the text that is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 1.2, Schema | Figure 1: Added footnote to specify that any remaining participants who discontinue study intervention for any reason will be discontinued from the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Figure 1: Added footnote to specify that imaging scans will no longer be assessed by BICR, and disease progression will be determined by the investigator per SOC imaging. | Refer to Section 1.1 rationale about strategic shift. |
| | Figure 1: Added a note to indicate the text that is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 1.3, Schedule of Activities (SoA) | Added a paragraph introducing a revised SoA and describing what is being discontinued and what should be continued as of Amendment 04. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a new SoA table listing only study procedures and assessments being continued as of Amendment 04. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement before the original SoA table to indicate it is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 2.2.4, Ongoing Clinical Studies | Added a statement to indicate the studies have been completed and referenced the IB. | The studies described are completed. |
| | Added a statement to indicate the text that is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| | Removed statement referring to the IB for ongoing clinical study data. | Refer to Section 2.2.4 rationale, studies are completed. |
| Section 3, Hypothesis, Objectives, and Endpoints | Added a statement to indicate that protocol-specified analyses, other than exploratory biomarker analyses, have been completed and that text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 4.1, Overall Design | As of Amendment 04, participants currently on treatment can stay on treatment until one of the conditions from the discontinuation criteria is met, and participants who discontinue study intervention for any reason will be discontinued from the study without further follow-up. | Refer to Section 1.1 rationale about strategic shift. |
| | For participants on treatment, imaging scans are no longer required to be submitted to central review, and continued imaging assessments will be performed per investigator discretion and SOC. | Refer to Section 1.1 rationale about strategic shift. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Pharmacokinetics/pharmacodynamics and biomarker samples will no longer be collected (but local safety laboratory assessments should continue as per institutional standards), and PROs will be discontinued. | Refer to Section 1.1 rationale about strategic shift. |
| | Described the final study visit for participants discontinuing from study intervention, and referred to Section 8.4.1 for safety reporting. | Refer to Section 1.1 rationale about strategic shift. |
| | Participants on efficacy or survival follow-up are considered to have completed the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the text that is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 4.4, Beginning and End of Study Definition | As of Amendment 04, participants in efficacy or survival follow-up will be discontinued from the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Removed the definition of participants lost to follow-up. | To remove unnecessary text. |
| | Added maximum duration of the study to attain final assessment. | To align with the EU CTR. |
| Section 5, Study Population | As of Amendment 04, no additional participants will be enrolled in the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the text that is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 7.1, Discontinuation of Study Intervention | Participants who discontinue study intervention for any reason will also discontinue the study without further follow-up. | Refer to Section 1.1 rationale about strategic shift. |
| | Removed the requirement for continued monitoring of participants who discontinue study intervention. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a bullet for participants who transition to a post-trial access program for olaparib. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8, Study Assessments and Procedures | Added a reference to the revised SoA. | Refer to Section 1.1 rationale about strategic shift. |
| | Prior/concomitant medication review and subsequent antineoplastic therapy status will continue to be collected until study discontinuation. | Refer to Section 1.1 rationale about strategic shift. |
| | Optional tumor collections are discontinued. | Refer to Section 1.1 rationale about strategic shift. |
| | Local tumor imaging assessments should continue per investigator discretion and SOC. Bone and brain scans will be performed as per SOC or clinical indication, and other imaging scans will be as per investigator discretion and SOC. | Refer to Section 1.1 rationale about strategic shift. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Tumor response assessments by BICR will be discontinued. The investigator will assess tumor response as per investigator discretion and SOC. | Refer to Section 1.1 rationale about strategic shift. |
| | Local safety laboratory assessments will be performed as per institutional standards. | Refer to Section 1.1 rationale about strategic shift. |
| | Other safety assessments to be continued are listed. | Refer to Section 1.1 rationale about strategic shift. |
| | PROs will be discontinued. | Refer to Section 1.1 rationale about strategic shift. |
| | Pharmacokinetics/pharmacodynamics and biomarker samples will no longer be collected. | Refer to Section 1.1 rationale about strategic shift. |
| | Efficacy and survival follow-up will be discontinued. | Refer to Section 1.1 rationale about strategic shift. |
| | Participants on study intervention and experiencing clinical benefit may continue until discontinuation criteria are met. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.1.1.1, General Informed Consent | Treatment beyond progression will no longer be offered except where participants are already receiving it or approved to receive it beyond progression. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.1.5.3, Subsequent Antineoplastic Therapy | Information about subsequent antineoplastic therapy after study intervention discontinuation will no longer be collected. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.1.9, Discontinuation and Withdrawal | Participants who complete study treatment or meet EOT criteria will be discontinued from the study after the EOT/30-day Safety Follow-up Visit. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.1.12.2, Tumor Tissue for Biomarker Analysis | Optional tumor collection at EOT/DC is no longer required. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.2.1, Tumor Imaging and Assessment of Disease | Tumor imaging will be completed at investigator discretion, per SOC, and images will no longer undergo central review. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.2.1.2, Tumor Imaging During the Study | Tumor imaging will be completed at investigator discretion, per SOC, and images will no longer undergo central review. | Refer to Section 1.1 rationale about strategic shift. |
| | Investigators should use RESIST 1.1 to assess tumor response and progressive disease. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.2.1.3, End of Treatment and Follow-up Tumor Imaging | Participants discontinuing study intervention for any reason will discontinue from the study with no further follow-up. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.2.1.4, RECIST 1.1 and PCWG-Modified RECIST 1.1 Assessment of Disease | Tumor images will no longer undergo central review, and investigators should use RESIST 1.1 to assess tumor response and progressive disease. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.2.2, Quality of Life Assessments | PROs will no longer be required. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information | Table 10: Updated periods and duration for potential DILI events meeting biochemical criteria of Hy's Law. | To maintain continued regulatory reporting compliance in alignment with new health authority DILI reporting requirements. |
| | Table 10: Revised text for Pregnancy/Lactation Exposure row. | To add details not previously specified. |
| | Table 10: Updated text in ECI rows. | Revised due to potential DILI events now having a separate row. |
| Section 8.4.3, Follow-up of AE, SAE, and Other Reportable Safety Event Information | Added potential DILI events meeting biochemical criteria of Hy's Law to list of other reportable safety events. | Refer to Section 8.4.1 rationale about DILI reporting requirements. |
| Section 8.4.4, Regulatory Reporting Requirements for SAE | Added a statement describing how to report SUSARs. | Refer to Section 4.4 rationale about the EU CTR. |
| Section 8.4.7, Events of Clinical Interest (ECIs) | ECI updated to include potential DILI meeting biochemical criteria of Hy's Law, with associated reporting requirements. | Refer to Section 8.4.1 rationale about DILI reporting requirements. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.6, Pharmacokinetics | PK samples are no longer required. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.7, Pharmacodynamics | Pharmacodynamic samples are no longer required. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.10, Biomarkers | Biomarker samples will no longer be collected. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.12.4.1, Safety Follow-up Visit | Specified that the Safety Follow-up Visit should be combined with the EOT Visit. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.12.4.2, Efficacy Follow-up Visits | Efficacy follow-ups are no longer required, and participants on efficacy follow-up will be discontinued from the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following paragraphs are retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 8.12.4.3, Survival Follow-up Assessments | Survival follow-ups are no longer required, and participants on survival follow-up will be discontinued from the study. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following paragraphs are retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 9, Statistical Analysis Plan | Added a statement to indicate the protocol-specified analyses other than exploratory biomarker analyses have been completed. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following paragraphs are retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 10.1.1, Code of Conduct for Clinical Trials | Updated wording to include additional standards and regulations. | Refer to Section 4.4 rationale about the EU CTR. |
| Section 10.1.3, Data Protection | Added text regarding Sponsor's EU-approved Binding Corporate Rules. | Refer to Section 4.4 rationale about the EU CTR. |
| Section 10.1.6, Compliance With Study Registration and Results Posting Requirements | Updated referenced EU regulation and added a submission website link. | Refer to Section 4.4 rationale about the EU CTR. |
| Section 10.1.7, Compliance with Law, Audit, and Debarment | Added text for investigators located in countries with serious breach reporting requirements. | Refer to Section 4.4 rationale about the EU CTR. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.1.8, Data Quality Assurance | Added the EU CTR requirement for a longer retention period for records and documents. | Refer to Section 4.4 rationale about the EU CTR. |
| Section 10.2, Appendix 2: Clinical Laboratory Tests | Hematology and chemistry panels will be performed as per institutional standards. | Refer to Section 1.1 rationale about strategic shift. |
| | Added a statement to indicate the following text is retained for historical perspective. | Refer to Section 1.1 rationale about strategic shift. |
| Section 10.3.3, Definition of SAE | Added potential DILI events meeting biochemical criteria of Hy's Law to definition of SAE. | Refer to Section 8.4.1 rationale about DILI reporting requirements. |
| Section 10.3.4, Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR) | Added section. | Refer to Section 8.4.1 rationale about details not previously specified. |
| | Renumbered former Sections 10.3.4 through 10.3.6 to current Sections 10.3.5 through 10.3.7. | Renumbering due to addition of new Section 10.3.4. |
| Throughout | Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document. | To ensure clarity and accurate interpretation of the intent of the protocol. |

# Table of Contents

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Phase 2 Study of Olaparib Monotherapy in Participants with Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer

**Short Title:** Olaparib Monotherapy in HRRm or HRD Positive Cancer

**Acronym:** Not applicable

**Hypotheses, Objectives, and Endpoints:**

No hypothesis testing will be performed.

Male and female participants with previously treated, advanced (metastatic and/or unresectable) HRRm and/or HRD positive solid tumors will be enrolled as:

- *BRCA1/2* mutated (excluding *BRCA*m breast and ovarian cancers); hereafter referred to as Cohort 1
- HRRm (*BRCA1/2* non-mutated, including breast and ovarian cancers) and/or HRD positive (HRR non-mutated); hereafter referred to as Cohort 2
- Somatic *BRCA*m (s*BRCA*m) breast cancer; hereafter referred to as Cohort 3

| Primary Objectives | Primary Endpoints |
|---|---|
| - Objective: To evaluate the objective response rate (ORR) as assessed by blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) or Prostate Cancer Working Group (PCWG)-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | - Objective response (OR): complete response (CR) or partial response (PR). |

| Secondary Objectives | Secondary Endpoints |
|---|---|
| - Objective: To evaluate the duration of response (DOR) as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | - DOR: the time from the date a response was first documented until either disease progression or death due to any cause, whichever occurs first. |
| - Objective: To evaluate overall survival (OS), following administration of olaparib in Cohort 1, Cohort 2, and Cohort 3. | - OS: the time from the date of the first dose to death due to any cause. |
| - Objective: To evaluate progression-free survival (PFS) as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | - PFS: the time from the date of the first dose until either disease progression or death due to any cause, whichever occurs first. |
| - Objective: To evaluate the safety and tolerability of olaparib in Cohort 1, Cohort 2, and Cohort 3. | - Adverse events (AEs).<br>- Study intervention discontinuation due to AEs. |
| - Objective: To evaluate the ORR, DOR, OS, and PFS in participants who are (1) HRRm, (2) HRD positive, and (3) in all participants regardless of biomarker status following olaparib administration in Cohort 1 and Cohort 2. | - OR<br>- DOR<br>- OS<br>- PFS |
| - Objective: To assess time to earliest progression by CA-125 following olaparib administration in participants with *BRCA1/2* non-mutated ovarian cancer. | - CA-125 ≥2 × ULN on 2 occasions, 1 week apart<br>- CA-125 ≥2 × the nadir value on 2 occasions, 1 week apart (for participants with elevated CA-125 ≥ULN at baseline) |
| - Objective: To evaluate the PSA response rate to olaparib administration in participants with prostate cancer. | - PSA response: a reduction in the PSA level of 50% or more from baseline measured twice at least 3 weeks apart. |
| - Objective: To evaluate progression-free survival after next-line treatment (PFS2), as assessed by the investigator, in participants with s*BRCA*m breast cancer. | - PFS2: the time from the date of the first dose to subsequent disease progression on the next-line of treatment or death, whichever occurs first. |

## Overall Design:

| | |
|---|---|
| Study Phase | Phase 2 |
| Primary Purpose | Treatment |
| Indication | The treatment of participants with HRRm or HRD positive cancer |
| Population | Participants with advanced HRRm and/or HRD positive cancer not amenable to curative treatment |
| Study Type | Interventional |
| Intervention Model | Single Group<br>This is a multi-site study |
| Type of Control | No treatment control |
| Study Blinding | Unblinded Open-label |
| Masking | No Masking |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 8 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact |

## Number of Participants:

Approximately 390 participants with HRRm or HRD positive cancer not amenable to curative treatment will be enrolled in this study. Enrollment may be expanded to approximately 500 participants if sufficient evidence of activity is observed.

**Intervention Groups and Duration:**

| | |
|---|---|
| Intervention Groups | All participants will receive olaparib 300 mg twice daily (BID). Eligible participants will be grouped as follows:<br>• Cohort 1 (~84 participants): *BRCA*m (excluding *BRCA*m breast and ovarian cancers).<br>Note: If sufficient evidence of activity is observed, enrollment of participants with *BRCA*m tumors into Cohort 1 may be expanded to ~150 participants.<br>• Cohort 2 (~286 participants): ~174 participants with HRRm (*BRCA1/2* non-mutated) and ~112 participants with HRD positive (*BRCA1/2* non-mutated and no mutations detected in the remaining 13 gene HRR panel).<br>Note: If sufficient evidence of activity is observed, enrollment of participants with HRD positive, HRR non-mutated tumors into Cohort 2 may be expanded to ~156 participants.<br>• Cohort 3 (~20 participants): s*BRCA*m breast cancer<br>Note: Cohort 3 will not be open for enrollment in Japan.<br>HRRm, HRD positive, *BRCA*m, and *BRCA1/2* non-mutated tumors are defined as follows:<br>**HRRm:** Participants with tumors that harbor known or suspected deleterious mutations in *BRCA1, BRCA2, ATM*, or 1 of the other 12 genes specified among the 15 genes involved in HRR (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L*) based on the Lynparza HRR-HRD Assay.<br>**HRD:** Participants with tumors that harbor a known or suspected deleterious mutation in *BRCA1 or BRCA2* or have a loss of heterozygosity score equal to or greater than the cutoff of 16 based on the Lynparza HRR-HRD Assay.<br>***BRCA*m**: Participants with tumors that harbor known or suspected deleterious mutations in *BRCA1* or *BRCA2* based on the Lynparza HRR-HRD Assay.<br>***BRCA1/2* non-mutated**: A known or suspected deleterious mutation in *BRCA1* or *BRCA2* is not detected in the Lynparza HRR-HRD Assay.<br>**s*BRCA*m** – Participants with tumors that harbor known or suspected deleterious mutations in *BRCA1* or *BRCA2* based on the Lynparza HRR-HRD Assay and do not harbor a germline *BRCA1* or *BRCA2* mutation. |

<table>
<tr><td></td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period/ Vaccination Regimen</th><th>Use</th></tr>
<tr><td>Eligible Participants</td><td>Olaparib</td><td>300 mg</td><td>Twice daily</td><td>Oral</td><td>Daily</td><td>Test Product</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>One arm</td></tr>
<tr><td>Duration of Participa-tion</td><td>As of Amendment 04, participants currently on treatment can remain on study intervention until one of the conditions for discontinuation is met. Those who discontinue study intervention for any reason—eg, adverse event, progressive disease, physician or patient choice, or transition to a post-trial access program for olaparib—will also discontinue from the study without efficacy or survival follow-up. Participants receiving study intervention will no longer be required to submit imaging scans for central review, and continued imaging assessments will be performed per investigator discretion and standard of care (SOC). Pharmacokinetics, pharmacodynamics, biomarker samples, and patient-reported outcomes (PROs) will no longer be collected for these participants. Local safety laboratory assessments (hematology and chemistry) will be performed as per institutional standards.<br><br>The final study visit for participants who discontinue from study intervention should be the combined End-of-Treatment (EOT)/30-day Safety Follow-up Visit, as appropriate. Standard safety reporting per Section 8.4.1 should continue, as applicable.<br><br>Participants on efficacy or survival follow-up are considered to have completed the study.<br><br>The following text is retained for historical perspective.<br><br>Each participant will participate in the study from the time the participant provides documented informed consent form (ICF) through the final protocol-specified contact.<br><br>After a screening phase of up to 42 days, each participant will be assigned to receive study intervention until disease progression is radiographically documented, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of study intervention, investigator’s decision to discontinue the participant, or administrative reasons requiring cessation of treatment.<br><br>After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.1.</td></tr>
</table>

| | |
|---|---|
| | Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer), an increase in CA-125 either ≥2 × the normal value on 2 occasions (performed 1 week apart) or ≥2 × the lowest level it has been during the study (for participants with *BRCA1/2* non-mutated ovarian cancer) on 2 occasions (performed 1 week apart), in the absence of radiologically documented disease progression that is associated with worsening symptomatology and/or performance status, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. Note: In all cases the progression of CA-125 must be clinically significant for the investigator to consider stopping therapy. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.<br><br>Once the participant has achieved the study objective or study has ended, the participant is discontinued from this study. |

**Study Governance Committees:**

| | |
|---|---|
| Executive Oversight Committee | No |
| Data Monitoring Committee | No |
| Clinical Adjudication Committee | No |
| Study governance considerations are outlined in Appendix 1. | |

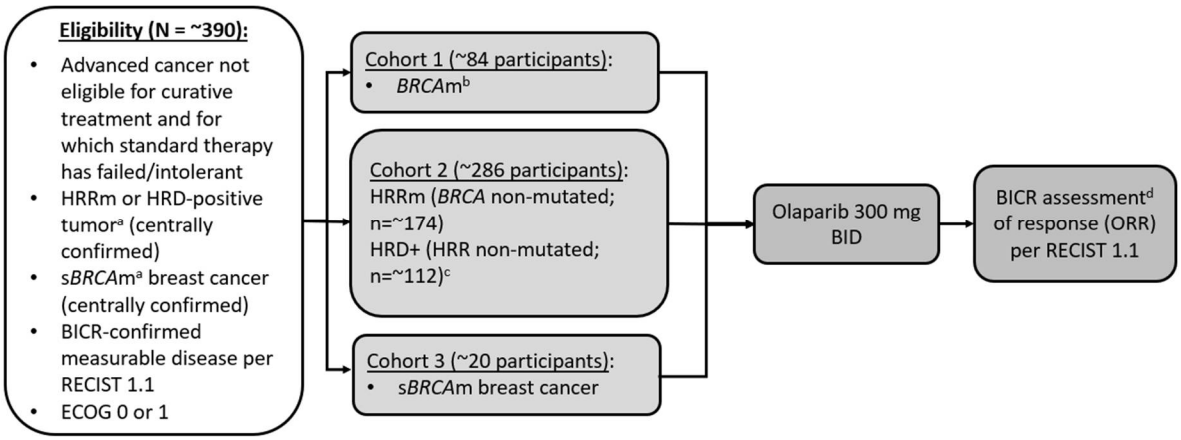
**Study Accepts Healthy Volunteers:** No

A list of abbreviations used in this document can be found in Appendix 8.

## 1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design




BICR = blinded independent central review; BID = twice daily; *BRCA*m = *BRCA* mutated (germline or somatic); ECOG = Eastern Cooperative Oncology group; HRD = homologous recombination deficiency; HRRm = homologous recombination repair mutation; s*BRCA*m = somatic *BRCA* mutated.

a. HRRm, *BRCA* non-mutated is defined as a known or suspected deleterious mutations in *ATM*, or 1 of the other 12 genes specified among the 15 genes involved in HRR (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L*). HRD-positive, HRR non-mutated is defined as an LOH score equal to or greater than the cutoff of 16 based on the Lynparza HRR-HRD Assay. *BRCA* mutated (*BRCA*m) is defined as a known or suspected deleterious mutations in *BRCA1* or *BRCA2.* Participants with *BRCA*m ovarian cancer (germline or somatic) or germline *BRCA*m breast cancer are not eligible for the study. Participants with s*BRCA*m breast cancer may be eligible for Cohort 3. Note: Cohort 3 will not be open for enrollment in Japan.

**As of Amendment 04, any remaining participants who discontinue study intervention for any reason will be discontinued from the study. The following 2 footnotes are retained for historical perspective.**

b. Enrollment of participants with *BRCA*m tumors in Cohort 1 may be expanded to ~150 participants, if sufficient evidence of activity is observed.

c. Enrollment of participants with HRD positive, HRR non-mutated tumors in Cohort 2 may be expanded to ~156 participants, bringing the total in Cohort 2 to ~330 participants, if sufficient evidence of activity is observed.

d. **As of Amendment 04, imaging scans will no longer undergo BICR assessment. Disease progression will be determined by the investigator according to SOC imaging.**

**The following text is retained for historical perspective.**

Note: Specific cohort(s) may be terminated early and/or further enrollment stopped as noted in Section 4.1.1.

## 1.3 Schedule of Activities (SoA)

**As of Amendment 04, the following SoA will apply to ongoing participants.** Imaging scans will no longer undergo central review. However, local tumor imaging assessments should continue as per investigator discretion and SOC. Pharmacokinetics/pharmacodynamics and biomarker samples will no longer be collected, but local safety laboratory assessments (hematology and chemistry panels) will be performed as per institutional standards. PROs will no longer be required. Participants on efficacy or survival follow-up are considered to have completed the study and will be discontinued from the study.

| **Study Period** | **Treatment Period** | | | | | | **EOT/ 30-Day Safety Follow-up Visit[a, b]** | **Notes** |
|---|---|---|---|---|---|---|---|---|
| **Week** | **0** | **4** | **8** | **12** | **16** | **20+[c]** | | |
| **Visit Number** | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **+7** | |
| **Administrative Procedures** | | | | | | | | |
| Prior/concomitant medication review | X | X | X | X | X | X | X | Include blood transfusions during review of concomitant medication |
| Subsequent antineoplastic therapy status | | | | | | | X | |
| **Administration of Study Intervention** | | | | | | | | |
| Olaparib dispensed | X | X | X | X | X | X | | Continuous daily dose of 300 mg BID |
| Container returned | | X | X | X | X | X | X | |
| **Efficacy Procedures** | | | | | | | | **As of Amendment 04, imaging scans will no longer undergo central review. However, local tumor imaging assessments should continue as per investigator discretion and SOC.**<br>**Imaging should continue to be performed until PD is documented (if possible) by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.** |
| ***Cohorts 1 and 2:***<br>Tumor imaging (Chest, Abdomen, and Pelvis required. Imaging of other areas of disease as needed) | SOC[d] | | | | | | | |

| **Study Period** | **Treatment Period** | | | | | | **EOT/ 30-Day Safety Follow-up Visit[a, b]** | **Notes** |
|---|---|---|---|---|---|---|---|---|
| **Week** | **0** | **4** | **8** | **12** | **16** | **20+[c]** | | |
| **Visit Number** | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **+7** | |
| ***Cohort 3:*** Tumor imaging (Chest, Abdomen, and Pelvis required. Imaging of other areas of disease as needed) | SOC[d] | | | | | | | |
| Bone imaging | SOC[d] | | | | | | | |
| Brain imaging | SOC[d] | | | | | | | |
| **Safety Procedures** | | | | | | | | **As of Amendment 04, local safety laboratory assessments (hematology and chemistry panels) will be performed as per institutional standards.** |
| AE monitoring | X | X | X | X | X | X | X | AEs and SAEs that occur through 30 days following cessation of study intervention should be followed and recorded. |
| Complete physical examination | | | | | | | X | |
| Directed physical examination | X | X | X | X | X | X | | Directed physical exam performed as clinically indicated prior to treatment administration. |
| Weight | X | X | X | X | X | X | X | |
| Vital Signs (HR, DBP, SBP, RR, temperature) | X | X | X | X | X | X | X | Assessments performed prior to treatment administration. |
| 12-lead ECG | | | | | | | X | 12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated. |
| Hematology[e] | X | X | X | X | X | X | X | On-treatment samples collected prior to administration of study intervention. |
| Urinalysis[e] | | | | | | | X | |
| Chemistry[e] | X | X | X | X | X | X | X | |
| Urine or Serum β-hCG - WOCBP only | X | X | X | X | X | X | X | Serum test is only required if urine test is positive or is not evaluable. |
| ECOG performance status | | X | X | X | X | X | X | ECOG performance status will be performed prior to the administration of study intervention and at DC. |

| Study Period | Treatment Period | | | | | | EOT/ 30-Day Safety Follow-up Visit[a, b] | Notes |
|---|---|---|---|---|---|---|---|---|
| **Week** | **0** | **4** | **8** | **12** | **16** | **20+[c]** | | |
| **Visit Number** | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **+7** | |

AE = adverse event; β-hCG = β-human chorionic gonadotropin; CR = complete response; BID = twice daily; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Cancer Group; EOT = end of treatment; HR = heart rate; IRT = interactive response system; PD = progressive disease; PRO = patient-reported outcome; Q6W = every 6 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; SOC = standard of care; WOCBP = women of childbearing potential.

a. After the last dose of study drug, each participant should attend a combined EOT/30-day Follow-up Visit. AEs/SAEs will be collected for 30 days after the last dose of study intervention. See Section 8.4.1 for details.
b. All participants will be discontinued from the study once the combined EOT/Safety Follow-up Visit is completed.
c. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.
d. Imaging will be performed as per SOC with no central review.
e. Hematology and chemistry panels and urinalysis will be performed as per institutional standards.

## The following SoA table is retained for historical perspective only and does not apply to Amendment 04.

| Study Period | Screening | | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| **Administrative Procedures** | | | | | | | | | | | | | |
| Prescreening ICF (optional) | X | | | | | | | | | | | | Only for participants who agree to provide an archival tumor tissue from a previous biopsy and/or a blood sample. To be signed before signing main ICF. Participants may sign prescreening ICF while on prior treatment, except as described in Section 5.2. Participants may be rescreened if the 42-day window expires. |
| Informed Consent | X | | | | | | | | | | | | Consent must be obtained prior to performing any protocol-specific procedures. |
| FBR ICF (optional) | X | | | | | | | | | | | | Participants can still participate in the study if they decline to sign the Future Biomedical Research ICF. |
| Inclusion/Exclusion Criteria | X | X | | | | | | | | | | | |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Participant ID card | X | | | | | | | | | | | | At the time of Visit Number 2/Week 0, site personnel should add the allocation number to the Participant ID card. |
| Demographics and medical history | X | | | | | | | | | | | | |
| Cancer history | X | | | | | | | | | | | | |
| History of blood transfusions | X | | | | | | | | | | | | Include history of blood transfusion within previous 120 days from start of study intervention and the reasons, eg, bleeding or myelosuppression |
| Prior/concomitant medication review | | X | X | X | X | X | X | X | X | X | X | | Include blood transfusions during review of concomitant medication |
| Prior platinum use | | X | | | | | | | | | | | Including history of response or progression while on or within 4 weeks of completing the platinum-containing regimen. |
| Obtain allocation number using IRT | | | X | | | | | | | | | | Visit 2/Week 0 study intervention must be administered within 3 days of obtaining allocation number. |
| Subsequent anti-neoplastic therapy status | | | | | | | | | X | X | X | X | |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Survival status | | | ←---------- | ---------- | ---------- | ---------- | ---------- | ----------→ | | | | X | Continued after Investigator determined PD or start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study |
| **Administration of Study Intervention** | | | | | | | | | | | | | |
| Olaparib dispensed | | | X | X | X | X | X | X | | | | | Continuous daily dose of 300 mg BID |
| Container returned | | | | X | X | X | X | X | X | | | | |
| **Efficacy Procedures** | | | | | | | | | | | | | **Imaging should continue to be performed until PD is documented (if possible) by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, or death, whichever occurs first.** |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| ***Cohorts 1 and 2:*** Tumor imaging (Chest, Abdomen, and Pelvis required. Imaging of other areas of disease as needed) | | X | X | | | | | | X[f] | | X | | All imaging visits have a visit window of ±7 days.<br>Screening images are to be captured within 28 days prior to the first dose.<br>For participants with GBM: imaging of the chest, abdomen, and pelvis are not required unless clinically indicated.<br>During the first year, until Week 48, images will be captured Q8W from the date of the first dose.<br>After ~1 year/Week 48, images will be captured Q12W (1st Q12 week image due at Week 60).<br>Imaging timing should follow **calendar days** and should not be adjusted for delays in study intervention. |

| Study Period | Screening | | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| ***Cohort 3:*** Tumor imaging (Chest, Abdomen, and Pelvis required. Imaging of other areas of disease as needed) | | X | X | | | | | | X[f] | | X | | All imaging visits have a visit window of ±7 days.<br>Screening images are to be captured within 28 days prior to the first dose.<br>During the first 6 months, until Week 24, images will be captured Q6W from the date of the first dose.<br>After Week 24, images will be captured Q12W (1st Q12 week image due at Week 36).<br>Imaging timing should follow **calendar days** and should not be adjusted for delays in study intervention. |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Bone imaging | X | | X | | | | | | X[f] | | | | All imaging visits have a visit window of ±7 days.<br>For participants with prostate cancer, a bone scan is required at screening (within 42 days of the first dose) and at all scheduled time points.<br>For all other tumor types, perform within 42 days prior to the first dose ONLY for participants with a history of bone metastases, or who are clinically symptomatic. On-study imaging to be performed as clinically indicated.<br>Perform at CR for participants who were positive at baseline. |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Brain imaging | | X | X | | | | | | X[f] | | | | All imaging visits have a visit window of ±7 days.<br>For participants with GBM, perform at screening (within 28 days of first dose) and at all scheduled time points.<br>For all other tumor types, perform at baseline ONLY for participants with previously documented brain metastases (to confirm stability) or who are clinically symptomatic (see Exclusion Criterion #4). On-study imaging to be performed as clinically indicated.<br>Perform at CR for participants who were positive at baseline. |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| **Safety Procedures** | | | | | | | | | | | | | |
| AE monitoring | X | X | X | X | X | X | X | X | X | X | X | | Any AEs noted prior to ICF should be recorded as medical history.<br>AEs and SAEs that occur through 30 days following cessation of study intervention should be followed and recorded.<br>Any SAE of MDS/AML or new primary malignancy occurring after the 30-day follow-up period should be reported regardless of the assessment of causality. |
| Complete physical examination including height | X | | | | | | | | X | | | | Height at screening only |
| Directed physical examination | | | X | X | X | X | X | X | | | | | Directed physical exam performed as clinically indicated prior to treatment administration. |
| Weight | X | | X | X | X | X | X | X | X | | | | |
| Vital Signs (HR, DBP, SBP, RR, temperature) | X | | X | X | X | X | X | X | X | X | | | Assessments performed prior to treatment administration. |
| 12-lead ECG | X | | | | | | | | X | | | | 12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated. |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Hematology | | X | X | X | X | X | X | X | X | X | | | Screening samples collected within 10 days of first dose of treatment intervention.<br>If screening samples are collected within 5 days of Day 1/Week 0, they do not need to be repeated for Day 1/Week 0 unless clinically indicated in the opinion of the investigator.<br>On treatment samples collected prior to administration of study intervention. |
| Urinalysis | | X | | | | | | | | X | | | |
| Chemistry | | X | X | X | X | X | X | X | X | X | | | |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| CA-125 | | X | X | | X | | X | X | X | X | | | Only to be collected in participants with ovarian cancer.<br>If screening samples are collected within 5 days of Day 1/Week 0, they do not need to be repeated for Day 1/Week 0 unless clinically indicated in the opinion of the investigator.<br>During the first year, until Week 48, samples will be collected Q8W from the date of the first dose.<br>After ~1 year/Week 48, samples will be collected Q12W.<br>CA-125 values ≥2 × the normal value or ≥2 × the lowest level it has been during the study will be repeated within 1 week to confirm the elevation. |
| PSA | | X | X | X | X | X | X | X | X | X | | | Only to be collected in participants with confirmed prostate cancer at Screening. |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| Subsequent progression on next-line therapy (PFS2) assessment | | | | | | | | | | | | X | Progression on next line of therapy or death, whichever occurs first to be documented only for participants enrolled into Cohort 3. |
| HBV and HCV testing | X | | | | | | | | | | | | Refer to Appendix 2. |
| HIV testing | X | | | | | | | | | | | | Testing at screening is only required if mandated by local health authority or local/institutional guidelines. Refer to Appendix 7 for country-specific requirements. |
| Urine or Serum β-hCG - WOCBP only | | X | X | X | X | X | X | X | X | X | | | WOCBP require a negative urine test at screening within either 24 hr (urine) or 72 hr (serum) prior to the first dose of study intervention.<br>Serum test is only required if urine test is positive or is not evaluable.<br>If the pregnancy test during screening is performed within either 24 hr (urine) or 72 hr (serum) of the first dose of study intervention, it does not need to be repeated at Visit 2 (Week 0). |

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Post-Treatment Visits** | | | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a]** | | **0** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | **Safety Follow-up[c]** | **Efficacy Follow-up[c, d]** | **Survival Follow-up[e]** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | | | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **+3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | **30 Days After Last Dose (+7 days)** | **Q8W in Year 1, Q12W thereafter post DC (± 14 days)** | **Q12W (± 14 days)** | |
| PT or INR and aPTT | | X | | | | | | | | | | | Screening samples collected within 10 days of treatment initiation.<br>PT or INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period. |
| ECOG performance status | | X | | X | X | X | X | X | X | | | | Screening assessment to be performed within 7 days prior to treatment initiation.<br>ECOG performance status will also be performed prior to the administration of study intervention and at DC. |
| **Patient-Reported Outcome** | | | | | | | | | | | | | **PROs are to be administered in the order listed, prior to all assessments/procedures**<br>For the first year of study intervention (until Week 48), PROs will be assessed Q8W from the date of the first dose.<br>After 1 year/Week 48 of study intervention, PROs will be assessed Q12W. 1st Q12 week PROs due at Week 60). |
| PGI-S | | | X | | X | | X | X | X | X | | | |
| EuroQol EQ-5D | | | X | | X | | X | X | X | X | | | |
| EORTC QLQ-C30 | | | X | | X | | X | X | X | X | | | |

| Study Period | Screening | | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Screening[a] | | 0 | 4 | 8 | 12 | 16 | 20+[b] | DC | Safety Follow-up[c] | Efficacy Follow-up[c, d] | Survival Follow-up[e] | |
| Visit Number | 1 | | 2 | 3 | 4 | 5 | 6 | 7+ | | | | | |
| Scheduling Window (Days): | –42 to -1 | –28 to –1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | At time of DC | 30 Days After Last Dose (+7 days) | Q8W in Year 1, Q12W thereafter post DC (± 14 days) | Q12W (± 14 days) | |
| CCI | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |

| Study Period | Screening | | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Screening[a] | | 0 | 4 | 8 | 12 | 16 | 20+[b] | DC | Safety Follow-up[c] | Efficacy Follow-up[c, d] | Survival Follow-up[e] | |
| Visit Number | 1 | | 2 | 3 | 4 | 5 | 6 | 7+ | | | | | |
| Scheduling Window (Days): | –42 to -1 | –28 to –1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | At time of DC | 30 Days After Last Dose (+7 days) | Q8W in Year 1, Q12W thereafter post DC (± 14 days) | Q12W (± 14 days) | |
| [redacted] | | | | | | | | | | | | | CCI |
| [redacted] | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | |

| Study Period | Screening | | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Screening[a] | | 0 | 4 | 8 | 12 | 16 | 20+[b] | DC | Safety Follow-up[c] | Efficacy Follow-up[c, d] | Survival Follow-up[e] | |
| Visit Number | 1 | | 2 | 3 | 4 | 5 | 6 | 7+ | | | | | |
| Scheduling Window (Days): | –42 to -1 | –28 to –1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | At time of DC | 30 Days After Last Dose (+7 days) | Q8W in Year 1, Q12W thereafter post DC (± 14 days) | Q12W (± 14 days) | |
| [redacted] | | | | | | | | | | | | | CCI [redacted] |
| [redacted] | | | | | | | | | | | | | [redacted] |
| [redacted] | | | | | | | | | | | | | [redacted] |
| [redacted] | | | | | | | | | | | | | [redacted] |

| Study Period | Screening | Treatment Period | | | | | | EOT | Post-Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | Screening[a] | 0 | 4 | 8 | 12 | 16 | 20+[b] | DC | Safety Follow-up[c] | Efficacy Follow-up[c, d] | Survival Follow-up[e] | |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7+ | | | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | CCI [redacted] | [redacted] | |
| [redacted] | [redacted] | | | | | | | [redacted] | | | | [redacted] |

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = β-human chorionic gonadotropin; BICR = blinded independent central review; BID = twice daily; CA-125 = cancer antigen-125; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Cancer Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EOT = end of treatment; EuroQol EQ-5D = European Quality of Life Five-dimension Five-level Scale Questionnaire; FBR = Future Biomedical Research; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRT = hormone replacement therapy; ICF = informed consent form; ID = identification; INR = International Normalized Ratio; IRT = interactive response system; PD = progressive disease; PGI-S = patient global impression of severity; PRO = patient-reported outcome; PSA = prostate-specific antigen; PT = prothrombin time; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SBP = systolic blood pressure; SOC = standard of care; WOCBP = women of childbearing potential.

a. All screening procedures should be performed within 42 days of allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.
c. If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.
d. Efficacy Follow-Up visits may be scheduled to coincide with Follow-Up imaging. For participants who DC for reasons other than Investigator-documented PD, imaging continues until Investigator-documented PD or initiation of a new anti-neoplastic therapy.
e. Participants who either DC for documented PD or start a new anticancer therapy will enter the Survival Follow-up Phase. Survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
f. Imaging to be performed at DC (±4 weeks [28 days]). If an imaging assessment was obtained within 4 weeks (28 days) prior to the date of DC, imaging is not required at the EOT visit. For participants who DC for PD, this is the final required tumor imaging.
g. Final ctDNA should be collected at the time of PD. Collect at Discontinuation/EOT if participant discontinues study intervention due to PD. Collect at final discontinuation visit in Follow-up if participant discontinues Follow-up due to PD.

# 2 INTRODUCTION

This clinical study will study the PARP inhibitor, olaparib, in the treatment of advanced solid tumors positive for HRRm or HRD.

## 2.1 Study Rationale

Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. The deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have much greater impact on the survival of the tumor cells than on normal cells. This study will evaluate the antitumor effect of olaparib, a PARP inhibitor in advanced cancers with deficiencies in the HRR pathway. Olaparib has demonstrated the ability to selectively kill tumor cells with DNA repair deficiencies in vitro, in vivo, and in clinical studies.

Deficiencies in the HRR pathway constitute a "second hit" for several solid tumor types in vitro and in vivo by limiting the ability of the cells to respond to DNA single strand breaks (SSBs). Olaparib stalls PARP at the replication fork thereby eliminating cellular ability to resume replication. Because high replication defines tumor cells, ORR should reflect the impact of olaparib irrespective of tumor type. Multiple solid tumor types with *BRCA1/2* mutations (*BRCA*m) including ovarian, prostate, breast, and pancreatic tumors have demonstrated a high and durable ORR to olaparib monotherapy. Genomic *BRCA* mutations indicate HRR deficiency and defects in DNA repair and have predicted responses to olaparib treatment in breast, ovarian, pancreas, and prostate cancer. In addition, ATM mutations have been associated with long-term control of prostate cancer by olaparib (TOPARP A). In contrast, gain of function mutations in 5 HRR genes (*BRCA1/2,* partner and localizer of *BRCA2* [*PALB2*]*,* and DNA repair protein RAD51 homolog C/D [*RAD51C/D*]) have been associated with acquired clinical resistance to PARP inhibitors [Wang, X. 2011] [Daemen, A., et al 2012]. Thus, HRRm mutations (in addition to germline *BRCA*m [g*BRCA*m]) and HRD may predict response to olaparib treatment in any advanced solid tumor and support a tumor-agnostic approach.

In 2017, the FDA approved pembrolizumab for the treatment of a variety of MSI-H cancer, regardless of histology or anatomic site of origin. This was the first tumor-agnostic approval of a cancer drug in a biomarker-defined cancer across histologies.

The Phase 2 study described in this protocol will evaluate if HRRm or HRD predicts response to olaparib treatment across multiple tumor types, regardless of tumor histology. The ultimate goal of this study is to gain regulatory approval for olaparib treatment across multiple tumor types.

## 2.2 Background

Approximately 1.4 million adults in the US were newly diagnosed with solid tumors in 2019, 23% with Stage IV disease at diagnosis. Despite recent advances in treatment for most cancer types, disease progression typically leads to treatment with chemotherapies which are generally associated with low response rates, short DOR, and often cumulative toxicities.

Few patients with advanced cancer that have progressed following a first-line therapy will survive longer than 5 years. Thus, those patients without satisfactory alternative treatment options whose disease has progressed after SOC therapies comprise a high unmet medical need population.

Advanced or metastatic cancer patients with HRRm or HRD cancers who fail previous therapies continue to be treated with minimally effective SOC therapies, mainly combination chemotherapy, underlining the high unmet medical need to develop treatments for this unique subset of cancer patients. A high-level review of select clinical studies of advanced cancers with higher HRRm or HRD prevalence (eg, TNBC, pancreatic cancer) demonstrate that, except for platinum-sensitive ovarian cancer, the observed response rate to current SOC chemotherapy does not exceed 21% (Table 1).

Table 1 Clinical Outcomes With Current Standard of Care Treatment Options for Select Tumor Types

| | **Second-Line** | **Third-line** |
|---|---|---|
| | **ORR** | **ORR** |
| Pancreatic [Wang-Gillam, A., et al 2016] | 16% | – |
| Ovarian | | |
| Platinum-sensitive [Pfisterer, J., et al 2006] | – | 31 – 47% |
| Platinum-resistant [Markman, M., et al 2006] [Sehouli, J., et al 2011] | 21% | 19%[a] |
| TNBC [Kaufman, P. A., et al 2015] [Brufsky, A., et al 2012] | 11 – 18% | – |
| Biliary [Lamarca, A., et al 2019] [Lamarca, A., et al 2019a] | 5% | – |
| CRC [Van Cutsem, E., et al 2012] [Grothey, A., et al 2013] | 11% | 1% |
| Sarcoma [Demetri, G. D., et al 2016] | 6.9 – 9.9% | – |
| Prostate [de Wit, R., et al 2019] | – | 12% |

Abbreviations: CRC = colorectal cancer; ORR = objective response rate; TNBC = triple-negative breast cancer.
a. Response rate for conventional daily dose schedule.

### 2.2.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP1, 2, and 3) that is being developed as an oral anticancer therapy, both as monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with HRD, such as ovarian cancers in patients with *BRCA*m, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib traps the inactive form PARP on DNA at sites of SSBs, thereby preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012]. Olaparib has demonstrated efficacy in ovarian, prostate, and pancreatic tumors with *BRCA1* and *BRCA2* mutations and has shown proof-of-concept in tumors with *ATM* mutated (*ATM*m) and other indicators of HRD. The specificity of olaparib for binding PARP at the replication fork during DNA replication is believed to have applicability to tumors associated with mutations in HRR.

Refer to the IB/approved labeling for detailed background information on olaparib.

### 2.2.2 Pharmaceutical and Therapeutic Background

#### 2.2.2.1 Inhibition of PARP as a Target for Cancer

PARP1 and PARP2 are zinc-finger DNA-binding enzymes that play a critical role in DNA repair [Ame, J. C., et al 2004] by sensing DNA damage and converting it into intracellular signals that activate the BER and SSB repair pathways. When a break in DNA occurs, PARP enzymes are recruited to, and bind at, the end of the broken DNA strands, activating their enzymatic activity. PARP subsequently catalyzes the addition of long polymers of ADP ribose onto several other proteins associated with chromatin (eg, PARP, histones, DNA repair proteins), resulting in chromatin relaxation, rapid recruitment of DNA repair proteins, and efficient repair of the break.

Under normal conditions, HRR is the preferred pathway for repairing DNA damage as it is associated with a lower rate of errors compared with other forms of DNA repair [Moynahan, Mary Ellen, et al 1999] [Moynahan, Mary Ellen, et al 2001] [Prakash, R., et al 2015]. During DNA replication (S phase), pre-existing or chemotherapy-induced SSBs are converted to DSBs if not adequately repaired by intracellular mechanisms [Moynahan, Mary Ellen, et al 1999] [Moynahan, Mary Ellen, et al 2001] [Prakash, R., et al 2015], such as HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for homologous recombination, such as *BRCA1* or *BRCA2*) are more likely to use the error-prone NHEJ or alternative (alt)-NHEJ pathways to repair these DSBs and risk accumulating multiple lesions or LOH due to an increase in deletions and accompanying genomic instability. Over time, the accumulation of excessive DNA errors in combination with the inability to complete S phase (ie, because of stalled replication forks due to PARP inhibitor administration), leads to cell death demonstrating that PARP inhibition is synthetic lethal in the context of *BRCA*m [Farmer, H., et al 2005] [Bryant, H. E., et al 2005]. Cells without SSBs or with intact HRR, such as somatic tissue, replicate normally in the presence of a PARP inhibitor, thereby minimizing toxicity.

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill cancer cells with deficiencies in DNA repair pathways.

#### 2.2.2.2 Homologous Recombination Repair in Solid Tumors

Defects in DNA repair drive the genesis of several solid tumors, most notably ovarian and pancreatic. DNA strand breaks occur both as part of the recombination and replication process as well as following intercalating chemotherapy or DNA damaging radiotherapy.

HRR defective tumors are intrinsically sensitive to PARP inhibitors, both in tumor models in vivo [Rottenberg, S., et al 2008] [Hay, T., et al 2009] and in the clinic [Fong, Peter C., et al 2009] [Tutt, A., et al 2010] [Mateo, J., et al 2015] [Kaufman, B., et al 2015]. The main mechanism of action for olaparib results from the trapping inactive PARP on SSBs preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012] and excessive conversion into the more serious DSBs, which are lethal, or results in incomplete/inaccurate repair of the damaged strand leading to a LOH with subsequent aberrant protein translation and function.

Normally, the process of HRR corrects DSBs using proteins such as *BRCA1* and *BRCA2*; however, the HRR armamentarium includes proteins coded by at least 13 other genes including *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*. For example, the protein coded by the *ATM* gene also is involved in the repair of DSB. ATM is activated by DSB and phosphorylates diverse cellular proteins leading to cell cycle arrest (eg, mediator of DNA damage checkpoint 1 [MDC1], checkpoint kinase 2), activates the tumor suppressor p53, contributes to chromatin relaxation and remodeling, and activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Defective *ATM* increases the risk of breast, gastrointestinal, lung, and lymphoid cancers. Moreover, defective *ATM* also appears to correlate with a poor prognosis; however, the risk conferred has not been quantified.

A small percentage of tumors have loss of function mutations in HRR genes, with *BRCA1, BRCA2*, and *ATM* the best characterized and most frequently mutated [Choi, M., et al 2016] [Lord, C. J. 2016]. Approximately half of the HRRm detected are germline mutations [Mateo, J., et al 2015]. While an adverse prognostic impact of germline *BRCA2* mutations has been described in prostate cancer [Castro, E., et al 2015], it is less clear if other germline or somatic HRR gene mutations are associated with similar adverse clinical outcomes. To date, HRRm has not been associated with specific patient or tumor characteristics.

#### 2.2.2.3 Homologous Recombination Deficiency (HRD) in Solid Tumors

Defects in DNA repair can be associated with germline or somatic mutations in genes that encode proteins involved in the HRR pathway, most notably *BRCA1* and *BRCA2*. However, non-*BRCA1/2* deficiencies in HRR produce a similar biologic behavior as mutations in *BRCA1* or *BRCA2*, termed *BRCA*ness [Lord, C. J. 2016]. Cells with non-*BRCA*m HRD have normal *BRCA* structure and function but dysfunctional SSB repair with subsequent synthetic lethality [Lord, C. J. 2016]. Translocations, LOH, and certain insertions-deletions (indels) can contribute to HRD by disrupting genomic repair by inactivation of tumor suppressor genes or expression of recessive harmful alleles. Involvement of the telomere by LOH has predicted response to platinum chemotherapy in ovarian cancer, even in *BRCA* wild-type patients [Vanderstichele, A., et al 2017]. In ARIEL2, the number of LOH aberrations correlated with increased progression-free survival (PFS) to rucaparib (HR= 0.62, p=0.011) in high-grade serous ovarian cancer [Swisher, E. M., et al 2017].

Ovarian cancers with HRD but no *BRCA*m had the same characteristics and behavior as their *BRCA*m counterparts [Murata, S., et al 2016]. Furthermore, only 15% of ovarian epithelial cancers and 5-10% of breast and ovarian cancers with *BRCA*-like behavior had mutations of either *BRCA1* or *BRCA2* [Turner, N., et al 2004] [Lord, C. J. 2016]. In contrast, the Cancer

Genome Atlas Network identified that approximately half of high-grade ovarian tumors have *BRCA*ness mutations [Cancer Genome Atlas Research Network 2011] while approximately 25% of breast cancers manifested *BRCA*ness [Turner, N., et al 2004] [Lord, C. J. 2016].

At least some of the common pathology seen in *BRCA*m and *BRCA*ness-impacted cells may arise from the mutation of genes involved in *BRCA* regulation. For example, X-ray repair cross-complementing protein 1 (XRCC1), microRNA-182 (miR-182), and transforming growth factor (TGF) regulate homologous repair and cells with defects in the genes encoding these proteins/microRNA are sensitive to olaparib in breast cancer models [Gadducci, A. 2017]. Similarly, cyclin-dependent kinase 12 (CDK12) regulates DNA repair in ovarian cancer and tumors harboring mutations in *CDK12* have demonstrated sensitivity to olaparib. Finally, Aurora kinase A and mitochondrial DNA negatively regulate homologous repair and display *BRCA*ness when mutated or depleted, respectively [Gadducci, A. 2017].

In addition, several clinical studies have demonstrated an association between HRD and clinical response to PARP inhibitors. For example, ovarian cancer with *BRCA*ness (HRD) but without germline *BRCA1* mutations responded to olaparib in a Phase 2 study that enrolled 65 patients with advanced high-grade serous and/or undifferentiated ovarian carcinoma and 26 patients with triple-negative breast cancer [Gelmon, K. A., et al 2011]. In the ovarian cancer cohort, confirmed ORs occurred in 7 (41%; 95% CI: 22 to 64) of 17 patients with *BRCA1* or *BRCA2* mutations and 11 (24%; 14 to 38) of 46 without mutations. No confirmed ORs were reported in patients with breast cancer (Table 2).

Table 2 Confirmed Therapeutic Response to Olaparib in Patients With Wild-Type and Mutated *BRCA1* and/or *BRCA2*

| | **Ovarian Cancer** | | | | | | **Breast Cancer** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***BRCA* (N=17)** | | | | **Non-*BRCA* (N=46)** | **Total (N=63)** | ***BRCA* (N=8)** | | | | **Non-*BRCA* (N=15)** | **Total (N=23)** |
| **Response[a]** | ***BRCA1* n (%)** | ***BRCA2* n (%)** | **Both n (%)** | **Total n (%)** | **n (%)** | **n (%)** | ***BRCA1* n (%)** | ***BRCA2* n (%)** | **Both n (%)** | **Total n (%)** | **n (%)** | **n (%)** |
| **Confirmed objective response** | **4 (24)** | **3 (18)** | **0** | **7 (41)** | **11 (24)** | **18 (29)** | **0** | **0** | **0** | **0** | **0** | **0** |
| CR | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PR | 4 (24) | 3 (18) | 0 | 7 (41) | 11 (24) | 18 (29) | 0 | 0 | 0 | 0 | 0 | 0 |
| SD[b] | 5 (29) | 1 (6) | 0 | 6 (35) | 18 (39) | 24 (38) | 2 (25) | 3 (38) | 0 | 5 (63) | 2 (13) | 7 (30) |
| PD | 1 (6) | 1 (6) | 1 (6) | 3 (18) | 13 (28) | 16 (25) | 1 (13) | 2 (25) | 0 | 3 (38) | 12 (80) | 15 (65) |
| Not evaluable | 1 (6) | 0 | 0 | 1 (6) | 4 (9) | 5 (8) | 0 | 0 | 0 | 0 | 1 (7) | 1 (4) |

*BRCA* = breast cancer susceptibility gene; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

a. Data are only for those patients assessable for objective response by Response Evaluation Criteria in Solid Tumors (measurable lesions at baseline). One patient with non-*BRCA* mutated ovarian cancer (best response was progressive disease); and 1 patient with *BRCA1*, 1 with *BRCA2*, and 1 with non-*BRCA* mutated breast cancer (all best responses were stable disease) were excluded.

b. Stable disease for ≥8 weeks.

Adapted from Gelmon et al, 2011 [Gelmon, K. A., et al 2011].

#### 2.2.2.4 Lynparza HRR-HRD Assay

Participants will be enrolled into the study based upon a biomarker-positive result from a tumor tissue-based assay. The Lynparza HRR-HRD Assay is an assay that is under development in partnership with Foundation Medicine, Inc. (FMI). The assay, which is performed in FMI's CLIA-certified and CAP-accredited laboratory, is based on the FoundationOne® comprehensive cancer panel, a test that analyzes the coding sequence of 310 cancer-related genes plus select introns from 31 genes. The Lynparza HRR-HRD Assay detects base substitutions, insertions and deletions, homozygous deletions, and truncating rearrangements in each of the 15 HRR genes (Section 2.2.2.2). Each gene variant is evaluated to check if it is a qualifying HRR mutation positive variant based on the predefined custom Lynparza HRR-HRD Assay classification algorithm. In addition, the assay computes the percent genomic LOH for each tumor by inferring LOH regions across the 22 autosomal chromosomes using the genome-wide copy number profile and minor allele frequencies of more than 3500 germline SNPs. The results for *BRCA*m and percent LOH are used to determine HRD status.

A participant has a qualifying mutation if any deleterious or suspected deleterious mutation is found in the HRR genes (Section 2.2.2.2). A mutation is regarded as deleterious if it results in protein truncation (which includes nonsense, frameshift, or consensus splice site mutations), or select missense mutations well-known to be deleterious in ClinVar/Breast Cancer Information Core databases. Furthermore, larger scale alterations such as genomic truncating rearrangements or homozygous deletions will also be classified as qualifying.

### 2.2.3 Preclinical and Clinical Studies

The preclinical experience with olaparib is fully described in the IB. Olaparib, as monotherapy, shows activity in tumor cells lacking *BRCA1* (*BRCA1*$^{-/-}$) and/or *BRCA2* (*BRCA2*$^{-/-}$). Studies indicate that loss of *BRCA1* and *BRCA2* sensitizes cells to PARP inhibition, resulting in selective cell death of *BRCA1* $^{-/-}$ and *BRCA2* $^{-/-}$ cells in tumor models in vivo [Rottenberg, S., et al 2008] [Hay, T., et al 2009] and in the clinic [Fong, Peter C., et al 2009]. Additionally, olaparib selectively inhibits tumor cell lines in vitro and in xenograft *BRCA*$^{-/-}$ models, either as a stand-alone treatment or in combination with chemotherapy, without adversely impacting non-tumor tissue [Farmer, H., et al 2005]. The antitumor activity of olaparib has also been investigated in a number of pediatric tumor cell lines. In vitro, olaparib inhibited the growth of cell lines derived from Ewing sarcoma (half-maximal inhibitory concentration [$IC_{50}$] ≤1.5 μM) and medulloblastoma ($IC_{50}$ ≤2.4 μM); however, growth inhibition of cell lines derived from neuroblastoma, osteosarcoma, and breast carcinoma varied ($IC_{50}$ 2.5 μM to ~100 μM). Despite the observed differences in growth inhibition, treatment of these cell lines with olaparib (1 μM) for 48 hours resulted in 90% PARP inhibition (range 86–93%) [Norris, R. E., et al 2014].

Preclinical data also support LOH as a primary contributor to HRD. Abkevich, et al (2012) tested 57 cell lines (21 ovarian, 32 breast, 3 colon, and 1 pancreatic) and found a positive correlation between LOH of >15 Mb but less than the full chromosome and homologous repair deficiency [Abkevich, V., et al 2012].

Proof-of-concept clinical studies have demonstrated the antitumor activity of olaparib in *BRCA*m ovarian, breast, prostate, and pancreatic cancers. In a first-in-human Phase 1 dose escalation study of olaparib in patients who harbored g*BRCA*m, PARP inhibition with olaparib resulted in a response (CR, PR, or SD) in 9/15 (60%) participants with ovarian cancer based on combined RECIST and Gynecological Cancer Intergroup CA-125 criteria [Fong, Peter C., et al 2009]. These finding were confirmed in patients with breast, ovarian, prostate, and pancreatic cancers in patients who harbored g*BRCA*m [Tutt, A., et al 2010] [Audeh, M. William, et al 2010] [Mateo, J., et al 2015] [Kaufman, B., et al 2015]. In addition, several large Phase 2 and Phase 3 studies have demonstrated the safety and efficacy of PARP inhibitors in ovarian, breast, prostate, endometrial, peritoneal, and fallopian tube cancers.

***SOLO2***

SOLO2 was a randomized, double-blind, placebo-controlled Phase III study that evaluated olaparib (300 mg twice daily [BID]) for the maintenance treatment of platinum-sensitive, relapsed ovarian cancer in patients with g*BRCA*m. Compared to placebo, olaparib significantly improved mPFS as assessed by the Investigator (19.1 months vs. 5.5 months; hazard ratio [HR] 0.30; 95% CI: 0.22 to 0.41; p<0.0001) and BICR (30.2 months vs. 5.5 months; HR 0.25; 95% CI: 0.18 to 0.35; p<0.0001). Olaparib also significantly improved PFS2 (time from randomization to second progression) compared to placebo (HR 0.50; 95% CI: 0.34 to 0.72; p=0.0002). Overall survival (OS) data were immature at the data cutoff [Pujade-Lauraine, E., et al 2017].

***OLYMPIAD***

OLYMPIAD was a randomized, open-label, Phase 3 study that evaluated olaparib monotherapy (300 mg BID) versus TPC chemotherapy for the treatment of metastatic, human epidermal growth factor receptor 2 negative (HER2–), g*BRCA*m breast cancer in patients who had received ≤2 previous chemotherapy regimens. Compared to TPC, olaparib significantly improved mPFS as assessed by BICR (7.0 months vs. 4.2 months; HR= 0.58; 95% CI: 0.43 to 0.80; p<0.001). Additionally, olaparib significantly improved the median PFS2 (13.2 months vs. 9.3 months; HR: 0.57; 95% CI: 0.40 to 0.83; p=0.003). Finally, the ORR for olaparib was 59.9% (95% CI: 52.0 to 67.4; 9% CR) compared to 28.8% (95% CI: 18.3 to 41.3; 1.5% CR) for TPC [Robson, M., et al 2017].

***TOPARP***

TOPARP was an open-label, multicenter, Phase 2 Investigator-initiated single-arm study (NCT01682772) of olaparib (400 mg BID) for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) in patients who had progressed after 1 or 2 prior treatment regimens. All patients must have received prior docetaxel. The primary endpoint, composite response rate, was defined as an OR by RECIST 1.1, a reduction in prostate-specific antigen (PSA) ≥50%, or a decrease in the number of circulating tumor cells from ≥5 to <5 per 7.5 mL blood (Veridex™). The secondary endpoints included safety, tolerability, PFS, and OS. Of 49 evaluable patients, 16 (32.7%) responded to olaparib (95% CI: 20.0 to 47.5), and 12 patients remained on treatment for greater than 6 months. Six of 32 patients with RECIST

1.1-measurable disease had radiological responses (18.8 %) and 11 patients had a biochemical response (≥50% decrease in PSA). Four responses lasted more than 1 year. Next-generation sequencing identified homozygous deletions and/or deleterious mutations in DNA repair genes in 16/49 (32.7%) cases, including 7 patients with *BRCA2* mutations and 5 patients with *ATM* alterations. Of the 16 patients with DNA repair mutations, 14 patients (87.5%) responded to olaparib by response rate including all 7/7 patients with *BRCA2* loss (4 bi-allelic somatic loss; 3 germline mutations) and 4/5 patients with *ATM* aberrations. Few responses were observed in biomarker-negative patients (2/33 = 6% ORR). Median PFS of the 16 biomarker-positive patients was 9.8 months with a median OS of 13.8 months. In contrast, in the biomarker-negative group, mPFS was 2.7 months and median OS was 7.5 months [Mateo, J., et al 2015].

***Study 42***

Study 42 was a nonrandomized, open-label, multicenter, Phase 2 study of olaparib in patients with advanced ovarian, breast, pancreatic, or prostate cancers and g*BRCA*m. The ORRs reported were 26.2% (78/298, 95% CI: 21.3 to 31.6) for the total study population, 31.1% (60/193; 95% CI: 24.6 to 38.1) for ovarian, 12.9% (8/62; 95% CI: 5.7 to 23.9) for breast, 21.7% (5/23; 95% CI: 7.5 to 43.7) for pancreatic, and 50.0% (4/8; 95% CI: 15.7 to 84.3) for prostate cancer [Kaufman, B., et al 2015].

In summary, olaparib monotherapy treatment has resulted in favorable ORRs in a variety of HRRm advanced solid tumors including breast, ovarian, and prostate cancers. This broad response suggests that a strong association between HRRm and olaparib response may be tumor-agnostic.

***ARIEL3***

In the ARIEL3 clinical study (N=564), women with platinum-sensitive high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma were enrolled in a randomized double-blind study of rucaparib 600 mg. Among women *BRCA*m carcinoma, mPFS was 16.6 months (95% CI: 13.4 to 22.9) in patients in the rucaparib group versus 5.4 months (95% CI: 3.4 to 6.7) in the placebo group (HR: 0.23, 95% CI: 0.16 to 0.34; p<0·0001). Similar efficacy was reported in the HRD subgroup (N=354): rucaparib mPFS was 13.6 months (95% CI: 10.9 to 16.2) versus 5.4 months (95% CI: 5.1 to 5.6) in the placebo group (HR=0.32, 95% CI: 0.24 to 0.42, p<0.0001). Among women with LOH, mPFS was 9.7 months (95% CI: 7.9 to 13.1) in rucaparib patients versus 5.4 months (95% CI: 4.1 to 5.7) in the placebo group (HR= 0.44, 95% CI: 0.29 to 0.66, p<0.0001). As the HRD participants excluded *BRCA*m women; increased mPFS among women with high-LOH compared to low-LOH carcinoma suggested that other HRRm may identify responsive tumors with wild-type *BRCA*. The ORR in the *BRCA*m population was 38% (95% CI: 23 to 54) in the rucaparib arm versus 9% (95% CI: 1 to 28) in the placebo arm. Among women with non-*BRCA*m HRD, the ORR was 27% (5% CI: 18 to 38) in the rucaparib arm versus 7% (95% CI: 1 to 20) in the placebo arm [Coleman, R. L., et al 2017].

***NOVA***

Mirza, et al assigned 553 ovarian cancer patients to 1 of 2 main cohorts based on the presence of g*BRCA*m. In g*BRCA*m patients, niraparib significantly extended mPFS compared to placebo (21.0 months vs. 5.5 months; HR = 0.27, 95% CI: 0.17 to 0.41). When HRD tumors (myChoice® HRD test; Myriad Genetics) were retrospectively analyzed in an exploratory analysis out of the non-g*BRCA*m group, niraparib conveyed a 62% reduction in the risk of progression (PFS 12.9 months vs. 3.8 months; HR = 0.38, 95% CI: 0.24–0.59). Non-g*BRCA*m and negative HRD patients treated with niraparib demonstrated a smaller but significant extension of PFS compared to placebo (9.3 months vs. 3.9 months; HR = 0.45, 95% CI: 0.34 to 0.61) [Mirza, M. R., et al 2016].

In summary, HRD also may serve as a predictive tumor-agnostic biomarker for olaparib monotherapy in the clinical management of advanced solid malignancies. Although the bulk of clinical evidence for PARP inhibition comes from tumors with *BRCA* or *ATM* mutations, clinical data suggest a role for PARP inhibition in tumors sustaining mutations in other genes that impact HRR. The robust responses seen with PARP inhibitors among tumors with a variety of DNA repair defects presents both hope and challenge as researchers and physicians grapple with identifying potential candidates for treatment. The specificity of olaparib for cancerous cells suggests a tolerable safety profile.

### 2.2.4 Ongoing Clinical Studies

**As of Amendment 04, the studies below have been completed.** Refer to the IB for more information. The following paragraphs are retained for historical perspective.

The Phase 3 PROfound clinical study (NCT02987543) is evaluating olaparib in participants with mCRPC who progressed on prior nonhormonal treatments. Participants are randomly assigned based on mutations in genes associated with HRD by the Lynparza HRR-HRD Assay to Cohort A (*BRCA1*, *BRCA2*, or *ATM*m [n=240]) or Cohort B (men with a mutation in 1 of the 12 other HRR genes [n=100]) (Section 2.2.2.2). Participants are randomly assigned (2:1) to receive either olaparib or physician's choice of enzalutamide or abiraterone. The primary endpoint is radiographic PFS, and secondary efficacy endpoints include ORR, time to pain progression, and OS.

The Phase 3 POLO clinical study (NCT02184195) is evaluating olaparib as monotherapy in participants with metastatic pancreatic cancer with g*BRCA*m and whose tumors have not progressed on at least 16 weeks of platinum-base chemotherapy. Participants are randomly assigned in a 3:2 ratio to either olaparib (300 mg BID) or placebo. The primary endpoint is PFS, and secondary efficacy endpoints include OS, PFS2, time from randomization to first subsequent therapy or death (TFST), time from randomization to second subsequent therapy or death (TSST), time from randomization to discontinuation or death (TDT), ORR, and disease control rate.

The Phase 3 SOLO3 clinical study (NCT02282020) is evaluating olaparib in participants with relapsed g*BRCA*m ovarian cancer who have progressed at least 6 months after their last platinum treatment and have received at least 2 prior platinum treatments. Participants are

randomly assigned to either olaparib 300 mg BID or physician's choice of chemotherapy. The primary endpoint is PFS, and secondary efficacy endpoints include OS, PFS2, time to earliest progression by RECIST 1.1, CA-125, or death, time to deterioration of health-related quality of life (HRQoL), TFST, TSST, and TDT.

### 2.2.5 Information on Other Study-related Therapy

Not applicable for this study.

## 2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The proposed study will enroll biomarker-positive participants (ie, those with known or suspected deleterious mutations in HRR genes or the HRD phenotype) for whose malignancies may be particularly susceptible [Mateo, J., et al 2015] [Kaufman, B., et al 2015] and, as olaparib has been found to be well-tolerated across various tumor types, a positive benefit/risk profile is expected.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

# 3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

**All protocol-specified analyses other than exploratory biomarker analyses have been completed. The following paragraphs and table are retained for historical perspective.**

No hypothesis testing will be performed.

Male and female participants with previously treated, advanced (metastatic and/or unresectable) HRRm and/or HRD positive solid tumors will be enrolled as:

- *BRCA1/2* mutated (excluding *BRCA*m breast and ovarian cancers); hereafter referred to as Cohort 1
- HRRm (*BRCA1/2* non-mutated, including breast and ovarian cancers) and/or HRD positive (HRR non-mutated); hereafter referred to as Cohort 2
- Somatic *BRCA*m (s*BRCA*m) breast cancer; hereafter referred to as Cohort 3

| Objectives | Endpoints |
|---|---|
| Primary | |
| • Objective: To evaluate the objective response rate (ORR) as assessed by blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) or Prostate Cancer Working Group (PCWG)-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | • Objective response (OR): complete response (CR) or partial response (PR). |
| Secondary | |
| • Objective: To evaluate the duration of response (DOR) as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | • DOR: the time from the date a response was first documented until either disease progression or death due to any cause, whichever occurs first. |
| • Objective: To evaluate overall survival (OS), following administration of olaparib in Cohort 1, Cohort 2, and Cohort 3. | • OS: the time from the date of the first dose to death due to any cause. |
| • Objective: To evaluate progression-free survival (PFS) as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1, following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | • PFS: the time from the date of the first dose until either disease progression or death due to any cause, whichever occurs first. |
| • Objective: To evaluate the safety and tolerability of olaparib in Cohort 1, Cohort 2, and Cohort 3. | • Adverse events (AEs).<br>• Study intervention discontinuation due to AEs. |

| Objectives | Endpoints |
|---|---|
| • Objective: To evaluate the ORR, DOR, OS, and PFS in participants who are (1) HRRm, (2) HRD positive, and (3) in all participants regardless of biomarker status following olaparib administration in Cohort 1 and Cohort 2. | • OR<br>• DOR<br>• OS<br>• PFS |
| • Objective: To assess time to earliest progression by CA-125 following olaparib administration in participants with *BRCA1/2* non-mutated ovarian cancer. | • CA-125 ≥2 × ULN on 2 occasions, 1 week apart<br>• CA-125 ≥2 × the nadir value on 2 occasions, 1 week apart (for participants with elevated CA-125 ≥ULN at baseline) |
| • Objective: To evaluate the PSA response rate to olaparib administration in participants with prostate cancer. | • PSA response: a reduction in the PSA level of 50% or more from baseline measured twice at least 3 weeks apart. |
| • Objective: To evaluate progression-free survival after next-line treatment (PFS2), as assessed by the investigator, in participants with s*BRCA*m breast cancer. | • PFS2: the time from the date of the first dose to subsequent disease progression on the next-line of treatment or death, whichever occurs first. |
| Tertiary/Exploratory | |
| • Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of olaparib. | • Germline genetic variation, genetic (DNA) mutations from tumor, tumor and blood RNA variation, proteomics and immunohistochemistry, and other blood-derived biomarkers. |
| • Objective: To evaluate changes from baseline in the Global Health Status/Quality of Life (GHS/QoL) score using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core 30 (QLQ-C30). | • The QoL and symptom scores from the GHS/QoL scale of the EORTC QLQ-C30. |

| Objectives | Endpoints |
|---|---|
| • Objective: To characterize health utility using the European Quality of Life Five-dimension Five-level Scale Questionnaire (EuroQol EQ-5D-5L) and global severity of symptoms using the Patient Global Impression of Severity (PGI-S). | • Health utility and global severity of symptoms using the EuroQol EQ-5D-5L and PGI-S. |
| • Objective: To evaluate the relationship between clinical response to olaparib and biomarker status defined as (1) HRD positive/*BRCA1/2* non-mutated and no mutations detected in the other 13 genes involved in HRR, (2) *BRCA*m or *ATM* mutated, (3) biallelic loss of function, (4) genetic aberration by tumor type, (5) by mutation of individual HRR genes, and (6) by genomic instability score. | • OR<br>• DOR<br>• PFS<br>• OS |
| • Objective: To evaluate the ORR, DOR, and PFS in solid tumors (excluding prostate tumors) as assessed by BICR according to traditional RECIST 1.1 following olaparib administration in Cohort 1, Cohort 2, and Cohort 3. | • ORR<br>• DOR<br>• PFS |
| • Objective: To assess the exposure to olaparib. | • Olaparib plasma concentration data |

# 4 STUDY DESIGN

## 4.1 Overall Design

**As of Amendment 04, participants currently on treatment can remain on study intervention until one of the conditions for discontinuation is met.** Those who discontinue study intervention for any reason—eg, adverse event, progressive disease, physician or patient choice, or transition to a post-trial access program for olaparib—will also discontinue from the study without efficacy or survival follow-up. Participants receiving study intervention will no longer be required to submit imaging scans for central review, and continued imaging assessments will be performed as per investigator discretion and SOC. Pharmacokinetics, pharmacodynamics, biomarker samples, and PROs will no longer be collected for these participants. Local safety laboratory assessments (hematology and chemistry panels) will be performed as per institutional standards.

The final study visit for participants who discontinue from study intervention should be the combined EOT/30-day Safety Follow-up Visit, as appropriate. Standard safety reporting per Section 8.4.1 should continue, as applicable.

Participants on efficacy or survival follow-up are considered to have completed the study.

**The following text is retained for historical perspective.**

This is a Phase 2, nonrandomized, multicenter, single-arm, open-label study of olaparib monotherapy in participants with multiple types of advanced (unresectable and/or metastatic) HRRm and/or HRD-positive cancer that have progressed after standard therapy.

Approximately 390 eligible participants with advanced HRRm or HRD positive cancer not amenable to curative treatment will be enrolled in this study. All participants will receive olaparib 300 mg twice daily. Eligible participants will be grouped as follows:

- Cohort 1 (~84 participants): *BRCA*m
  Note: Participants with *BRCA*m ovarian cancer (germline or somatic) and g*BRCA*m breast cancer are not eligible for the study. Participants with somatic *BRCA*m (s*BRCA*m) breast cancer are not eligible for Cohort 1 but may be eligible for Cohort 3.

  Note: If sufficient evidence of activity is observed, enrollment of participants with *BRCA*m tumors into Cohort 1 may be expanded to ~150 participants
- Cohort 2 (~286 participants): ~174 participants with HRRm (*BRCA1/2* non-mutated) and ~112 participants with HRD positive (*BRCA1/2* non-mutated and no mutations detected in the remaining 13 gene HRR panel [HRR non-mutated])
  Note: participants with *BRCA1/2* non-mutated breast and ovarian cancers are eligible for the study.

  Note: If sufficient evidence of activity is observed, enrollment of participants with HRD positive, HRR non-mutated tumors into Cohort 2 may be expanded to ~156 participants.
- Cohort 3 (~20 participants): s*BRCA*m breast cancer.
  Note: Cohort 3 will not be open for enrollment in Japan.

HRRm, HRD positive, *BRCA*m, *BRCA1/2* non-mutated, and s*BRCA*m tumors are defined as follows:

- **HRRm**: Participants with tumors that harbor known or suspected deleterious mutations in *BRCA1, BRCA2, ATM*, or 1 of the other 12 genes specified among the 15 genes involved in HRR (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L*) based on the Lynparza HRR-HRD Assay
- **HRD**: Participants with tumors that harbor a known or suspected deleterious mutation in *BRCA1* or *BRCA2* or have a LOH score equal to or greater than the cutoff of 16 based on the Lynparza HRR-HRD Assay

- ***BRCA*m**: Participants with tumors that harbor known or suspected deleterious mutations in *BRCA1* or *BRCA2* based on the Lynparza HRR-HRD Assay
- ***BRCA1/2* non-mutated**: A known or suspected deleterious mutation in *BRCA1* and *BRCA2* is not detected by the Lynparza HRR-HRD Assay
- **s*BRCA*m** – Participants with breast cancer whose tumors harbor known or suspected deleterious mutations in *BRCA1* or *BRCA2* and do not harbor a germline *BRCA1* or *BRCA2* mutation.

Table 3 provides a summary of Cohorts 1, 2 and 3 and how they will be grouped for the primary, secondary, and major exploratory analyses.

Table 3 Summary of Study Cohorts and Analysis Grouping

| Biomarker Group | Cohort | Aberration Required[a] | | |
|---|---|---|---|---|
| | | ***BRCA1* and/or *BRCA2* Mutation** | **Mutations in 1 of the 13 Other HRR Genes** | **LOH Score ≥16** |
| *BRCA*m[b, c] | 1 | Yes | N/R | N/R |
| HRRm (*BRCA1/2* non-mutated)[d] | 2 | No | Yes | N/R |
| HRD positive (*BRCA1/2* non-mutated and HRR non-mutated)[e] | 2 | No | No | Yes |
| s*BRCA*m breast cancer[f] | 3 | Yes | N/R | N/R |

Abbreviations: *BRCA* = breast cancer susceptibility gene; HRD = homologous recombination deficiency; HRR = homologous recombination repair; HRRm = homologous recombination repair mutated; LOH = loss of heterozygosity.

a. No = not allowed; Yes = required; N/R = not required.
b. Known or suspected deleterious mutations in *BRCA1* and/or *BRCA2* required for enrollment into Cohort 1. Participants who are *BRCA*m are enrolled into Cohort 1 whether or not they are HRRm for the 13 genes or whether they have LOH score of 16 or greater.
c. Excluding *BRCA*m breast and ovarian cancers.
d. Known or suspected deleterious mutations in *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* or *RAD54L* and a known or suspected deleterious mutation in *BRCA1* and *BRCA2* is not detected based on the Lynparza HR-HRD assay.
e. A known or suspected deleterious mutation is not detected in any of the 15 genes on the Lynparza HRR-HRD assay but the tumor has a LOH score equal to or greater than the cutoff of 16.
f. Known or suspected deleterious somatic mutations in *BRCA1* and/or *BRCA2* required for enrollment into Cohort 3. Note: Cohort 3 will not be open for enrollment in Japan.

Ongoing enrollment monitoring will be done to ensure enrollment biomarker targets are met. All participants will receive olaparib 300 mg BID. A tumor specimen will be required to confirm mutations in genes involved in HRRm and HRD. Enrollment of participants who have received 3 or more prior lines of chemotherapy will be capped at 20% of the total population. Enrollment will be monitored by tumor type and specific gene mutation; a cap for tumor type and genetic aberration may be considered as the study progresses. Determination of the upper limit of any one specific population will be based on accumulating data for that specific population and the extent to which there is existing data for PARP inhibition in the specific population.

Efficacy will be evaluated using ORR using RECIST 1.1, as determined by BICR. DOR and PFS will also be assessed by BICR using RECIST 1.1. For participants with prostate cancer, efficacy (ORR, DOR, and PFS) will be determined using PCWG-modified RECIST 1.1 [Scher, H. I., et al 2016].

Although there will not be formal hypothesis testing in this study, one interim analysis is planned for a futility check of the efficacy of olaparib in the subgroup of participants who are HRD positive but *BRCA1/2* non-mutated and have no detectable mutations in the 13 other genes involved in HRR based on the Lynparza HRR-HRD Assay. Additional interim analyses may be performed (Section 9.7).

Participants will be evaluated with radiographic imaging to assess response to intervention at regular intervals. On-study imaging will be assessed as outlined in Section 8.2.1.2. All imaging obtained on-study, including imaging showing Investigator-assessed progressive disease (PD), will be submitted to the central imaging vendor for BICR, which will assess the images using RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer) for the determination of efficacy (Section 8.2.1.4).

Adverse event (AE) monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4. AEs will be reported by the investigator or delegate from informed consent through 30 days following cessation of study intervention. Serious AEs (SAEs) will be reported by the investigator or delegate from informed consent through 30 days following cessation of study intervention (refer to Section 8.4.1 for specific reporting requirements).

Study intervention will continue until documented PD, unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, participant withdrawal of consent, pregnancy of the participant, or administrative reasons requiring cessation of study intervention (Section 7.1).

Participants who discontinue study intervention for reasons other than documented PD will have post-treatment follow-up for disease status (including imaging) until PD, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow-up.

After documented PD each participant will be contacted by telephone approximately every 12 weeks (84 ± 7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

### 4.1.1 Early Termination of Cohort(s) and/or Discontinuation of Cohort Enrollment

Specific cohort(s) within the study may be terminated early and/or further enrollment stopped for 1 or both of the following reasons:

- Extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population in the specific cohort(s) is unacceptable.
- Emerging information from other studies is such that the participant safety or the risk/benefit ratio to a cohort population is unacceptable.

Continuation of study intervention may be allowed for a study participant who benefits from ongoing study intervention, if justified by the investigator and documented in a Sponsor consultation form.

## 4.2 Scientific Rationale for Study Design

The goal of this study is to evaluate whether HRRm and HRD positivity can be used as tumor-agnostic biomarkers that predict sensitivity to olaparib, beyond tumors with an established response to PARP inhibitors (eg, *BRCA*m breast and ovarian cancers). In order to support the tumor-agnostic biomarker approach, eligible participants will be enrolled in this study into a single-arm and analyzed as detailed in Table 11. As there is relatively little data available for the use of HRD positivity as a biomarker to predict response to olaparib, the primary purpose of the interim analysis is to test futility of HRD positive subgroup to evaluate the overall contribution of HRD to the tumor-agnostic biomarker approach.

### 4.2.1 Rationale for Enrollment of Participants with HRRm or HRD Positive Cancer

This study will enroll approximately 450 participants with any advanced cancer with known or suspected deleterious mutations in HRRm or with HRD. Participants with HRRm and HRD cancer have responded to olaparib in preliminary studies; however, the prevalence of these tumors may be low. By enrolling participants with any cancer that is HRRm or HRD positive, the study can target accurate assessment of the clinical activity of olaparib in HRRm and HRD advanced cancer. In addition, this study may be able to demonstrate the utility of HRRm and HRD in predicting response to olaparib agnostic of tumor histology. Based on data from participants in several olaparib studies in multiple cancer types, HRRm and HRD evaluated in the proposed study may potentially predict response. The purpose of this study is to determine if these biomarkers will identify participants who will clinically respond to olaparib.

Participants with *BRCA*m ovarian cancer (germline or somatic) and g*BRCA*m breast cancer are not eligible for this study. The response of these tumors to olaparib is well documented and the goal of this study is to evaluate olaparib sensitivity beyond *BRCA1/2* mutations in these established tumors [Robson, M., et al 2017] [Pujade-Lauraine, E., et al 2017]. However, as little is known about the efficacy of olaparib in patients with somatic *BRCA*m breast cancer, the study will evaluate the efficacy of olaparib in participants with somatic *BRCA*m breast cancer.

### 4.2.2 Rationale for Endpoints

#### 4.2.2.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the antitumor effect of olaparib in participants with any of one of a "basket" of advanced malignancies. This study will use ORR based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. For participants with prostate cancer, efficacy will be based on PCWG-modified RECIST 1.1 as assessed by BICR [Scher, H. I., et al 2016]. This study will also use OS and PFS as secondary endpoints.

ORR and PFS are acceptable measures of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR and PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to HRRm/HRD status to minimize bias in the response assessments.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

DOR is considered an acceptable measure of clinical benefit when considered with ORR.

##### 4.2.2.1.1 RECIST 1.1

Efficacy will be evaluated using RECIST 1.1 or PCWG-modified RECIST 1.1 [Scher, H. I., et al 2016] for ORR, DOR, and PFS as assessed by BICR. For the primary analyses, both methods will be modified to follow a maximum of 10 target lesions in total and a maximum of 5 target lesions per organ; hereafter referred to as modified RECIST 1.1. Traditional RECIST 1.1 criteria (a maximum of 5 target lesions in total and a maximum of 2 target lesions per organ) will be used for the exploratory analysis of ORR, DOR, and PFS for all tumor types except for prostate cancer; hereafter referred to as traditional RECIST 1.1.

#### 4.2.2.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

#### 4.2.2.3 Patient-Reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this study, Health-related quality of life (HRQoL) and disease-related symptoms will be investigated among all participants via the following assessment tools: Patient Global Impression of Severity (PGI-S), European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 and, European Quality of Life

(EuroQol) EQ-5D-5L questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and study intervention tolerability. EQ-5D-5L will also be used to calculate health utilities for health economic models.

**PGI-S**

The PGI-S is a standard single item questionnaire for assessing the severity of disease-related symptoms. The response options of the PGI-S are as follows: No Symptoms, Very Mild, Mild, Moderate, Severe, and Very Severe.

**EuroQoL EQ-5D-5L**

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions addressed in this instrument are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. The EuroQoL EQ-5D-5L will always be completed by participants first, prior to completing any other PRO instruments. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

**EORTC QLQ-C30**

The EORTC QLQ-C30 was developed to assess the QoL of participants with cancer. It has been translated and validated in over 100 languages and used in more than 3000 studies worldwide. It contains 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) [Aaronson, N. K., et al 1993]. It is scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 1 global health status/QoL scale that uses 7-point scale scoring with anchors (1=very poor and 7=excellent).

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

### 4.2.3 Rationale for the Use of Comparator/Placebo

Not applicable for this study.

## 4.3 Justification for Dose

### 4.3.1 Rationale for Olaparib Dosing Regimen

The dose of olaparib used in this study is 300 mg BID (tablet formulation), which is the currently approved dose.

### 4.3.2 Maximum Dose/Exposure for This Study

There is no maximum duration of exposure for olaparib.

## 4.4 Beginning and End of Study Definition

**As of Amendment 04, participants in efficacy or survival follow-up will be discontinued from the study.**

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent.

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the EEA, the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 8 years to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

### 4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

## 5 STUDY POPULATION

**As of Amendment 04, no additional participants will be enrolled in the study.** The following text is retained for historical perspective.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Male and female participants with advanced HRRm or HRD positive cancer and at least 18 years of age will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

**Type of Participant and Disease Characteristics**

**Cohorts 1 and 2:**

1. Participant has a histologically- or cytologically-confirmed advanced (metastatic and/or unresectable) solid tumor (except ovarian cancer whose tumor has a germline or somatic *BRCA* mutation and breast cancer whose tumor has a germline *BRCA* mutation) that is not eligible for curative treatment and for which standard of care therapy has failed. Participants must have progressed on or be intolerant to standard of care therapies that are known to provide clinical benefit. There is no limit on the number of prior treatment regimens.

   Note: Standard of care therapy includes anti-neoplastic systemic chemotherapy or biological therapy, targeted therapy, or an anticancer hormonal therapy.

Note: Enrollment of participants who have received 3 or more prior lines of cytotoxic chemotherapy (as defined in Section 8.1.5.1.1) will be capped at approximately 20% of the total study population.

Note: Enrollment of different subgroups will be closely monitored and further enrollment of a specific tumor type or genetic abnormality may be closed at the discretion of the Sponsor.

2. Participant has either centrally-confirmed known or suspected deleterious mutations in at least 1 of the specified 15 genes involved in HRR (*ie, BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L*) or centrally-confirmed HRD based on the Lynparza HRR-HRD Assay.

3. If participants have received prior platinum (cisplatin, carboplatin, oxaliplatin, etc., either as monotherapy or in combination) for advanced (metastatic and/or unresectable) solid tumor, they are eligible to enter the study provided there has been no evidence of disease progression during the platinum chemotherapy or ≤4 weeks of completing the platinum-containing regimen.

   Note: Participants do not need to have received a previous platinum regimen to be considered eligible.

**Cohorts 1, 2, and 3:**

4. Participant has measurable disease per RECIST 1.1 or PCWG-modified RECIST 1.1 as assessed by the local site Investigator/radiology and confirmed by BICR. BICR must confirm the presence of radiologically measurable disease based on RECIST 1.1 or PCWG-modified RECIST 1.1 for the participant to be eligible for the study. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: For non-GBM histologies, metastatic lesions situated in the brain are not considered measurable and should be considered non-target lesions. For participants with GBM, lesions situated in the brain may be selected as measurable disease.

5. Participant is able to provide a newly obtained core or excisional biopsy of a tumor lesion or either an archival formalin-fixed paraffin-embedded (FFPE) tumor tissue block or slides. A newly obtained biopsy is preferred, but not required if archival tissue is available for analysis.

   Note: FFPE tumor blocks are preferred to slides. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 48 hours from the date the slides are cut (refer to Section 8.1.12.2).

6. Participant has a life expectancy of at least 3 months.

## Demographics

7. Participant is Male or Female who is at least 18 years of age at the time of signing the informed consent.

8. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of either 0 or 1, as assessed within 7 days of treatment initiation.

## Male Participants

9. A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 95 days (3 months and 5 days), corresponding to time needed to eliminate any study intervention(s) (ie, olaparib) plus a spermatogenesis cycle, after the last dose of study intervention and refrain from donating sperm during this period. Refer to Appendix 5 for additional guidance.

## Female Participants

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    - Not a woman of childbearing potential (WOCBP)

      OR

    - A WOCBP and:

        - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

            - Olaparib: 180 days

          The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

        - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. If a urine test cannot be confirmed as negative

(eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5 (Section 10.5.3).

- Abstains from breastfeeding during the study intervention period and for at least 30 days after the last dose of study intervention.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

**Informed Consent**

11. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

**Additional Categories**

12. Participant has adequate organ function, as detailed in Table 4; all screening laboratory tests should be performed within 10 days prior to the first dose of study intervention.

**Cohort 3:**

13. Participant has histologically- or cytologically-confirmed breast cancer with evidence of metastatic disease.

14. Participant has a known or suspected deleterious mutation in *BRCA1 or BRCA2* and does not harbor a germline *BRCA1* or *BRCA2* mutation.

    Note: Participation requires a *BRCA*m-positive tissue test and a g*BRCA*m-negative blood test, either of which can be locally obtained or centrally tested. Blood and tissue samples must be provided by all participants.

15. Participant must have received treatment with an anthracycline (eg, doxorubicin, epirubicin) unless contraindicated and a taxane (eg, paclitaxel, docetaxel) in either the neoadjuvant/adjuvant or metastatic setting.

    Note: Participants eligible for Cohort 3 cannot have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease. Participants with s*BRCA*m breast cancer who have received prior platinum-based chemotherapy are eligible if the platinum-based chemotherapy was administered as neoadjuvant/adjuvant treatment for breast cancer and ≥12 months have elapsed since the last dose of platinum-based chemotherapy and the first dose of study intervention. There must have been no evidence of disease progression during the platinum-based chemotherapy.

16. Participants with estrogen and/or progesterone receptor-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic), or have disease that the treating physician believes to be inappropriate for endocrine therapy.

Table 4 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | ≥1500 cells/µL |
| Platelets | ≥100 000 cells/µL |
| Hemoglobin | ≥10.0 g/dL or ≥6.2 mmol/L[1] |
| Renal | |
| Serum creatinine OR<br>Estimated creatinine clearance using the Cockcroft-Gault equation, or based on a 24-hour urine test[2] | ≤1.5 × ULN OR<br>≥51 mL/min |
| Hepatic | |
| Total bilirubin | ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN (≤5 × ULN for participants with liver metastases) |
| Coagulation | |
| International normalized ratio (INR) OR prothrombin time (PT)<br>Activated partial thromboplastin time (aPTT) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants |

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; ULN = upper limit of normal.

1. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 28 days.
2. Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

## 5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

**Medical Conditions**

1. Participant has a known additional malignancy that is progressing or has required active treatment in the last 5 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, ductal carcinoma in situ, or cervical carcinoma in situ that has undergone potentially curative therapy are not excluded.

2. Participant has MDS/AML or with features suggestive of MDS/AML.

3. Participant has persistent toxicities (>CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.

4. Participant has known central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 4 weeks (28 days) by repeat imaging [repeat imaging should be performed during study screening]), clinically stable, and without requirement for steroid treatment for at least 14 days prior to the first dose of study intervention.

   Note: Participants with GBM may participate and must be neurologically stable (eg, without a progression of neurologic symptoms or requiring escalating doses of systemic steroid therapy for at least 14 days prior to the first dose of study intervention) and clinically stable.

5. Participant has an active infection requiring systemic therapy.

6. Participant has a history or current evidence of any condition (eg, cytopenia, transfusion-dependent anemia, or thrombocytopenia), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's involvement for the full duration of the study, or is not in the best interest of the participant to be involved, in the opinion of the treating Investigator.

7. Participant received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 28 days prior to the first dose of study intervention.

8. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

9. Participant has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.

10. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV at screening is only required if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

11. Participant has known active hepatitis (ie, Hepatitis B or C)

    - Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Participants with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible.

    - Participants positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

12. Participant is unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).

**Prior/Concomitant Therapy**

13. Participant has received prior therapy with olaparib or with any other PARP inhibitor.

14. Participant has a known hypersensitivity to the components or excipients in olaparib.

15. Participant is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 2 weeks.
    *Note: a current list of strong/moderate inhibitors of CYP3A4 can be found at the following website:* https ://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

16. Participant is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents.

    *Note: a current list of strong/moderate inducers of CYP3A4 can be found at the following website:* https ://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

17. Participant has received previous allogenic bone marrow transplant or double umbilical cord transplantation (dUCBT).

18. Participant has received a whole blood transfusion in the last 120 days prior to the first dose of study intervention. Packed red blood cells and platelet transfusions are acceptable if not performed within 28 days of the first dose of study intervention.

**Prior/Concurrent Clinical Study Experience**

19. Participant is currently enrolled in and receiving study therapy, was enrolled in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks (28 days) of the first dose of study intervention.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks (28 days) after the last dose of the previous investigational agent.

**Diagnostic Assessments**

None

**Other Exclusions**

20. Participant either had major surgery within 2 weeks of starting study intervention or has not recovered from any effects of any major surgery.

21. Participant is involved in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).

22. Participant, in the judgment of the Investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.

23. Participant has received any anti-neoplastic systemic chemotherapy or biological therapy, targeted therapy, or an anticancer hormonal therapy within 3 weeks prior to the first dose of study intervention.

Note: Participants must have recovered from all AEs due to previous therapies, excluding alopecia, to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy who are clinically stable may be eligible.

24. Participant has a primary cancer of unknown origin.

25. Participant has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions

Participants should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St. John's Wort (tablet or tea) while receiving study intervention. Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

## 5.5 Participant Replacement Strategy

A participant who is discontinued from study intervention will not be replaced.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 5.

Table 5 Study Interventions

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level (s) | Route of Administration | Regimen/ Treatment Period | Use | IMP or NIMP/ AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N/A | Experi-mental | Olaparib | Drug | Tablet | 150 mg; 100 mg | 300 mg BID | Oral | BID | Test Product | IMP | Central |

Abbreviations: BID = twice daily; EEA=European Economic Area; IMP = investigational medicinal product; N/A = not applicable; NIMP/AxMP = non-investigational/auxiliary medicinal product.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.
300 mg dose should be made up of 2 × 150 mg tablets; 100 mg tablets are provided for dose reductions as outlined in Section 6.6.1.

All supplies indicated in Table 5 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

### 6.1.1 Medical Devices

Not applicable for this study.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

### 6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Intervention Assignment

Treatment allocation will occur centrally using an interactive response technology (IRT) system. Ongoing enrollment monitoring will be done to ensure enrollment biomarker targets are met.

### 6.3.2 Stratification

Other than stratification by cohort (ie, Cohort 1, Cohort 2, and Cohort 3), no stratification based on age, sex, or other characteristics will be used in this study.

### 6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

## 6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for ≥4 weeks (28 days) will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants should be given clear instructions on how and when to take their study intervention. Participants will self-administer olaparib except when a clinic visit is scheduled. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the participant but will be retained by the investigative site until reconciliation is completed by the study monitor. All participants must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

## 6.5 Concomitant Therapy

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered >30 days after the last dose of study intervention should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 8.4.7.

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, organic-anion-transporting polypeptide (OATP)1B1, organic cation transporter (OCT)1/2/3, and multidrug and toxic compound extrusion (MATE)1/2 and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered. A current list of substrates can be found at the following website:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter products, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

### 6.5.1 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during Screening and during the study intervention phase of the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on-study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

1. Anti-neoplastic systemic chemotherapy or biological therapy not specified in this protocol.

2. Investigational agents other than olaparib.

3. Radiation therapy for disease control.

    - Note: Palliative radiation therapy to non-target symptomatic lesions or to the brain is allowed following Sponsor consultation.

4. Live vaccines while participating in the study, and within 30 days of the last dose of study intervention. See Appendix 7 for country-specific requirements.

    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

    - Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed

5. Anticancer hormonal therapy (eg, anti-estrogens)

    - *Note: hormonal replacement therapy and androgen deprivation therapy with LHRH agonists (eg, Lupron) and LHRH antagonists (eg, Degarelix) for participants with prostate cancer are allowed.*

6. Strong and moderate inducers or inhibitors of CYP3A4 that cannot be discontinued for the duration of the study.

    - *Note: a current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website:*
      https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

    - Note: Exceptions are outlined in Section 6.6.1.5.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in study for assessment of disease status and survival.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

### 6.5.2 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

## 6.6 Dose Modification (Escalation/Titration/Other)

### 6.6.1 Olaparib Dosing Modifications

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeated interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If the interruption is any longer, the Sponsor must be informed.

The dose of olaparib can be reduced to 250 mg BID initially and then to 200 mg BID as needed. If the 200 mg BID dose is not tolerable, no further dose reduction is allowed and study intervention should be discontinued. Once the dose has been reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors [Table 9]).

The reason for the dose interruption or reduction should be captured on the appropriate eCRF.

#### 6.6.1.1 Management of Hematological Toxicities

Any hematological toxicity observed during the study could be managed by a brief interruption of study intervention or a dose reduction of olaparib (Table 6 and Table 7). Repeated interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If the interruption is any longer, the Sponsor must be informed.

Table 6 Management of Anemia

| Toxicity | NCI CTCAE Grade | Action Taken |
|---|---|---|
| Hemoglobin (Hb) | Grade 2<br>(<10 but ≥8 g/dL) | **First Occurrence:**<br>Give appropriate supportive treatment and investigate causality.<br>• Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 4 weeks (28 days). Treatment can be restarted if Hb has recovered to >9 g/dL.<br>**Subsequent Recurrence:**<br>• **Hb <10 but ≥9 g/dL**: Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for maximum of 4 weeks (28 days). Upon recovery, a dose reduction to 250 mg BID as a first step or 200 mg BID as a second step may be considered.<br>• **Hb <9 but ≥8 g/dL**: Interrupt olaparib for a maximum of 4 weeks (28 days) until Hb improves to >9 g/dL. Upon recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur |
| | Grade 3<br>(<8 g/dL) | Give appropriate supportive treatment (eg, transfusion) and investigate causality.<br>• Interrupt olaparib, for a maximum of 4 weeks (28 days), until Hb improves to ≥9 g/dL.<br>• Upon recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur. |
| Abbreviations: BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; Hb = hemoglobin; NCI = National Cancer Institute.<br>Note: Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anemia may require blood transfusions. The management of prolonged hematological toxicities is detailed in Section 6.6.1.2. | | |

Table 7 Management of Neutropenia, Leukopenia, and Thrombocytopenia

| Toxicity | NCI CTCAE Grade | Action Taken |
|---|---|---|
| Neutropenia, Leukopenia, or Thrombocytopenia | Grades 1 or 2 | Investigator judgment to either continue olaparib or interrupt dosing for a maximum of 4 weeks (28 days). Give appropriate supportive treatment and investigate causality. |
| | Grades 3 or 4 | • Interrupt olaparib, for a maximum of 4 weeks (28 days), until event recovers to ≤Grade 1.<br>• Repeated incidence: reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional Grade 3 or 4 events occur. |

Abbreviations: BID = twice daily; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

- AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs.
- Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for PEGylated G-CSF) of the last dose of study intervention unless absolutely necessary.
- Platelet transfusions, if indicated, should be done according to local hospital guidelines.
- The management of prolonged hematological toxicities is detailed in Section 6.6.1.2.

### 6.6.1.2 Management of Prolonged Hematological Toxicities

If a participant develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse anemia and/or the development of blood transfusion dependence
- ≥2 week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L)
- ≥2 week interruption/delay in study intervention due to NCI CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50 \times 10^9$/L)

Differential blood count, including reticulocytes and peripheral blood smear, should be checked weekly. If any blood parameters remain clinically abnormal after the dosing of olaparib has been interrupted for ≥4 weeks (≥28 days), the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered, according to local regulation and/or standard institutional hematological practice. Study intervention should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 4 weeks (28 days) of dose interruption.

Development of confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to the Sponsor as outlined in Section 8.4.4. Olaparib intervention should be discontinued for confirmed MDS and/or AML (Section 7.1).

#### 6.6.1.3 Management of Non-Hematologic Toxicity

Repeated dose interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If toxicity reoccurs following rechallenge with study intervention, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 6.6.1) or the participant must permanently discontinue study intervention.

Treatment must be interrupted if any NCI CTCAE Grade 3 or 4 AE occurs that the investigator considers to be related to administration of olaparib.

##### 6.6.1.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study intervention dosing is recommended and further diagnostic workup (including a HRCT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study intervention can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Clinical Director.

##### 6.6.1.3.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib intervention. These events are generally mild to moderate (NCI CTCAE Grade 1 or 2) in severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of intervention for nausea and within the first 6 months of intervention for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study intervention; however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local regulations or institutional guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN]), generally a single-agent anti-emetic should be considered (eg, dopamine receptor antagonist, antihistamines, or dexamethasone).

#### 6.6.1.3.3 Management of Renal Impairment

If, subsequent to study entry and/or while still on study therapy, a participant's estimated creatinine clearance (CrCl) falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for participants who develop moderate renal impairment (calculated CrCl between 31 and 50 mL/min as calculated by either Cockcroft-Gault equation or based on a 24-hour urine test) for any reason during the course of the study (Table 8).

Table 8 Dose Reduction of Olaparib to Manage Moderate Renal Impairment

| **Initial Dose** | **Moderate Renal Impairment[a]** |
|---|---|
| 300 mg BID | 200 mg BID |
| Abbreviation: BID = twice daily.<br>a. Creatinine clearance of 31 to 50 mL/min as calculated by either Cockcroft-Gault equation or based on 24-hour urine test. | |

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in participants with severe renal impairment (CrCl ≤30 ml/min) or end-stage renal disease; if participants develop severe impairment or end-stage disease it is recommended that olaparib be discontinued.

### 6.6.1.4 Interruptions for Intercurrent Non-Toxicity-Related Events

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart study intervention within 4 weeks (28 days) for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Clinical Director, and approved via a Sponsor Communication Form.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Olaparib should be stopped at least 3 days prior to planned surgery and can be restarted when the wound has healed. It is not required to stop olaparib for any needle biopsy procedure.

Olaparib should be discontinued for a minimum of 3 days before a participant undergoes radiation treatment and should be restarted within 4 weeks (28 days) as long as any bone marrow toxicity has recovered. Radiation is prohibited unless radiation therapy is to symptomatic lesions or to the brain following Sponsor consultation.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, participants should be advised to use caution while driving or using machinery if these symptoms occur.

#### 6.6.1.5 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration as described in Table 9. After the washout of the inhibitor is complete (Section 5.2), the olaparib dose can be re-escalated. The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A4 inhibitor use.

Table 9 Dose Reduction of Olaparib With a Strong or Moderate CYP3A4 Inhibitor

| Initial Dose | Strong CYP3A Inhibitor | Moderate CYP3A Inhibitor |
|---|---|---|
| 300 mg BID | 100 mg BID | 150 mg BID |
| Abbreviation: BID = twice daily. | | |

## 6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

## 6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (olaparib [150 mg or 100 mg]) is included in the label text; random code/disclosure envelopes or lists are not provided.

## 6.9 Standard Policies

For studies using controlled substances, all Federal, State, Province, Country, etc., regulations must be adhered to in regard to their shipping, storage, handling, and dispensing. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc., laws in which the study is being conducted.

### 6.9.1 Study Site Retention Samples

Not applicable.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

**As of Amendment 04, any participant who discontinues study intervention for any reason—eg, adverse event, progressive disease, physician or patient choice, or transition to a post-trial access program for olaparib—will be discontinued from the study without further follow-up.**

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Documented radiographic disease progression outlined in Section 8.2.1.
- An increase in CA-125 either ≥2 × the normal value on 2 occasions (performed 1 week apart) or ≥2 × the lowest level it has been during the study (for participants with *BRCA1/2* non-mutated ovarian cancer) on 2 occasions (performed 1 week apart), in the absence of radiologically documented disease progression that is associated with worsening symptomatology and/or performance status.

  Note: In all cases the progression of CA-125 must be clinically significant for the investigator to consider stopping therapy
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires treatment.
- Unacceptable AEs or toxicities (Section 6.6.1).
- Bone marrow findings consistent with MDS or AML.
- Administration of study intervention is interrupted for more than 28 consecutive days without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive pregnancy test.
- The participant transitions to a post-trial access program for olaparib.

For participants who are discontinued from study intervention, all visits and procedures, as outlined in the SoA, should be completed.

## 7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

## 7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

# 8 STUDY ASSESSMENTS AND PROCEDURES

**As of Amendment 04, the following will apply:**

- Study procedures and their timing are summarized in the revised SoA for Amendment 04 (Section 1.3).

- Prior/concomitant medication review and subsequent antineoplastic therapy status will continue to be collected until study discontinuation.

- Optional tumor collections are discontinued.

- Local tumor imaging assessments should continue as per investigator discretion and SOC.
- Bone and brain scans will be performed as clinically indicated, as per SOC.
- Any other imaging scans will be at the discretion of the investigator and as per SOC.
- Imaging scans will no longer be submitted to the imaging vendor and central tumor response will no longer be assessed by BICR.
- Tumor response will be assessed by the investigator in accordance with SOC.
- Local safety laboratory assessments (hematology and chemistry panels) will be performed as per institutional standards.
- Other safety procedures to be continued are AE monitoring, physical examinations, weight, vital signs, ECG, β-hCG, and ECOG performance status.
- PROs will no longer be collected.
- Pharmacokinetics/pharmacodynamics and biomarker samples will no longer be collected.
- Participant efficacy follow-up will no longer be conducted.
- Participant survival follow-up status will no longer be collected.
- Participants who are on study intervention and experiencing clinical benefit will continue until the discontinuation criteria are met. The criteria will be determined by local tumor imaging according to the SOC schedule.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline

purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Administrative and General Procedures

### 8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant or their legally acceptable representative prior to participating in this clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

#### 8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent. **As of Amendment 04, treatment beyond progression will no longer be offered. Any participant already receiving (or approved to receive) treatment beyond progression will be able to complete treatment as planned.**

Specifics about the study and the study population are to be included in the study ICF.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

#### 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

### 8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

### 8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

### 8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

Refer to Appendix 7 for country-specific requirements.

#### 8.1.4.1 Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's specific-cancer.

### 8.1.5 Prior and Concomitant Medications Review

#### 8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study intervention. The investigator or qualified designee will also determine the prior use of platinum-based therapy, including history of response or progression while on or within 4 weeks of completing the platinum-containing regimen.

##### 8.1.5.1.1 Prior Lines of Therapy

All systemic cytotoxic chemotherapy, including an antibody–drug conjugate with a cytotoxic warhead, is considered a prior line of therapy. Prior neoadjuvant or adjuvant systemic cytotoxic chemotherapy used in the initial treatment is not considered a prior line of therapy, unless the date of disease progression/recurrence occurred is less than 12 months after completing neoadjuvant or adjuvant chemotherapy.

For the purposes of this study, prior treatment with the following agents/modalities of anticancer treatment are not considered a prior line of cytotoxic chemotherapy: biologics (eg, anti-PD-1, anti-PD-L1, anti-HER2), targeted therapies (eg, TKIs including VEGF inhibitors, mTOR inhibitors), hormonal therapies (eg, anti-estrogens, androgen deprivation), definitive surgery with curative intent, radiation therapy, and systemically administered radiopharmaceutical therapy.

If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Interruptions (eg, oxaliplatin in FOLFOX) or switching (eg, from cisplatin to carboplatin) due to toxicity, will not be considered a line of therapy. However, if a regimen is interrupted or discontinued for any reason, and then restarted at a later time point, following the administration of 1 or more other regimens in between, it should be counted as 2 lines. (eg, rechallenge with platinum in ovarian cancer).

Maintenance regimens administered with the purpose of maintaining response following any prior line of treatment will not be considered a line of therapy.

Sponsor consultation is recommended if further clarification or delineation of what is considered a prior line of therapy is needed.

#### 8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication (including blood transfusions), if any, taken by the participant during the study.

#### 8.1.5.3 Subsequent Antineoplastic Therapy

**As of Amendment 04, information about subsequent antineoplastic therapy after study intervention discontinuation will no longer be collected.** The following text is retained for historical perspective.

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of study intervention, will be collected. Reasons for starting subsequent anti-neoplastic therapies including access to other PARP inhibitors or investigational drugs will be collected.

### 8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to allocation to study intervention. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.2.

### 8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be non-randomly allocated and will receive a treatment number. The treatment number identifies the participant for all procedures occurring after treatment allocation. Once a treatment number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment number.

### 8.1.8 Study Intervention Administration

Olaparib will be administered by the investigator and/or study staff at each clinic visit. Participants will then self-administer olaparib orally for the remainder of the 28 day treatment regimen.

Study intervention should begin within 3 days of treatment allocation/assignment.

#### 8.1.8.1 Timing of Dose Administration

##### 8.1.8.1.1 Olaparib

At each clinic visit, the first dose of olaparib will be administered after all assessments and procedures have been completed, with the exception of post-dose PK sampling at Visit 3 (Section 1.3). Olaparib tablets should be taken with one glass of water twice a day at the same time each day, approximately 12 hours between doses. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. If a participant misses a scheduled dose for any reason (eg, as a result of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after

that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the participant should take their allotted dose at the next scheduled time.

### 8.1.9 Discontinuation and Withdrawal

**As of Amendment 04, participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT/30-day Safety Follow-Up Visit.** The following text is retained for historical perspective.

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (End of Treatment) should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

#### 8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

### 8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

### 8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible.

Documentation of equipment calibration must be retained as source documentation at the study site.

### 8.1.12 Tissue and Blood Collection

#### 8.1.12.1 Tumor Tissue for HRRm and HRD Biomarkers

Participants are required to have an excisional or core biopsy collected/submitted during the screening period for determination of either HRR or HRD status by central laboratory.

#### 8.1.12.2 Tumor Tissue for Biomarker Analysis

**As of Amendment 04, optional tumor collection at EOT/DC is no longer required.** The following text is retained for historical perspective.

Participation in this study will be dependent upon participants supplying tumor tissue for this mandatory biomarker analysis. Accurate information about the date of actual collection must be recorded.

A tumor specimen for biomarker assessment will be required for enrollment of all participants. A new tumor specimen, if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study) is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the participant (including (but not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel), an archival specimen should be submitted. Tissue from tumor progressing at a site of prior radiation may be allowed for biomarker characterization, based on the Sponsor's approval.

A core or excision biopsy of a tumor lesion is preferred. Submission of either FFPE tumor blocks or unstained slides is acceptable; FFPE tumor blocks are preferred. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 48 hours from the date the slides are cut, otherwise a new sample will be requested.

If possible, an additional optional core or excisional biopsy may be collected at the time of screening and discontinuation. This is in addition to the mandatory biomarker sample required for determination of study eligibility.

Participants must sign the main study ICF prior to submitting existing tissue samples and/or undergoing a new biopsy.

#### 8.1.12.3 Blood Collection for Germline *BRCA* Mutation Status

Participants with breast cancer being considered for Cohort 3 are required to have a blood sample collected and submitted during the screening period.

> Note: Participation requires a g*BRCA*m-negative blood test, which can be locally obtained or centrally tested. Blood samples must be provided by all participants.

## 8.2 Efficacy/Immunogenicity Assessments

### 8.2.1 Tumor Imaging and Assessment of Disease

**As of Amendment 04, tumor imaging will be completed at investigator discretion as per SOC (refer to Section 1.3).** Images will no longer undergo central review. The following text is retained for historical perspective.

The process for image collection and transmission to the central imaging vendor can be found in the site imaging manual (SIM). Tumor imaging is strongly preferred to be acquired by CT. Imaging of the chest, abdomen, and pelvis anatomical locations are required as are any other areas of disease noted outside of these anatomical regions. For participants with GBM, imaging of the chest, abdomen, and pelvis anatomical locations are not required unless clinically indicated. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Brain imaging is required for participants with GBM at screening and at all scheduled time points. For all other tumor types, brain imaging is required at screening for those participants with brain metastases at baseline (ie, to confirm stability) or who are clinically symptomatic. MRI is the preferred modality for imaging the brain; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans are required for participants with prostate cancer at screening and at all scheduled time points. For all other tumor types, bone scans are also required for participants with a history of bone metastases and/or for those participants who are clinically symptomatic (eg, with new bone pain). Any supplemental imaging done to support a positive or negative bone scan, such as plain X-rays that may be acquired for correlation, should be submitted to the central imaging vendor.

Expedited confirmation of measurable disease based on RECIST 1.1 or PCWG-modified RECIST 1.1 by BICR at Screening will be used to determine participant eligibility. Confirmation by the central imaging vendor that the participant’s imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 or PCWG-modified RECIST 1.1 is required prior to participant allocation.

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

#### 8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of the first dose. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1 or PCWG-modified RECIST 1.1 (Appendix 9). A bone scan is required at screening (within 42 days of the first dose) for participants with prostate cancer. For all other tumor types, a bone scan is required at screening ONLY for participants with a history of bone metastases or who are clinically symptomatic (eg, with new bone pain). A brain scan is required at baseline (within 28 days of the first dose) ONLY for participants with protocol eligible brain metastases (ie, to confirm stability) or who are clinically symptomatic.

The screening images must be submitted to the central imaging vendor for confirmation of measurable disease per RECIST 1.1 or PCWG-modified RECIST 1.1 for eligibility prior to allocation.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of the first dose and can be assessed by the central imaging vendor.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

#### 8.2.1.2 Tumor Imaging During the Study

**As of Amendment 04, tumor imaging will be completed at investigator discretion as per SOC (refer to Section 1.3).** Images will no longer undergo central review. Investigators should use RECIST 1.1 to assess tumor response and progressive disease. The following text is retained for historical perspective.

***Cohorts 1 and 2:***

The first on-study imaging assessment should be performed at 8 weeks (56 days +7 days) from the date of the first dose of study intervention. Subsequent tumor imaging should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated.

After approximately 1 year (Week 48 ± 7 days), participants who remain on study intervention will have imaging performed every 12 weeks (84 days ±7 days). The first imaging after Week 48 should be at Week 60 to follow the 12-week (84 days ± 7 days) schedule.

Imaging timing should follow calendar days from the date of the first dose and should not be adjusted for delays in study intervention. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, pregnancy, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

***Cohort 3:***

The first on-study imaging assessment should be performed at 6 weeks (42 days +7 days) from the date of the first dose of study intervention. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated.

After approximately 6 months (Week 24 ± 7 days), participants who remain on study intervention will have imaging performed every 12 weeks (84 days ±7 days). The first imaging after Week 24 should be at Week 36 to follow the 12-week (84 days ± 7 days) schedule. Imaging timing should follow calendar days from the date of the first dose and should not be adjusted for delays in study intervention. Participants in Cohort 3 will be evaluated until radiographic disease progression by RECIST 1.1 and then followed for second progression until death, participant withdrawal of consent, or notification by the Sponsor, whichever occurs first.

***All Cohorts:***

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks (at least 28 days) after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks (<28 days) later; tumor imaging may resume at the subsequent scheduled imaging time point.

#### 8.2.1.2.1 Determination of Radiographic Progression of Advanced Prostate Cancer

Radiographic progression for soft tissue and bone lesions will be determined as described in the consensus guidelines of the PCWG (PCWG-modified RECIST 1.1) [Scher, H. I., et al 2016]. Radiographic progression of bone lesions will be defined as the appearance of ≥2 new bone lesions on radionuclide bone scan. Progression in bone at the first scheduled assessment at Week 8, if unaccompanied by soft tissue progression, requires a second radionuclide bone scan ≥6 weeks later. Progression is confirmed to have occurred at the first scheduled assessment if the confirmation bone scan shows ≥2 additional new lesions. Radiographic bone progression after the 8-week assessment must be confirmed ≥6 weeks later, if unaccompanied by soft tissue progression. Progression is confirmed if the confirmation bone scan shows the persistence of ≥2 new bone lesions.

### 8.2.1.3 End of Treatment and Follow-up Tumor Imaging

**As of Amendment 04, participants who discontinue study intervention for any reason—eg, adverse event, progressive disease, physician or patient choice, or transition to a post-trial access program for olaparib—will also discontinue from the study without further follow-up.** The following text is retained for historical perspective.

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained

within 4 weeks (28 days) prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 8 weeks in Year 1 [until Week 48] or every 12 weeks after Year 1) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

#### 8.2.1.4 RECIST 1.1 and PCWG-Modified RECIST 1.1 Assessment of Disease

**As of Amendment 04, tumor images will no longer undergo central review.** Investigators should use RECIST 1.1 to assess tumor response and progressive disease. The following text is retained for historical perspective.

Modified RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response and date of disease progression. Traditional RECIST 1.1 will also be used by BICR when assessing tumor response and disease progression. Modified RECIST 1.1 will be used by the investigator as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention).

For participants with prostate cancer, the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention) will be PCWG-modified RECIST 1.1. Assessment of treatment response in the soft tissues will be according to RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Assessment of treatment response in bone will be according to the PCWG rules, as described in Appendix 9.

Soft tissue and bone response assessments will be combined to produce an overall radiographic response, as follows:

| Soft tissue response (RECIST 1.1) | Bone Scan Result (PCWG) | PCWG-modified RECIST 1.1 |
|---|---|---|
| PD | Any | PD |
| Any | PD-u | PD-u |
| NE | ND or Non-PD | NE |
| NED | NE | NE |
| NED | Non-PD | Non-CR/Non-PD |
| NED | ND | NED |
| SD | Non-PD, NE, or ND | SD |
| Non-CR/Non-PD | Non-PD, ND, or NE | Non-CR/Non-PD |
| PR | NE, ND, or Non-PD | PR |
| CR | Non-PD or NE | PR |
| CR | ND | CR |

Abbreviations: CR = complete response; ND = no disease; NE = non-evaluable; NED = no evidence of disease; PCWG = Prostate Cancer Working Group; PD = progressive disease; PD-u = unconfirmed progressive disease; PR = partial response; RECIST 1.1 = response evaluation criteria in solid tumors version 1.1; SD = stable disease.

### 8.2.2 Quality of Life Assessments

**As of Amendment 04, PROs will no longer be required.** The following text is retained for historical perspective.

For patient-reported outcomes (PROs), the PGI-S, EQ-5D-5L, and EORTC QLQ-C30, questionnaires will be administered by trained study site personnel and completed by the participants themselves.

PROs are to be administered prior to other study procedures and assessments including drug administration, AE evaluation, and disease status notification. The PROs are to be completed in the following order: PGI-S first, then EQ-5D-5L, and finally EORTC QLQ-C30 at the time points specified in Section 1.3.

The PROs will also be completed at the treatment discontinuation visit and 30-day safety follow-up visit. If the participant does not complete the PROs for any reason, the "Miss Mode" form must be completed to capture the reason the assessment was not performed.

## 8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in the Procedures Manual.

Planned time points for all safety assessments are provided in the SoA.

### 8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard as outlined in the SoA (Section 1.3). Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, as clinically indicated, prior to administration of study intervention. Weight should also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.3.2 Vital Signs

The investigator or qualified designee will measure vital signs at the time points specified in the SoA (Section 1.3) and will include temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate.

### 8.3.3 Electrocardiograms

A standard 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Clinically significant abnormal findings at Screening should be recorded as medical history. Additional ECGs should be performed when clinically necessary.

### 8.3.4 Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

#### 8.3.4.1 Bone Marrow or Blood Cytogenetic Samples

Bone marrow or blood cytogenetic samples may be collected for participants with prolonged hematological toxicities as defined in Section 6.6.1.2.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample.

### 8.3.5 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status at screening (within 7 days of the first dose), prior to the administration of the first dose of each study intervention and during the follow-up period as specified in the SoA (Section 1.3).

## 8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc., the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

### 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

1. All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

2. All AEs from the time of treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

3. All AEs meeting serious criteria, from the time of treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

4. All pregnancies from the time of treatment allocation/randomization through 30 days for females or 90 days for males who impregnate their partner following cessation of study intervention must be reported by the investigator. All exposure during breastfeeding from the time of treatment allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

5. For pharmacovigilance purposes and characterization, any SAE of MDS/AML or new primary malignancy occurring after the 30-day follow-up period should be reported to the Sponsor regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked during the regular follow-up for OS if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

6. Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered drug related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 10.

Table 10 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

| Type of Event | **Reporting Period:** Consent to Randomization/Allocation | **Reporting Period:** Randomization/Allocation Through Protocol-specified AE Collection Period | **Reporting Period:** After the Protocol-specified AE Collection Period | Time Frame to Report Event and Follow-up Information to Sponsor: |
|---|---|---|---|---|
| NSAE | Report if:<br>– due to protocol-specified intervention<br>– causes exclusion<br>– participant is receiving placebo run-in or other run-in treatment | Report all | Not required | Per data entry guidelines |
| SAE, Cancer, or Overdose | Report if:<br>– due to protocol-specified intervention<br>– causes exclusion<br>– participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>– drug related (Follow ongoing to outcome) | Within 24 hours of learning of event |
| Pregnancy/Lactation Exposure | – Report if participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in)<br>Exception: A positive pregnancy test at the time of initial screening is not a reportable event. | Report all | Previously reported<br>– Follow to completion/termination; report outcome | Within 24 hours of learning of event |
| Potential DILI events meeting biochemical criteria of Hy's Law (requiring regulatory reporting) | Report if:<br>– due to intervention<br>– causes exclusion | Report<br>– regardless of suspected etiology<br>– to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria | Previously reported<br>– Follow to completion/ termination; report outcome | Within 24 hours of learning of event |
| ECI (requires regulatory reporting) | Report if:<br>– due to intervention<br>– causes exclusion | Report<br>- requires regulatory reporting | Previously reported<br>– Follow to completion/ termination; report outcome | Within 24 hours of learning of event |

| Type of Event | **Reporting Period:** Consent to Randomization/Allocation | **Reporting Period:** Randomization/Allocation Through Protocol-specified AE Collection Period | **Reporting Period:** After the Protocol-specified AE Collection Period | Time Frame to Report Event and Follow-up Information to Sponsor: |
|---|---|---|---|---|
| ECI (does not require regulatory reporting) | Report if:<br>– due to intervention<br>– causes exclusion | Report<br>– those not requiring regulatory reporting | Previously reported<br>– Follow to completion/ termination; report outcome | Within 5 calendar days of learning of event (unless an SAE) |

Abbreviations: DILI = drug-induced liver injury; ECI = event of clinical interest; NSAE = nonserious adverse event; OME = other important medical event; SAE = serious adverse event.

### 8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including potential DILI events meeting biochemical criteria of Hy's Law, pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

### 8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

### 8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

### 8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

### 8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious AEs are also known as ECIs and must be reported to the Sponsor.

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
- An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,

- At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

Additional ECIs for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

- Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported whether it is considered a nonserious AE (eg non-melanoma skin cancer) or SAE and regardless of investigator’s assessment of causality.

## 8.5 Treatment of Overdose

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol (ie, 300 mg BID) should be reported as an overdose.

No specific information is available on the treatment of overdose of olaparib. In the event of overdose, the study intervention should be discontinued and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

### 8.10.1 Immunogenicity Assessments

Not applicable for this study.

## 8.11 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits, from the time of treatment allocation through 90 days following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

## 8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

### 8.12.1 Prescreening

The prescreening period may be utilized to determine biomarker eligibility based on HRRm/*BRCA*m/HRD status using an archival tumor biopsy sample and/or blood sample. After providing a prescreening consent, participant will be assigned a screening number.

Participants who do not have an archival tumor biopsy sample and/or blood sample available must provide written consent for the main study (Section 8.1.1.1) before the tumor biopsy or any other protocol-specified procedures can occur.

### 8.12.2 Screening

Approximately 42 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV (if required by local health authority) and hepatitis testing which may be done up to 42 days prior to the first dose of study intervention. Refer to Appendix 7 for country-specific requirements.

- Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.

- For WOCBP, a urine pregnancy test will be performed within 24 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Screening images are to be captured within 28 days of allocation.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

### 8.12.3 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1. Assessments/procedures should be performed, prior to the administration of study intervention.

### 8.12.4 Post-treatment Visit

#### 8.12.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be combined with the EOT Visit and should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

#### 8.12.4.2 Efficacy Follow-up Visits

**As of Amendment 04, efficacy follow-ups are no longer required.** Participants currently on efficacy follow-up are considered to have completed the study and will be discontinued from the study. The following text is retained for historical perspective.

Participants who discontinue study intervention for a reason other than disease progression will move into the efficacy follow-up phase and should be assessed every 8 weeks (56 days ± 14 days) in Year 1 or every 12 weeks (84 days ± 14 days) after Year 1, from the study drug/EOT discontinuation visit, by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, pregnancy, death, or the end-of-study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

#### 8.12.4.3 Survival Follow-up Assessments

**As of Amendment 04, survival follow-ups are no longer required.** Participants currently on survival follow-up are considered to have completed the study and will be discontinued from the study**.** The following paragraphs are retained for historical perspective.

Participant survival follow-up status will be assessed approximately every 12 weeks from study drug/EOT discontinuation visit or from Follow-up discontinuation, to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first survival follow-up contact will be scheduled ~12 weeks after the EOT discontinuation visit.

- For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

### 8.12.5 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status.

## 9 STATISTICAL ANALYSIS PLAN

**The protocol-specified analyses, other than exploratory biomarker analyses, have been completed.** As of Amendment 04, the following sections are retained for historical perspective.

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

### 9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

| | |
|---|---|
| **Study Design Overview** | Phase 2 Study of Olaparib Monotherapy in Participants with Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer |
| **Treatment Assignment** | Olaparib 300 mg twice daily (BID), single treatment arm, open-label. |
| **Analysis Populations** | Efficacy and safety: All Participants as Treated (APaT) |
| **Primary Endpoint(s)** | ORR based on modified RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer) as assessed by blinded independent central review. |
| **Key Secondary Endpoints** | DOR<br>OS<br>PFS<br>PFS2 (Cohort 3 only) |
| **Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses** | For ORR, the point estimate and exact Clopper-Pearson confidence interval (CI) will be provided. |
| **Statistical Methods for Key Safety Analyses** | Safety will be evaluated using descriptive statistics. |

| | |
|---|---|
| **Interim Analyses** | One interim analysis (IA) is planned for a non-binding futility check of the efficacy of olaparib in approximately 30 participants who are HRD positive but *BRCA1/2* non-mutated and have no detectable mutations in the other 13 genes involved in HRR. Results will be reviewed by the Sponsor. |
| **Multiplicity** | No multiplicity adjustment is planned |
| **Sample Size and Power** | Approximately 390 participants will be enrolled in the study. The approximately 390 participants will consist of approximately 84 participants in Cohort 1, 286 participants in Cohort 2, and 20 participants in Cohort 3. If the observed ORR is 30% in Cohort 1, the 95% CI will be (20.3, 40.7); if the observed ORR is 30% in Cohort 2, the 95% CI will be (24.8, 35.8); if the observed ORR is 60% in Cohort 3, the 95% CI will be (36.1, 80.9).<br>If sufficient evidence of activity is observed, the sample sizes of Cohort 1 and Cohort 2 may be increased to 150 and 330, respectively. With the expanded sample sizes, if the observed ORR is 30% in Cohort 1, the 95% CI will be (22.8, 38.0); if the observed ORR is 30% in Cohort 2, the 95% CI will be (25.1, 35.3). |

## 9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a nonrandomized, open-label study, ie, participants, Investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned. Although the study is open-label, independent radiologist(s) will perform the central imaging review without knowledge of participant-level biomarker status.

## 9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

## 9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

### 9.4.1 Efficacy Endpoints

The primary efficacy endpoint is ORR, defined as the proportion of participants who have a best overall response of either CR or PR as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer), modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, at any time during the study. Response for the primary analysis will be determined by BICR, with confirmatory assessment as required per modified RECIST 1.1. Participants with unknown or missing response information will be treated as non-responders.

Secondary efficacy endpoints include:

1. DOR, defined in the subset of participants with a CR or PR as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer), modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurs first.

2. OS, defined as the time from the date of the first dose of study medication to the date of death due to any cause.

3. PFS, defined as the time from date of the first dose of study medication to the first documented disease progression as assessed by BICR according to modified RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer), modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or death due to any cause, whichever occurs first.

4. PFS2 by investigator, only for Cohort 3, defined as the time from the date of the first dose of study medication until subsequent disease progression on next-line treatment or death due to any cause, whichever occurs first.

5. Progression based on CA-125, defined as either CA-125 ≥2 × ULN on 2 occasions 1 week apart or CA-125 ≥2 × the nadir value on 2 occasions 1 week apart for participants with elevated CA-125 at baseline.

6. PSA response, defined as a reduction in the PSA level of 50% or more from baseline measured twice at least 3 weeks apart.

### 9.4.2 Safety Endpoints

A description of safety endpoint assessment is provided in Section 4.2.2.2.

The primary safety endpoints are AEs graded using NCI CTCAE (Version 4.0). Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received olaparib, including SAEs and ECIs. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

### 9.4.3 Exploratory Endpoints

Efficacy Endpoints Based on traditional RECIST 1.1 in participants with non-prostate tumors:

- ORR based on traditional RECIST 1.1 as assessed by BICR.

- DOR, defined in the subset of participants with a CR or PR as assessed by BICR according to traditional RECIST 1.1, as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurs first.

- PFS, defined as the time from date of the first dose of study medication to the first documented disease progression as assessed by BICR according to traditional RECIST 1.1, or death due to any cause, whichever occurs first.

**Patient-reported Outcome Endpoints**

- Global Health Status/Quality of Life (GHS/QoL) score using EORTC QLQ-C30.

- Health utility and global severity of symptoms using the EuroQoL EQ-5D-5L and PGI-S, respectively.

The ePRO analysis time points will be specified in the sSAP and will be tied to the median PFS from the literature.

## 9.5 Analysis Populations

Participants are enrolled in the study when they have received an allocation number via IRT (Section 6.3).

### 9.5.1 Efficacy Analysis Populations

Efficacy Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all allocated participants who received at least 1 dose of study intervention.

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### 9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all allocated participants who received at least 1 dose of study intervention.

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

### 9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

## 9.6 Statistical Methods

### 9.6.1 Statistical Methods for Efficacy Analyses

The primary efficacy endpoint is ORR based on modified RECIST 1.1 or PCWG-modified RECIST 1.1 (participants with prostate cancer), as assessed by BICR. The point estimate and exact Clopper-Pearson CI will be provided. Secondary efficacy endpoints of DOR, OS, and PFS will be summarized. The primary analysis will be conducted when all enrolled participants have at least 9 months follow-up. The timing of the final analysis will be based on the evolvement of the trial and will be documented in the sSAP. The primary efficacy analyses will be assessed in Cohort 1, Cohort 2 and Cohort 3, respectively. Additional analysis populations are listed in Table 11 and Section 9.5.1.

Concordance of OR between modified RECIST 1.1 and traditional RECIST 1.1 in participants with non-prostate tumors will be summarized.

Censoring rules for DOR are summarized in Table 12. Responses in participants who are alive, have not progressed, have not initiated new anticancer treatment, and have not been determined to be lost to follow-up, and who have had a disease assessment within approximately 5 months of the data cutoff date, are considered ongoing at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. For OS, censoring will be performed using the date of last known contact for those who are alive at the time of analysis. For PFS, if a participant does

not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment. The censoring rules for PFS are summarized in Table 13.

Table 12 Censoring Rules for Duration of Response

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No progression nor death, no new anticancer therapy initiated | Last adequate disease assessment | Censor (non-event) |
| No progression nor death, new anticancer therapy initiated | Last adequate disease assessment before new anticancer therapy initiated | Censor (non-event) |
| Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any | Earlier date of last adequate disease assessment prior to the ≥2 missed adequate disease assessments and new anticancer therapy, if any | Censor (non-event) |
| Death or progression after ≤1 missed adequate disease assessment and before new anticancer therapy, if any | PD or death | End of response (Event) |

Abbreviation: PD = progressive disease.
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

Table 13 Censoring Rules for Primary Analysis of PFS

| Situation | Primary Analysis |
|---|---|
| PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any | Progressed at date of documented PD or death |
| PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any | Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any |
| No PD and no death; and new anticancer treatment is not initiated | Censored at last disease assessment |
| No PD and no death; new anticancer treatment is initiated | Censored at last disease assessment before new anticancer treatment |

Abbreviations: PD = progressive disease; PFS = progression-free survival.

For DOR, if data warrant, Kaplan-Meier medians and quartiles will be provided. Descriptive summaries including swim lane plots will also be provided. For OS and PFS, if data warrant, Kaplan-Meier quartile estimates along with the 95% CI will be provided.

An analysis of PFS2, defined as the time from the date of the first dose of study medication to subsequent disease progression on next-line treatment or death from any cause, whichever occurs first, will be carried out. Participants alive and for whom subsequent disease progression on next-line treatment has not been observed will be censored at the last time the

participant was known to be alive and without disease progression. The same Kaplan-Meier analysis as for PFS will be provided.

Further details will be provided in the sSAP. Table 14 summarizes the analysis strategy for the key efficacy variables as below.

Table 14 Analysis Strategy for Key Efficacy Variables

| Endpoint/Variable (Description, Time Point) | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| **Primary Objectives** | | | |
| ORR per modified RECIST 1.1[a] or PCWG-modified RECIST 1.1 (participants with prostate cancer) by BICR | 95% CI calculated using the Clopper-Pearson method | APaT | Participants with missing data are considered non-responders |
| **Secondary Objectives** | | | |
| DOR per modified RECIST 1.1[a] or PCWG-modified RECIST 1.1 (participants with prostate cancer) by BICR | Summary statistics using Kaplan-Meier method | All responders in APaT | Non-responders are excluded in analysis |
| OS | Summary statistics using Kaplan-Meier method | APaT | Censored at last assessment |
| PFS per modified RECIST 1.1[a] or PCWG-modified RECIST 1.1 (participants with prostate cancer) by BICR | Summary statistics using Kaplan-Meier method | APaT | Censored according to rules in Table 12 |
| PFS2 by investigator | Summary statistics using Kaplan-Meier method | APaT (Cohort 3 only) | Participants alive and for whom no secondary disease progression has been served will be censored at the last time known to be alive and without second disease progression. |

Abbreviations: APaT = All Participants as Treated; BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PCWG = Prostate Cancer Working Group; PFS = progression-free survival; PFS2 = progression-free survival after next-line treatment; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

a. Modified RECIST 1.1 and PCWG-modified RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

### 9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Safety analyses will be assessed by biomarker.

**Adverse Events**

Events will be summarized based on number and proportion of total participants, by system organ class and preferred term. Separate summaries with descriptive statistics (counts and percentage) will be given for all AEs, treatment-related AEs, AEs by toxicity grade, SAEs and AEs leading to discontinuation of study intervention and dose modification.

ECIs will be identified and additional summaries provided.

The incidence of deaths and the primary cause of death will be summarized.

Further details on the statistical approach of safety analysis will be described in the sSAP.

### 9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

#### 9.6.3.1 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs. The number and percentage of participants screened and allocated and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

#### 9.6.3.2 Patient-Reported Outcomes Analyses

EORTC QLQ-C30, EuroQoL EQ-5D, and PGI-S data will be summarized as part of the prespecified exploratory analyses. Details will be included in the sSAP.

## 9.7 Interim Analyses

One interim analysis (IA) is planned. As there is relatively little data available for the use of HRD positivity as a biomarker to predict response to olaparib, the primary purpose of the IA is to test futility of HRD positive subgroup to evaluate the overall contribution of HRD to the tumor-agnostic biomarker approach. The IA will evaluate the efficacy of olaparib in the subgroup of participants who are HRD positive but *BRCA1/2* non-mutated and have no detectable mutations in the 13 other genes involved in HRR. Results will be reviewed by the Sponsor. The IA will be performed when approximately 30 participants in the subgroup had at least 6 months of follow-up. The primary endpoint of ORR will be summarized along with corresponding DOR. Confirmed and unconfirmed responses will be included in ORR calculations for the IA. Bayesian posterior probability that the ORR is greater than a cutoff value (eg, 30%) will be calculated. If the posterior probability is less than a certain level (eg,

10%), potential outcome would be the removal of HRD subgroup. The futility criteria will be non-binding.

Details regarding the timing and conduct of the IA will be further clarified in the sSAP.

Additional interim analyses may be performed. The timing and the details will be documented in the sSAP. The sample size may increase if there is sufficient evidence of efficacy of olaparib in participants with *BRCA*m cancer (Cohort 1) or in participants with HRD positive (HRR non-mutated) cancer (Cohort 2) based on the ORR. The details of the criteria for an increase in sample size will be described in the sSAP. The sSAP may also be updated as the study evolves.

## 9.8 Multiplicity

The cumulative data will be reviewed by the Sponsor on an ongoing basis, with no multiplicity control.

## 9.9 Sample Size and Power Calculations

Approximately 390 participants will be initially enrolled in the study.

The initial sample size for the primary analysis populations listed in Table 11 are:

- Cohort 1 (*BRCA*m): N = 84
- Cohort 2 (HRRm [*BRCA1/2* non-mutated] and HRD positive [*BRCA1/2* non-mutated and HRR non-mutated]): N = 286
- Cohort 3 (s*BRCA*m Breast): N = 20

The initial sample size for the secondary analysis populations listed in Table 11 are:

- All participants (includes participants who are HRRm or HRD positive in Cohorts 1 and 2): N = 370
- HRRm: N = 258 (includes 84 participants who are *BRCA*m and 174 participants who are 13 gene HRRm, *BRCA1/2* non-mutated)
- HRD: minimally N =196 (includes the 84 participants who are *BRCA*m and at least 112 participants who are either HRD positive *BRCA1/2* non-mutated with no detectable mutations in the 13 other genes involved in HRR or participants who are both HRD positive and 13 gene HRRm but *BRCA1/2* non-mutated)
- s*BRCA*: N= 20 (includes breast cancer participants who are s*BRCA*m)

The initial sample size for the exploratory analysis populations listed in Table 11 are:

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There is no hypothesis testing in the study. Except for platinum-sensitive ovarian cancer, the ORR for SOC across various tumor types ranges between <5% and 20% with ORR in most tumor types between 10% and 15% for patients who have failed SOC therapies (Table 1). A clinically meaningful improvement for olaparib over SOC in Cohorts 1, 2, and 3 will be determined considering the ORR achieved and the durability of responses. Table 15 shows the precision of the ORR point estimate for each analysis population.

Table 15 95% CI of the ORR Point Estimate

| Analysis Population | N | Observed ORR | 95% CI of ORR |
|---|---|---|---|
| **Primary** | | | |
| *BRCA*m (Cohort 1) | 84 | 15% | (8.5, 25.0) |
| | | 20% | (12.3, 30.4) |
| | | 25% | (16.2, 35.6) |
| | | 30% | (20.3, 40.7) |
| HRRm (*BRCA1/2* non-mutated) and/or HRD positive (*BRCA1/2* non-mutated and HRR non-mutated) (Cohort 2) | 286 | 15% | (11.1, 19.7) |
| | | 20% | (15.5, 25.0) |
| | | 25% | (20.3, 30.6) |
| | | 30% | (24.8, 35.8) |
| s*BRCA* (Cohort 3) | 20 | 60% | (36.1, 80.9) |
| **Secondary** | | | |
| All Participants (Cohorts 1 and 2) | 370 | 15% | (11.6, 19.2) |
| | | 20% | (16.0, 24.4) |
| | | 25% | (20.5, 29.6) |
| | | 30% | (25.4, 35.0) |
| HRRm | 258 | 15% | (11.0, 20.1) |
| | | 20% | (15.4, 25.6) |
| | | 25% | (19.7, 30.5) |
| | | 30% | (24.3, 35.8) |

| Analysis Population | N | Observed ORR | 95% CI of ORR |
|---|---|---|---|
| HRD | 196 | 15% | (10.1, 20.6) |
| | | 20% | (14.6, 26.2) |
| | | 25% | (19.1, 31.7) |
| | | 30% | (23.8, 37.1) |

Abbreviations: *BRCA1/2* = breast cancer susceptibility gene 1/2; *BRCA*m = known or suspected deleterious mutation detected in *BRCA1* or *BRCA2*; HRD = homologous recombination deficiency; HRR = homologous recombination repair; HRRm = homologous recombination repair mutated; ORR = objective response rate.

The sample size of Cohort 1 and the HRD positive, HRR non-mutated biomarker subgroup in Cohort 2 may be increased if sufficient evidence of activity is observed. Approximately 500 participants may be enrolled in the study.

The increased sample size for the primary analysis populations listed in Table 11 are:

- Cohort 1 (*BRCA*m): N = 150
- Cohort 2 (HRRm [*BRCA1/2* non-mutated] and/or HRD positive [*BRCA1/2* non-mutated and HRR non-mutated): N = 330

The increased sample size for the secondary analysis populations listed in Table 11 are:

- All participants (includes participants who are HRRm or HRD positive in Cohorts 1 and 2): N = 480
- HRRm: N = 324 (includes 150 participants who are *BRCA*m and 174 participants who are 13 gene HRRm, *BRCA1/2* non-mutated)
- HRD: minimally N = 306 (includes the 150 participants who are *BRCA*m and at least 156 participants who are either HRD, *BRCA1/2* non-mutated with no detectable mutations in the 13 other genes involved in HRR or participants who are both HRD positive and 13 gene HRRm but *BRCA1/2* non-mutated)

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Table 16 shows the precision of the ORR point estimate for each analysis population for Cohort 1 and Cohort 2 with increased sample sizes.

Table 16 95% CI of the ORR Point Estimate With Increased Sample Sizes

| Analysis Population | N | Observed ORR | 95% CI of ORR |
|---|---|---|---|
| **Primary** | | | |
| *BRCA*m (Cohort 1) | 150 | 15% | (9.4, 21.4) |
| | | 20% | (13.9, 27.3) |
| | | 25% | (18.6, 33.1) |
| | | 30% | (22.8, 38.0) |
| HRRm (*BRCA1/2* non-mutated) and/or HRD positive (*BRCA1/2* non-mutated and HRR non-mutated) (Cohort 2) | 330 | 15% | (11.5, 19.5) |
| | | 20% | (15.8, 24.7) |
| | | 25% | (20.3, 29.9) |
| | | 30% | (25.1, 35.3) |
| **Secondary** | | | |
| All Participants (Cohorts 1 and 2) | 480 | 15% | (11.9, 18.5) |
| | | 20% | (16.5, 23.9) |
| | | 25% | (21.2, 29.1) |
| | | 30% | (25.9, 34.3) |
| HRRm | 324 | 15% | (11.4, 19.5) |
| | | 20% | (15.8, 24.8) |
| | | 25% | (20.4, 30.1) |
| | | 30% | (25.3, 35.6) |
| HRD | 306 | 15% | (11.2, 19.5) |
| | | 20% | (15.6, 24.9) |
| | | 25% | (20.1, 30.1) |
| | | 30% | (25.0, 35.5) |

Abbreviations: BRCA1/2 = breast cancer susceptibility gene 1/2; BRCAm = known or suspected deleterious mutation detected in BRCA1 or BRCA2; HRD = homologous recombination deficiency; HRR = homologous recombination repair; HRRm = homologous recombination repair mutated; ORR = objective response rate.

Table 17 shows the precision of the point estimate of ORR under different sample sizes and number of responders for the exploratory analyses where single indications/gene mutations might be assessed.

Table 17 Confidence Intervals Under Different Sample Sizes and Number of Responders

| N | Number of Responders | ORR (%) | 80% CI | 90% CI | 95% CI |
|---|---|---|---|---|---|
| 10 | 2 | 20.0 | (5.5, 45.0) | (3.7, 50.7) | (2.5, 55.6) |
| | 3 | 30.0 | (11.6, 55.2) | (8.7, 60.7) | (6.7, 65.2) |
| | 4 | 40.0 | (18.8, 64.6) | (15.0, 69.6) | (12.2, 73.8) |
| 20 | 5 | 25.0 | (12.7, 41.5) | (10.4, 45.6) | (8.7, 49.1) |
| | 6 | 30.0 | (16.6, 46.7) | (14.0, 50.8) | (11.9, 54.3) |
| | 7 | 35.0 | (20.7, 51.8) | (17.7, 55.8) | (15.4, 59.2) |
| | 8 | 40.0 | (24.9, 56.7) | (21.7, 60.6) | (19.1, 63.9) |
| 30 | 8 | 26.7 | (16.2, 39.7) | (14.0, 43.0) | (12.3, 45.9) |
| | 9 | 30.0 | (19.0, 43.2) | (16.6, 46.5) | (14.7, 49.4) |
| | 10 | 33.3 | (21.8, 46.6) | (19.3, 49.9) | (17.3, 52.8) |
| | 11 | 36.7 | (24.8, 50.0) | (22.1, 53.3) | (19.9, 56.1) |
| | 12 | 40.0 | (27.7, 53.3) | (25.0, 56.6) | (22.7, 59.4) |
| 40 | 10 | 25.0 | (16.2, 35.9) | (14.2, 38.7) | (12.7, 41.2) |
| | 11 | 27.5 | (18.3, 38.5) | (16.3, 41.4) | (14.6, 43.9) |
| | 12 | 30.0 | (20.5, 41.2) | (18.3, 44.0) | (16.6, 46.5) |
| | 13 | 32.5 | (22.7, 43.8) | (20.4, 46.6) | (18.6, 49.1) |
| | 14 | 35.0 | (24.9, 46.3) | (22.6, 49.2) | (20.6, 51.7) |
| | 15 | 37.5 | (27.1, 48.9) | (24.7, 51.7) | (22.7, 54.2) |
| | 16 | 40.0 | (29.4, 51.4) | (26.9, 54.2) | (24.9, 56.7) |

Abbreviations: CI = confidence interval; ORR = objective response rate.

## 9.10 Subgroup Analyses

The treatment effect of the primary endpoint will be estimated and/or plotted within each category of the following classification variables:

- Age category (<65, ≥65 years)
- Sex (Female, Male)
- Race (white vs. other)

The subgroup analyses will be conducted within cohort if the sample size permits.

## 9.11 Compliance (Medication Adherence)

Drug accountability data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

## 9.12 Extent of Exposure

Extent of Exposure for a participant is defined as number of days in which the participant receives the study intervention. Summary statistics will be provided on Extent of Exposure for the APaT population.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1 Code of Conduct for Clinical Trials

**Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)**

**Code of Conduct for Interventional Clinical Trials**

**I. Introduction**

**A. Purpose**

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH-GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

**B. Scope**

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease-related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage

underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

**3. Site Monitoring/Scientific Integrity**

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

## B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

# III. Participant Protection

## A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

## B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

## C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

## D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

**IV. Financial Considerations**

**A. Payments to Investigators**

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

**B. Clinical Research Funding**

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

**V. Investigator Commitment**

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

### 10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### 10.1.3 Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

#### 10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

#### 10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

#### 10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

### 10.1.4 Committees Structure

Not applicable for this study.

### 10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

### 10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

### 10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

### 10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### 10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

## 10.2 Appendix 2: Clinical Laboratory Tests

**As of Amendment 4, hematology and chemistry panels will be performed as per institutional standards**. The following text and table are retained for historical perspective.

- The tests detailed in Table 18 will be performed by the local laboratory.
- Following Day 1 of Week 0 of the treatment period, collection of samples for predose laboratory assessments may be performed up to 3 days (72 hours) prior to dosing in subsequent cycles.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 18 Protocol-required Safety Laboratory Assessments

| **Laboratory Assessments** | **Parameters** | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit | RBC Indices:<br>MCV<br>MCH<br>Reticulocytes (reticulocytes/erythrocytes% or absolute reticulocytes) | WBC count with Differential[1]:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Chemistry | Blood Urea Nitrogen (BUN) or urea[2] | Potassium | Aspartate Aminotransferase (AST)/Serum Glutamic Oxaloacetic Transaminase (SGOT) | Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal) |
| | Albumin | Carbon dioxide ($CO_2$ or bicarbonate)[3] | Chloride | Phosphorous |
| | Creatinine or creatinine clearance[4] | Sodium | Alanine Aminotransferase (ALT)/Serum Glutamic Pyruvic Transaminase (SGPT) | Total Protein |
| | Glucose | Calcium | Alkaline phosphatase | Lactate dehydrogenase |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |

| Laboratory Assessments | Parameters |
|---|---|
| Other Screening Tests | • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only).<br>• Serum or urine β human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP).<br>• Serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody).<br>• Serology (HIV antibody) as required by local health authority or institutional regulations. Refer to Appendix 7 for country-specific information.<br>• Coagulation factors (PT or INR, and aPTT/PTT). Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. |
| Other Tests | • Bone marrow or blood cytogenetic analysis for prolonged hematological toxicities (Section 6.6.1.2). This should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity<br>• CA-125[5]<br>• PSA[6] |

Abbreviations: aPTT = activated partial thromboplastin time; CA-125 = cancer antigen-125; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PSA = prostate-specific antigen; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

Notes:

1. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
2. BUN is preferred; if not available, urea may be tested.
3. Performed only if considered the local standard of care.
4. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
5. Only performed in participants with ovarian cancer. CA-125 values ≥2 × the normal value or ≥2 × the lowest level it has been during the study will be repeated within 1 week to confirm the elevation.
6. Only performed in participants with prostate cancer.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

## 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1 Definitions of Medication Error, Misuse, and Abuse

**Medication Error**

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

**Misuse**

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

**Abuse**

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

### 10.3.2 Definition of AE

**AE definition**

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

**Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

**Events NOT meeting the AE definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

### 10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

### 10.3.4 Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse event that occurs during a clinical trial and meets the following criteria:

- unexpected, meaning the nature or severity of the event doesn't match the reference safety information (RSI)
- serious adverse event as defined in Section 10.3.3
- reasonable possibility the event was caused by the study drug

### 10.3.5 Additional Events Reported in the Same Manner as SAE

**Additional events that require reporting in the same manner as SAE**

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

### 10.3.6 Recording AE and SAE

**AE and SAE recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity**

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs//worksheets.

    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

    - Grade 4: Life threatening consequences; urgent intervention indicated

    - Grade 5: Death related to AE

**Assessment of causality**

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

  - If yes, did the AE resolve or improve?

  - If yes, this is a positive dechallenge.

  - If no, this is a negative dechallenge.

  - (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study); or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.7 Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

**AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool**

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

**SAE reporting to the Sponsor via paper CRF**

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

## 10.4 Appendix 4: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable for this study.

## 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

### 10.5.1 Definitions

**Women of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity).

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.5.2 Contraception Requirements

**Male Participants**

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following for either the minimum protocol-defined time frame in Section 5.1 or for the time frame detailed in the approved product label per local requirements, whichever is longer:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and female condom cannot be used together.

  Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

**Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 19 during the protocol-defined time frame in Section 5.1.

Table 19 Highly Effective Contraception Methods

| **Contraceptives allowed during the study include[a]:** |
|---|
| **Highly Effective Contraceptive Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Progestogen-only subdermal contraceptive implant[b,c]<br>• IUS[c,d]<br>• Non-hormonal IUD<br>• Bilateral tubal occlusion |
| • Azoospermic partner (vasectomized or secondary to medical cause)<br>This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.<br><br>Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. |
| **Sexual Abstinence**<br>• Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |
| a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>b. If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptive implants are limited to those which inhibit ovulation.<br>c. Male condoms must be used in addition to female participant hormonal contraception.<br>d. IUS is a progestin-releasing IUD.<br><br>Note: The following are not acceptable methods of contraception:<br>- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.<br>- Male condom with cap, diaphragm, or sponge with spermicide.<br>- Male and female condom should not be used together (due to risk of failure with friction). |

### 10.5.3 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing ([urine or serum] as required by local regulations) should be conducted every 4 weeks (28 days) during intervention.
  - Pregnancy testing ([urine or serum] as required by local regulations) should be conducted 30 days after the last dose of study intervention.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the individual's participation in the study.

## 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research[3,4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

## 3. Summary of Procedures for Future Biomedical Research[3,4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

## 4. Confidential Participant Information for Future Biomedical Research[3,4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

## 5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

## 6. Withdrawal From Future Biomedical Research[3,4]

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

## 7. Retention of Specimens[3,4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

## 8. Data Security[3,4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

## 9. Reporting of Future Biomedical Research Data to Participants[3,4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

## 10. Future Biomedical Research Study Population[3,4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

## 11. Risks Versus Benefits of Future Biomedical Research[3,4]

For future biomedical research, risks to the participant have been minimized and are described in the Future Biomedical Research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

## 12. Questions

Any questions related to the future biomedical research should be emailed directly to. clinical.specimen.management@MSD.com

## 13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

## 10.7 Appendix 7: Country-specific Requirements

### 10.7.1 Germany

***Section 1.3 Schedule of Activities***

| Study Period | Screening | | Treatment Period | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a] (Visit 1)** | | **1** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **±3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | |
| **Safety Procedures** | | | | | | | | | | |
| HIV testing | X | | | | | | | | | Testing is required. |

a. All screening procedures should be performed within 42 days of allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

***Section 5.2 Exclusion Criteria***

10. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

***Section 8.12.2 Screening***

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 42 days prior to the first dose of study intervention.

***Appendix 2 Clinical Laboratory Tests***

Other Screening Tests: Serology (HIV RNA).

## 10.7.2 United Kingdom

### *Section 1.3 Schedule of Activities*

| Study Period | Screening | | Treatment Period | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a] (Visit 1)** | | **1** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **±3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | |
| **Safety Procedures** | | | | | | | | | | |
| HIV testing | X | | | | | | | | | Testing is required. |

a. All screening procedures should be performed within 42 days of allocation, unless otherwise noted.

b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

### *Section 5.2 Exclusion Criteria*

10. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

### *Section 6.5.1 Prohibited Concomitant Medications*

4. Live vaccines while participating in the study, and within 90 days of the last dose of study intervention.

    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

    - Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

### *Section 8.12.2 Screening*

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 42 days prior to the first dose of study intervention.

### *Appendix 2 Clinical Laboratory Tests*

Other Screening Tests: Serology (HIV antibody).

## 10.7.3 Ireland

### Section 1.3 Schedule of Activities

| Study Period | Screening | | Treatment Period | | | | | | EOT | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a] (Visit 1)** | | **1** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **±3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | |
| **Safety Procedures** | | | | | | | | | | |
| HIV testing | X | | | | | | | | | Testing is required. |

a. All screening procedures should be performed within 42 days of allocation, unless otherwise noted.

b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

### *Section 5.2 Exclusion Criteria*

10. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

### *Section 6.5.1 Prohibited Concomitant Medications*

4. Live vaccines while participating in the study, and within 90 days of the last dose of study intervention.

    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, intranasal seasonal influenza, rabies, BCG, and typhoid (oral).

    - Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and, once confirmed, are allowed.

### *Section 8.1.4 Medical History*

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed that the investigator considers to be clinically significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

### *Section 8.12.2 Screening*

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HIV and hepatitis testing which may be done up to 42 days prior to the first dose of study intervention.

### *Appendix 2 Clinical Laboratory Tests*

Other Screening Tests: Serology (HIV antibody).

## 10.7.4 Romania

### Section 1.3 Schedule of Activities

| **Study Period** | **Screening** | | **Treatment Period** | | | | | | **EOT** | **Notes** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **Screening[a] (Visit 1)** | | **1** | **4** | **8** | **12** | **16** | **20+[b]** | **DC** | |
| **Visit Number** | **1** | | **2** | **3** | **4** | **5** | **6** | **7+** | | |
| **Scheduling Window (Days):** | **–42 to -1** | **–28 to –1** | **±3** | **±3** | **±3** | **±3** | **±3** | **±3** | **At time of DC** | |
| **Safety Procedures** | | | | | | | | | | |
| HIV testing | X | | | | | | | | | Testing is required. |

a. All screening procedures should be performed within 42 days of allocation, unless otherwise noted.
b. Following Week 20, visits are to occur approximately every 4 weeks (~28 days) until documented PD, death, withdrawal of consent, or the end of the study, whichever occurs first.

### *Section 5.2 Exclusion Criteria*

10. Participant has a known history of human immunodeficiency virus (HIV) infection. Testing for HIV is required at screening.

## 10.8 Appendix 8: Abbreviations

| Abbreviation | Expanded Term |
|---|---|
| ADL | Activities of daily living |
| ADP | Adenosine diphosphate |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| APaT | All Participants as Treated |
| AST | Aspartate aminotransferase |
| ATM | Ataxia-telangiectasia mutated |
| ATMm | ATM mutated (ie, with a known or suspected deleterious mutation in *ATM*) |
| β-hCG | β-human chorionic gonadotropin |
| BARD1 | *BRCA1* associated RING Domain 1 |
| BCG | Bacillus Calmette-Guérin |
| BER | Base excision repair |
| BICR | Blinded independent central review |
| BID | Twice daily |
| *BRCA1* | Breast cancer susceptibility gene 1 |
| *BRCA2* | Breast cancer susceptibility gene 2 |
| *BRCA*m | *BRCA1/2* mutated (ie, with a known or suspected deleterious mutation in *BRCA1/2*) |
| BRIP1 | *BRCA1* Interacting Protein C-terminal Helicase 1 |
| CA-125 | Cancer antigen-125 |
| CAP | College of American Pathologists |
| CDK12 | Cyclin-dependent kinase 12 |
| cfDNA | cell-free DNA |
| cfRNA | cell-free RNA |
| CHEK1/2 | Checkpoint kinase 1/2 |
| CI | Confidence interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| CNS | Central nervous system |
| CR | Complete response |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor deoxyribonucleic acid |
| CTR | Clinical Trials Regulation |
| CYP | Cytochrome P450 |
| DC | Discontinuation |
| DILI | Drug-induced liver injury |
| DNA | Deoxyribonucleic acid |
| DOR | Duration of response |
| DSB | Double strand break |
| ECG | Electrocardiogram |
| ECI | Event of clinical interest |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data collection |
| EEA | European Economic Area |
| ELISA | Enzyme-linked immunoassay |
| EORTC | European Organisation for Research and Treatment of Cancer |

| Abbreviation | Expanded Term |
|---|---|
| EOT | End of treatment |
| EU | European Union |
| EuroQoL | European quality of life |
| FANCL | Fanconi anemia, complementation group L |
| FAS | Full analysis set |
| FBR | Future Biomedical Research |
| FDA | US Food and Drug Administration |
| FDG-PET | Fluorodeoxyglucose-positron emission tomography |
| FFPE | Formalin-fixed paraffin-embedded |
| FMI | Foundation Medicine, Inc. |
| FOLFOX | Chemotherapy regimen that includes folinic acid, fluorouracil, and oxaliplatin |
| FPE | First patient enrolled |
| FSH | Follicle-stimulating hormone |
| FSR | First Site Ready |
| GBM | Glioblastoma |
| g*BRCA*m | Germline breast cancer susceptibility gene mutated |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GEP | Gene expression profile |
| GHS | Global Health Status |
| GM-CSF | Granulocyte-monocyte colony-stimulating factor |
| HBsAg | HBV surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HER2 | Human epidermal growth factor receptor 2 |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| HRCT | High Resolution Computed Tomography |
| HRD | Homologous recombination deficiency |
| HRQoL | Health-related quality of life |
| HRR | Homologous recombination repair |
| HRRm | Homologous recombination repair mutation |
| HRT | Hormone replacement therapy |
| IA(s) | Interim analysis(ses) |
| IB | Investigator's Brochure |
| $IC_{50}$ | Half-maximal inhibitory concentration |
| ICF | Informed Consent Form |
| ICH | International Council on Harmonization |
| ICMJE | International Committee of Medical Journal Editors |
| ICSR | Individual case safety report |
| IEC | Independent Ethics Committee |
| IMP | Investigational Medicinal Product |
| indels | Insertions-deletions |
| IRB | Institutional Review Board |
| IRT | Interactive response technology |
| IV | Intravenous |
| LHRH | Luteinizing hormone-releasing hormone |
| LOH | Loss of heterozygosity |
| LPLV | Last patient, last visit |
| mCRPC | Metastatic castrate-resistant prostate cancer |
| MDS | Myelodysplastic syndrome |
| mPFS | Median progression-free survival |

| Abbreviation | Expanded Term |
|---|---|
| MRI | Magnetic resonance imaging |
| mRNA | Messenger RNA |
| MSI | Microsatellite instability |
| MSI-H | Microsatellite instability-high |
| mTOR | Mammalian Target of Rapamycin |
| NCI | National Cancer Institute |
| NHEJ | Non-homologous end-joining |
| OME | Other important medical event |
| OR | Objective response |
| ORR | Objective response rate |
| OS | Overall survival |
| PALB2 | Partner and localizer of *BRCA2* |
| PARP | Polyadenosine 5′ diphosphoribose (poly[ADP ribose]) polymerization |
| PBMC | peripheral blood mononuclear cells |
| PCWG | Prostate Cancer Working Group |
| PD | Progressive disease |
| PD-L1 | Programmed cell death ligand 1 |
| PET | Positron emission tomography |
| PFS | Progression-free survival |
| PFS2 | Time from randomization to second progression |
| PGI-S | Patient Global Impression of Severity |
| PK | Pharmacokinetic |
| PPP2R2A | Protein Phosphatase 2 Regulatory Subunit B alpha |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PSA | Prostate-specific antigen |
| PT | Prothrombin time |
| QoL | Quality of life |
| QLQ | Quality of life questionnaire |
| RAD51 | DNA repair protein RAD51 homolog |
| RAD54 | DNA repair and recombination protein RAD54 |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors version 1.1 |
| RNA | Ribonucleic acid |
| RR | Respiratory rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| s*BRCA* | Somatic breast cancer susceptibility gene |
| SD | Stable disease |
| SIM | Site imaging manual |
| SLAB | Supplemental Laboratory Tests |
| SNP | Single nucleotide polymorphism |
| SoA | Schedule of activities |
| SOC | Standard of care |
| sSAP | Supplemental statistical analysis plan |
| SSB | Single strand break |
| SUSAR | Suspected unexpected serious adverse reaction |
| TDT | Time from randomization to discontinuation or death |
| TFST | Time from randomization to first subsequent therapy or death |
| TKI | Tyrosine kinase inhibitor |
| TNBC | Triple-negative breast cancer |
| TPC | Treatment of physician's choice |
| TSST | Time from randomization to second subsequent therapy or death |

| Abbreviation | Expanded Term |
|---|---|
| ULN | Upper limit of normal |
| US | United States |
| VEGF | Vascular endothelial growth factor |
| WOCBP | Woman/women of childbearing potential |

## 10.9 Appendix 9: Description of the Prostate Cancer Working Group (PCWG) Process for Assessment of Bone Lesions

The rules for evaluation of response and progression based on bone lesions were created by the Prostate Cancer Working Group, and published as part of both PCWG2 and PCWG3 [Scher, H. I., et al 2016]. All bone lesions are evaluated according to these rules, including assessment at screening/baseline and evaluation of response.

### Imaging Methods

The PCWG rules were designed based on the radionuclide (Tc-99m) bone scintigraphy. Other modalities, including FDG-PET, sodium fluoride PET, bone MRI, etc. may have individual advantages, but the PCWG rules were not created with the performance characteristics of these methods in mind and should not be used instead of radionuclide bone scan.

Only bone lesions seen by bone scan may be followed for assessment of tumor treatment response. Bone disease seen by CT only (not visible on bone scan) is presumed not to represent active disease, and should not be documented as a bone lesion (sclerotic lesions seen on CT may represent healed disease or non-malignant confounders such as bone infarcts or other benign findings).

### Documentation of Bone Lesions at Baseline

At baseline, individual bone lesions may be recorded as non-target lesions only, and the number of bone lesions should be noted.

### Assessment of Bone Response at Subsequent Imaging Time Points

At all follow-up time points, bone disease will be classified as showing PD (progressive disease), PD-U (progressive disease unconfirmed), Non-PD (no progressive disease), NED (no evidence of disease), or NE (non-evaluable). . The definitions are summarized in the following table, and described in more detail below.

| Bone Response | Definition |
|---|---|
| **PD** | 2 new lesions, not flare, persistent |
| **PD-U** | Temporary marker of possible PD, to be updated to PD or non-PD once a subsequent scan is available.<br>If this is the final visit, the response will remain as PDu; however, this is updated to PD during the analysis by the Sponsor. |
| **Non-PD** | At least one bone lesion present, but not enough to trigger PD |
| **NE** | Non-evaluable: Presence of bone lesions cannot be determined (scan quality, scan missing, etc.) |
| **NED** | No Evidence of Disease: No lesions seen on bone scan |

## Descriptions of Bone Response Categories

### *No Disease*

No lesions seen on bone scan at this visit. Either none were seen at baseline, or all completely resolved on subsequent imaging.

### *Non-progression (Non-PD)*

At least one bone lesion is present on the scan at this visit, but the conditions for progression have not been met, because there are not at least 2 new lesions present.

### *Unconfirmed Progressive Disease (PD-U)*

At least 2 new bone lesions are present, but an additional scan is required for confirmation.

### *Progressive Disease (PD)*

At least 2 new bone lesions are present, which have been confirmed to not represent flare or any other confounder (see below), and which are persistent for at least 6 weeks. The new bone lesions do not all have to appear at the same time. Thus if one new lesion appears at visit N, and another new lesion at visit N+1, visit N+1 is considered to represent progressive disease.

### *Confirmation of Progression*

Radiographic progression of bone lesions is defined as the appearance of ≥ 2 new bone lesions on radionuclide bone scan. When ≥ 2 new bone lesions are first observed, this is classified as PD-U, which marks the possibility of progression that will be resolved by the next scan.

*For new lesions within the flare window (<12 weeks)*

After a scan classified as PD-U within the first 12 weeks of treatment, if the next bone scan outside the flare window shows at least 2 additional new bone lesions (in addition to the new lesions seen on the prior scan), the initial progression is considered confirmed, and the bone scan response updated to PD. Because this requires at least 2 new lesions, followed by another 2 new lesions, this is known as the "2+2 rule".

If the next bone scan outside the flare window does not show at least 2 additional new bone lesions, the lesions seen on the prior scan within the flare window are considered to be pre-existing lesions that became more visible because of the tumor flare phenomenon.

- The bone response at the prior visit is updated to non-PD
- The bone lesions seen at the prior visit are ignored for the purposes of counting new lesions at later time points, since they were not new. This may be referred to as "re-baselining."

*For new lesions outside the flare window (>12 weeks)*

After a scan classified as PD-U after the first 12 weeks of treatment, if at least 2 of the new lesions seen on that scan persist on the next bone scan performed at least 6 weeks later, this confirms the initial progression. The prior response is then updated to PD. If the new lesions have disappeared on this later scan, the prior response is updated to non-PD because these lesions are presumed to be non-malignant in nature. No re-baselining of lesions will occur in this scenario.

***Superscan***

A "superscan" occurs when there is diffuse skeletal involvement by tumor, such that individual bone lesions are not distinguishable. The bone scan may initially appear normal, because the increase bone uptake may be uniform, but can be distinguished by the faint or absent activity in the kidneys and urinary tract.

If there is a true superscan at baseline, identifying individual new bone lesions, and determining progression based on bone lesions, may be impossible.

If a superscan occurs after baseline, the patient's bone response will be recorded as PD. No subsequent imaging will be required for confirmation, because a superscan is extremely unlikely to be caused by benign conditions or tumor flare.

***Management Following Confirmed PD***

If repeat imaging does confirm PD, participants will be discontinued from study treatment.

Note: If a participant has confirmed radiographic progression as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue.

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