| | |
|---|---|
| **Official Protocol Title:** | An Open-label, Randomized, Phase 2/3 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) (KEYLYNK-009) |
| **NCT number:** | NCT04191135 |
| **Document Date:** | 22-May-2023 |

# 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:** An Open-label, Randomized, Phase 2/3 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) (KEYLYNK-009)

**Protocol Number:** 009-03

**Compound Number:** MK-7339

**Sponsor Name:**

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

**Legal Registered Address:**

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

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

| | |
|---|---|
| IND | 140257 |
| EudraCT | 2019-001892-35 |
| EU CT | 2022-500418-24-00 |

**Approval Date: 22 May 2023**

## Sponsor Signatory

Typed Name: Date
Title:

**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: Date
Title:

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| Amendment 03 | 22-MAY-2023 | Protocol amended consistent with recommendations of the internal DMC to discontinue the study after a prespecified interim review of the data because the combination of pembrolizumab plus olaparib did not show an improvement in PFS compared with the combination of chemotherapy plus pembrolizumab. Participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) may have the option to continue on study treatment if they are deriving clinical benefit, until criteria for discontinuation are met. |
| Amendment 02 | 18-MAY-2022 | CCI [redacted] |
| Amendment 01 | 02-JUN-2021 | To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs). Additional minor corrections and clarifications were made throughout the protocol. |
| Original Protocol | 24-JUL-2019 | Not applicable |

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

**Amendment:** 03

**Overall Rationale for the Amendments:**

CCI [redacted]

**Summary of Changes Table:**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>4.1 Overall Design | CCI [redacted] | |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis, Estimated Duration of Study | Added that as of Amendment 03, the study is being discontinued based on the recommendation of the internal DMC, but participants who are still receiving study intervention may have the option of continuing with study treatment if they are deriving clinical benefit, and the study will remain open until the last participant who is continuing study treatment completes the Safety Follow-up visit. | To inform of the decision to discontinue this clinical study, clarify that participants may continue to receive study treatment if deriving clinical benefit, and how long the study will remain open. |
| 1.1 Synopsis, Duration of Participation | Added that as of Amendment 03, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR, but local tumor imaging assessments should continue per SOC schedule, and Survival Follow-up visits will no longer be conducted. | As of Amendment 03, further tumor scans and response assessments by BICR and Survival Follow-up visits are considered unnecessary. |
| 1.1 Synopsis, Study Governance Committees<br>10.1.4 Committees Structure | Added that as of Amendment 03, the Steering Committee and internal DMC are no longer applicable. | These committees will no longer review the study data. |
| 1.3.2 Post-induction | Added that as of Amendment 03, participants who are still receiving study intervention in post-induction may have the option of continuing with study treatment if they are deriving clinical benefit. If continuing on study treatment, participants will have local tumor imaging assessments per SOC schedule, but will no longer have ePRO assessments, biomarker samples, or tumor response assessments by BICR. | As of Amendment 03, further tumor scans and response assessments by BICR, ePRO assessments, and collection of additional samples for biomarker evaluation are considered unnecessary. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3.3 End-of-Treatment and Follow-up After Treatment Discontinuation | Added that as of Amendment 03, participants who discontinue from study treatment should complete the End-of-Treatment and Safety Follow-up visits. Disease Status Follow-up and Survival Follow-up visits will no longer be conducted, ePRO assessments will no longer be performed, and biomarker samples will no longer be collected. | As of Amendment 03, further Disease Status and Survival Follow-up visits, ePRO assessments, and collection of additional samples for biomarker evaluation are considered unnecessary. |
| 1.3.4 Second Course Retreatment<br>8.12.6 Second Course Retreatment | Added that as of Amendment 03, the study will be discontinued based on the recommendation of the internal DMC, and Second Course Retreatment is no longer an option for participants.<br>Added that participants who are already receiving Second Course Retreatment and deriving clinical benefit may continue Second Course Retreatment, local tumor imaging assessments should continue per SOC schedule, until radiographic disease progression per RECIST 1.1 as determined by investigator/site/local radiology review, and no treatment beyond progression will be authorized. | To update the status of the Second Course Retreatment phase of the study. |
| 4.1.3 End-of-Treatment | Clarified that after implementation of Amendment 03, disease progression will be determined by investigator/site/local radiology review and not verified by BICR. | As of Amendment 03, there will be no further response assessments by BICR. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 4.1.4 Planned Analyses | CCI [redacted] | Skipping IA1 and corresponding changes have been documented in sSAP Amendment 01, which was finalized on 09-FEB-2023.<br><br>To specify which analyses will be conducted and which will no longer be performed after implementation of Amendment 03. |
| 4.4.1 Clinical Criteria for Early Study Termination | Added that in the event of Sponsor decision to no longer supply study interventions, ample notification will be provided.<br><br>Added that as of Amendment 03, the study will be discontinued based on the recommendation of the internal DMC. | Clarification regarding supply of study interventions.<br><br>To inform of the decision to discontinue this clinical study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Study Intervention(s) Administered | Added that as of Amendment 03, the study is being discontinued based on the recommendation of the internal DMC. Participants who are still receiving study intervention may have the option of continuing on study treatment, if they are deriving clinical benefit, until radiographic disease progression per RECIST 1.1 as determined by investigator/site/local radiology review or other discontinuation criteria are met, and no treatment beyond progression will be authorized.<br><br>Added that participants who have experienced first disease progression by RECIST 1.1 in post-induction, who are continuing study treatment due to deriving clinical benefit and are being followed using the iRECIST criteria at the time of Amendment 03, may continue to receive study treatment only until the next confirmed disease progression (iCPD) by investigator/site/local radiology review, and no treatment beyond iCPD as determined by investigator/site/local radiology review will be authorized. | To inform of the decision to discontinue this clinical study and clarify that participants may continue to receive study treatment until radiographic disease progression per RECIST 1.1 if deriving clinical benefit. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 7.1 Discontinuation of Study Intervention | Added the following to the notes regarding discontinuation due to radiographic disease progression:<br>• As of Amendment 03, central tumor response assessments will no longer be performed. Participants who are continuing to receive study treatment will be assessed by investigator/site/local radiology review for disease progression per SOC schedule.<br>• Treatment beyond progression (by RECIST 1.1 or iRECIST) will no longer be authorized after implementation of Amendment 03. Participants who have experienced first disease progression by RECIST 1.1 in post-induction, who are continuing study treatment and are being followed using the iRECIST criteria at the time of Amendment 03, may continue to receive study treatment only until the next confirmed disease progression (iCPD) by investigator/site/local radiology review, and no treatment beyond iCPD as determined by investigator/site/local radiology review will be authorized. | To clarify that participants still on study treatment at the time of Amendment 03, because they are deriving clinical benefit, will be assessed by investigator/site/local radiology review for disease progression per SOC schedule, and that treatment beyond progression will no longer be authorized. |
| 7.1 Discontinuation of Study Intervention | Added the following to the notes regarding completion of study intervention:<br>• As of Amendment 03, Second Course Retreatment is no longer an option for participants. | To update the status of the Second Course Retreatment phase of the study. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.2.2 Tumor Scans and Assessment of Disease | Added that as of Amendment 03, central tumor response assessments will be discontinued.<br>Added that participants deriving clinical benefit may continue on study treatment until criteria for discontinuation are met; local tumor imaging should continue per SOC schedule. | As of Amendment 03, further efficacy assessments are considered unnecessary.<br>To clarify that participants still receiving study treatment at the time of this amendment because they are deriving clinical benefit will continue with local tumor imaging per SOC schedule. |
| 8.2.2.3.3 Determination of Radiographic Progression | Added that as of Amendment 03, central tumor response assessments will be discontinued, and participants with radiographically documented disease progression during post-induction as assessed by investigator/site/local radiology review according to RECIST 1.1 will be discontinued from study intervention. | As of Amendment 03, there will be no further response assessments by BICR. |
| 8.2.2.6 iRECIST Assessment of Disease During Post-induction<br>10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression During Post-induction | Added that as of Amendment 03, iRECIST assessment of disease is no longer applicable for participants who have an initial PD evaluated by RECIST 1:1, and participants who are currently being assessed by iRECIST may continue to be assessed per iRECIST until iCPD is determined by investigator/site/local radiology review. | As of Amendment 03, treatment beyond RECIST 1.1 progression will not be authorized, therefore assessment using iRECIST criteria will no longer be applicable. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.2.3 Patient-reported Outcomes | Added that PROs and Quality of Life assessments will be discontinued. | As of Amendment 03, PRO and Quality of Life assessments are considered unnecessary. |
| 8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events | Removed requirement for investigators to document if an AE was associated with medication error, misuse, or abuse. This requirement is applicable only for SAEs. | Clarification as per global Protocol Clarification Letter 29-JUN-2022.<br>The updated Regulation (EU) No 36/2014 on clinical trials includes language on the reporting of SUSARs associated with medication errors and use outside of what is foreseen in the protocol (misuse and abuse); therefore, the event must meet the definition for an SAE, and hence "AE" was removed. |
| 8.10 Biomarkers | Added that as of Amendment 03, biomarker sample collections will be discontinued, and biomarker samples already collected before implementation of Amendment 03 will be analyzed. | As of Amendment 03, collection of biomarker samples is considered unnecessary, but samples collected before Amendment 03 will be analyzed. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.11 Medical Resource Utilization and Health Economics | Added that as of Amendment 03, Medical Resource Utilization and Health Economics data collection will be discontinued. | As of Amendment 03, assessment of these data is considered unnecessary. |
| 8.12.4.2 Disease Status Follow-up | Added that as of Amendment 03, Disease Status Follow-up Visits will be discontinued. | As of Amendment 03, these visits are considered unnecessary. |
| 8.12.4.3 Survival Follow-up Contacts | Added that as of Amendment 03, Survival Follow-up visits will be discontinued. Participants remaining on study treatment should continue to be monitored in the study through the AE reporting period. | Survival follow-up is only for participants remaining on study at the time of this amendment, and participants will be followed for the duration of the AE reporting period. |
| 8.12.6.2 Treatment Requirements for Second Course Retreatment | In the last bullet point, updated “achieved or sustained a BICR-verified SD or better” to “achieved or sustained an SD or better”. | To clarify that achieving SD or better after completing 35 administrations of pembrolizumab is not verified by BICR as per global Protocol Clarification Letter 03-MAR-2023. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8.12.6.9 Tumor Scans During Second Course Retreatment | Added that as of Amendment 03, central tumor response assessments will be discontinued, and participants who are continuing study treatment will continue with local tumor imaging per SOC schedule. Participants with radiographically documented disease progression during Second Course Retreatment as assessed by investigator/site/local radiology review according to RECIST 1.1 will be discontinued from study intervention. Participants who are currently being assessed by iRECIST during Second Course Retreatment may continue to be assessed per iRECIST until iCPD is determined by investigator/site/local radiology review. Treatment beyond RECIST 1.1 progression or iCPD will no longer be authorized after implementation of Amendment 03.<br><br>Clarified that tumor scans in Second Course Retreatment should be assessed using RECIST 1.1 criteria and do not need to be submitted to or reviewed by BICR. | To clarify that participants still receiving Second Course Retreatment at the time of this amendment because they are deriving clinical benefit will continue with local tumor imaging per SOC schedule. As of Amendment 03, treatment beyond RECIST 1.1 progression or iCPD will not be authorized.<br><br>Clarification per global Protocol Clarification Letter 03-MAR-2023. |
| 9 Statistical Analysis Plan | Added that based on the data from a prespecified interim safety and efficacy analysis, the internal DMC recommended discontinuing the study.<br><br>Added that the prespecified final analysis of the study described in the SAP will not be performed. Selected safety analyses will be performed at the end of the study. | To inform of the decision to discontinue this clinical study.<br><br>To specify which analyses will be conducted and which will no longer be performed after implementation of Amendment 03. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.1 Statistical Analysis Plan Summary | CCI | To specify which analyses will be conducted and which will no longer be performed after implementation of Amendment 03.<br><br>Skipping IA1 and corresponding changes have been documented in sSAP Amendment 01, which was finalized on 09-FEB-2023.<br><br>To clarify that participants may continue to receive study treatment if deriving clinical benefit. |
| 9.7 Interim Analyses | Added that the prespecified final analysis of the study described in the SAP will not be performed. | To specify which analyses will be conducted and which will no longer be performed after implementation of Amendment 03. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.7.1 Efficacy Interim Analyses | CCI [redacted] | Skipping IA1 and corresponding changes have been documented in sSAP Amendment 01, which was finalized on 09-FEB-2023. The changes align the protocol with sSAP Amendment 01 and finalized efficacy IA. |
| 9.8.1 Progression-free Survival | Removed IA1 and IA2 from efficacy boundaries and properties for PFS analyses in Table 16. | Only a single PFS analysis is performed due to skipping IA1, as documented in sSAP Amendment 01, which was finalized on 09-FEB-2023. The changes align the protocol with sSAP Amendment 01 and finalized efficacy IA. |
| 9.8.2 Overall Survival | Added that if the actual number of OS events at the interim analyses differs from those specified in the table, the bounds will be adjusted by the spending function accordingly, and if the PFS null hypothesis is rejected at PFS final analysis, OS interim and final analysis test may be compared to its updated bounds, considering the α reallocation from the PFS hypothesis. | To clarify alpha spending due to skipping IA1, as documented in sSAP Amendment 01, which was finalized on 09-FEB-2023. The changes align the protocol with sSAP Amendment 01 and finalized efficacy IA. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.9 Sample Size and Power Calculations | Updated the HR at the boundary for success from 0.73 to 0.74 and updated the assumption of improvement over control from 2.2 to 2.1 months. | Due to skipping IA1, as documented in sSAP Amendment 01, which was finalized on 09-FEB-2023, the boundary and alpha changed. The changes align the protocol with sSAP Amendment 01 and finalized efficacy IA. |
| 9.10 Subgroup Analyses | Added subgroups by HRD status and for HRD combined with BRCA. | To fully explore the effect of these biomarkers, as documented in sSAP Amendment 01, which was finalized on 09-FEB-2023. The changes align the protocol with sSAP Amendment 01 and finalized efficacy IA. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 10.7.3 Japan | Added new section to clarify the category of drug of the clinical notification submitting to the regulatory authority. | Clarification as per Japan Protocol Clarification Letter 25-MAY-2022.<br>Since carboplatin and gemcitabine are already approved for use in this study population in Japan, it is categorized as “product(s) used in the clinical trial other than test product(s)" following Japan regulation. |
| Throughout Document | 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

# LIST OF TABLES

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** An Open-label, Randomized, Phase 2/3 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) (KEYLYNK-009)

**Short Title:** Olaparib Plus Pembrolizumab as Post-Induction Therapy in Triple Negative Breast Cancer

**Acronym:** KEYLYNK-009

*Note:* Based on the data from a prespecified interim safety and efficacy analysis for KEYLYNK-009 (data cutoff 15-DEC-2022), the internal DMC recommended discontinuing the study. The combination of pembrolizumab plus olaparib did not show an improvement in PFS compared with the combination of chemotherapy plus pembrolizumab. Participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) may have the option to continue on study treatment if they are deriving clinical benefit, until criteria for discontinuation are met.

As of Amendment 03, participants who discontinue study treatment for any reason will complete the End-of-Treatment and Safety Follow-up visits, but no further data will be collected. If continuing on study treatment, participants will no longer have tumor response assessments by BICR, but local tumor imaging assessments should continue per SOC schedule. For all participants, ePRO assessments will no longer be performed, biomarker samples will no longer be collected, and Disease Status Follow-up and Survival Follow-up visits will no longer be conducted.

**Hypotheses, Objectives, and Endpoints:**

The Phase 2/3 2-in-1 adaptive design will not be pursued and the study is now a stand-alone Phase 2 study.

In males and females at least 18 years of age with locally recurrent inoperable or metastatic TNBC after induction of clinical benefit (objective response or stable disease [SD]) with first-line (1L) chemotherapy plus pembrolizumab:

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

| Primary Objectives | Primary Endpoints |
|---|---|
| - Objective: To compare olaparib plus pembrolizumab to chemotherapy plus pembrolizumab with regards to progression-free survival (PFS) according to RECIST 1.1 by blinded independent central review (BICR).<br><br>Hypothesis (H1): Olaparib plus pembrolizumab is superior to chemotherapy plus pembrolizumab with respect to PFS according to RECIST 1.1 by BICR. | - PFS, the time from randomization until either the earliest date of documented disease progression or death due to any cause, whichever occurs first |
| - Objective: To compare olaparib plus pembrolizumab to chemotherapy plus pembrolizumab with regards to overall survival (OS).<br><br>Hypothesis (H2): Olaparib plus pembrolizumab is superior to chemotherapy plus pembrolizumab with respect to OS. | - OS, the time from randomization to death due to any cause |
| Secondary Objectives | Secondary Endpoints |
| - Objective: To evaluate OS, and PFS according to RECIST 1.1 by BICR, in participants with PD-L1 positive tumors (CPS $\geqslant$10) following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | - OS<br>- PFS |
| - Objective: To evaluate OS, and PFS according to RECIST 1.1 by BICR, in participants with BRCAm tumors following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | - OS<br>- PFS |

| | |
|---|---|
| - Objective: To evaluate health-related quality-of-life (HRQoL) and time to deterioration (TTD) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the breast cancer module (EORTC QLQ-BR23) in participants with BRCAm tumors and irrespective of BRCAm status following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | - HRQoL, a change from baseline in Patient-Reported Outcomes (PRO) scores obtained in post-induction<br>- Time to Deterioration (TTD), the time from baseline to the first onset of a confirmed* ⩾10-point deterioration from baseline in PRO scores<br>- For the following domains:<br>- EORTC QLQ-C30 global health status/QoL (Items 29 and 30)<br>- EORTC QLQ-C30 physical functioning (Items 1-5)<br>- EORTC QLQ-C30 emotional functioning (Items 21-24), and<br>- EORTC QLQ-BR23 systemic therapy side effects (Items 1-4, 6, 7, and 8)<br>*confirmed by a ⩾10-point deterioration from baseline in the subsequent PRO score |
| - Objective: To evaluate visual analogue scale (VAS) using the EuroQoL 5-dimension, 5-level questionnaire (EQ-5D-5L) in participants with BRCAm tumors and irrespective of BRCAm status following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | - Visual analogue scale (VAS), a change from baseline in EQ-5D-5L VAS score obtained in post-induction |
| - Objective: To evaluate the safety and tolerability of olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | - Adverse events (AEs)<br>- Study treatment discontinuation due to AEs |

## Overall Design:

| | |
|---|---|
| Study Phase | Phase 2* |
| Primary Purpose | Treatment |
| Indication | First-line treatment of locally recurrent inoperable or metastatic TNBC |
| Population | Females and males at least 18 years of age with previously untreated locally recurrent inoperable or metastatic TNBC |
| Study Type | Interventional |
| Intervention Model | Parallel<br>This is a randomized, 2-arm, multi-site study. |
| Type of Control | Active control |
| Study Blinding | Unblinded Open-label |
| Masking | No Masking |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 5 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.<br>As of Amendment 03, the study is being discontinued based on the recommendation of the internal DMC. However, participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) may have the option of continuing with study treatment if they are deriving clinical benefit. The study will remain open until the last participant who is continuing study treatment completes the Safety Follow-up visit. |

* Although the study title reflects the original Phase 2/3 2-in-1 adaptive design, following Amendment 02, the 2-in-1 adaptive design including the Phase 3 portion of the study will no longer be pursued and the study will be conducted as a stand-alone Phase 2 study with a revised SAP.

### Number of Participants:

Approximately 460 participants will be enrolled and treated with induction therapy, to ensure approximately 260 eligible participants being randomly assigned to post-induction therapy.

The approximations for enrollment into induction therapy are made from currently available efficacy and toxicity data.

### Intervention Groups and Duration:

| | |
|---|---|
| Intervention Groups | **Induction**<br>All participants will receive the study interventions (carboplatin + gemcitabine + pembrolizumab) in the nonrandomized induction.<br>• Carboplatin area under the concentration-time curve (AUC) 2 intravenous (IV) on Days 1 and 8 (Cycles 1-6)<br>• Gemcitabine 1000 mg/m$^2$ IV on Days 1 and 8 (Cycles 1-6)<br>• Pembrolizumab 200 mg every 3 weeks (Q3W) on Day 1 (Cycles 1-6)<br>**Post-induction**<br>Participants who achieve complete response (CR) or partial response (PR), or maintain SD, during induction after up to 6 cycles but not less than 4 cycles of treatment and meet the eligibility criteria for post-induction will be randomly assigned to Arm 1 (olaparib + pembrolizumab) or Arm 2 (carboplatin + gemcitabine + pembrolizumab).<br><u>Arm 1</u><br>• Olaparib 300 mg BID (twice daily) orally<br>• Pembrolizumab 200 mg Q3W<br><u>Arm 2</u><br>• Carboplatin AUC 2 IV on Days 1 and 8<br>• Gemcitabine 1000 mg/m$^2$ IV on Days 1 and 8<br>• Pembrolizumab 200 mg Q3W on Day 1<br>Olaparib, carboplatin, and gemcitabine may continue until a toxicity requires discontinuation or until disease progression.<br>Pembrolizumab may continue for up to 35 administrations, inclusive of induction administrations, until a toxicity requires discontinuation or until disease progression.<br>A summary of the study interventions, including dose strength, dose frequency, route of administration, treatment period, and use is presented in the table below. |

<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>Treatment Period</th><th>Use</th></tr>
<tr><td rowspan="3">Induction</td><td>Carboplatin</td><td>AUC 2</td><td>Days 1 and 8</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td>Gemcitabine</td><td>1000 mg/m$^2$</td><td>Days 1 and 8</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td>Pembrolizumab</td><td>200 mg</td><td>Day 1</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td rowspan="2">Post-induction Arm 1</td><td>Olaparib</td><td>300 mg</td><td>BID</td><td>Orally</td><td>Daily</td><td>Test product</td></tr>
<tr><td>Pembrolizumab</td><td>200 mg</td><td>Day 1</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td rowspan="3">Post-induction Arm 2</td><td>Carboplatin</td><td>AUC 2</td><td>Days 1 and 8</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td>Gemcitabine</td><td>1000 mg/m$^2$</td><td>Days 1 and 8</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td>Pembrolizumab</td><td>200 mg</td><td>Day 1</td><td>IV infusion</td><td>Every 21-day cycle</td><td>Test product</td></tr>
<tr><td colspan="7">Abbreviations: Admin = administration; AUC = area under the concentration-time curve; BID = twice daily; IV = intravenous.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>2 arms</td></tr>
<tr><td>Duration of Participa-tion</td><td>Each participant will participate in the study for approximately 2 to 5 years from the time the participant provides documented informed consent through the final protocol-specified contact.<br><br>After the screening period of up to 28 days, each participant will begin induction therapy with carboplatin and gemcitabine plus pembrolizumab. Participants who achieve CR or PR, or maintain SD, after 4 to 6 cycles will be randomized to receive either olaparib plus pembrolizumab (Arm 1) or to continue carboplatin and gemcitabine plus pembrolizumab (Arm 2).<br><br>Discontinuation criteria are outlined in Section 7.1, including discontinuation from a specific study intervention.<br><br>During induction, participants who discontinue all study interventions for any reason, and are therefore ineligible for randomization to post-induction treatment, will enter the 30-day safety follow-up, as outlined in Section 1.3.3 and as described under Section 8.12.4.1 and will not enter disease status follow-up or survival follow-up.</td></tr>
</table>

| | |
|---|---|
| | During post-induction, participants who discontinue all study interventions for reasons other than disease progression will enter the 30-day safety follow-up and disease status follow-up, as outlined in Section 1.3.3 and as described under Section 8.12.4.2 and will have post-treatment follow-up imaging to evaluate disease status until disease progression according to RECIST 1.1 is radiographically documented and verified by BICR, initiating a new anticancer therapy, a documented complete withdrawal of consent from the study, becoming lost to follow-up, pregnancy, or death. *Note:* As of Amendment 03, participants who are still on study treatment and deriving clinical benefit will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue per SOC schedule.<br><br>After all post-induction treatments are discontinued because of disease progression, each participant will enter the 30-day safety follow-up and the survival follow-up, as outlined in Section 1.3.3 and as described under Section 8.12.4.1 and Section 8.12.4.3, respectively. Participants who enter survival follow-up will be contacted by telephone to determine OS until death, a complete documented withdrawal of consent from the study, or the end of the study, whichever occurs first. *Note*: As of Amendment 03, Survival Follow-up visits will no longer be conducted. |

**Study Governance Committees:**

| | |
|---|---|
| Steering Committee | Yes |
| Executive Oversight Committee | No |
| Data Monitoring Committee | Yes |
| Clinical Adjudication Committee | No |
| Study governance considerations are outlined in Appendix 1.<br>The DMC will be an internal DMC (see Section 10.1.4.2).<br>As of Amendment 03, the Steering Committee and internal DMC are no longer applicable. | |

**Study Accepts Healthy Volunteers:** No

A list of abbreviations used in this document can be found in Appendix 10.

## 1.2 Schema

The study design is depicted in Figure 1.

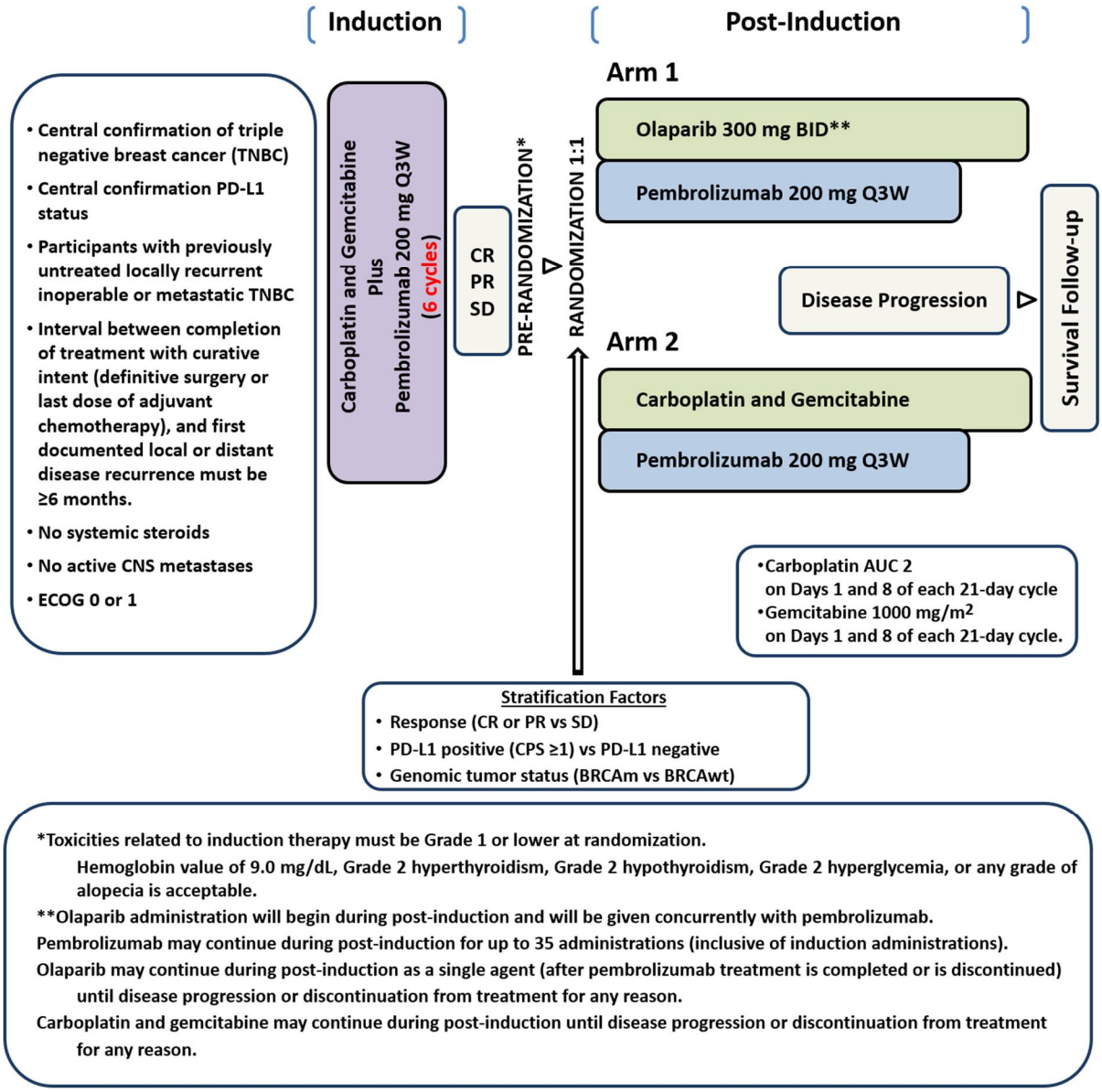


Figure 1 Study Schema

AUC=area under the concentration-time curve; BID=twice daily; BRCAm=breast cancer susceptibility gene mutation; BRCAwt=breast cancer susceptibility gene wild type; CNS=central nervous system; CPS=combined positive score; CR=complete response; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed cell death-ligand 1; PR=partial response; Q3W=every 3 weeks; SD=stable disease; TNBC=triple negative breast cancer.

## 1.3 Schedule of Activities (SoA)

### 1.3.1 Screening and Induction

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Administrative Procedures** | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | Screening Window does not apply for informed consent. Main study informed consent is required before screening procedures. Consent for FBR is optional and can be provided before or after Cycle 1, Day 1. |
| Informed Consent for FBR | X | | | | | | | | | | | | | |
| Inclusion / Exclusion Criteria | X | | | | | | | | | | | | | |
| Participant Identification Card | X | | | | | | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | | | | | | |
| Menopausal Status | X | | | | | | | | | | | | | |
| Prior/Concomitant Medication | X | <---------- | | | | | | | | | | | ----------> | |
| **Quality of Life and Physical Performance Measures** | | | | | | | | | | | | | | |
| ePROs<br>EORTC QLQ-C30<br>EORTC QLQ-BR23<br>EQ-5D-5L™ | | X | | | | | | X | | X | | X | | Should be completed in the order listed and within 3 days prior to visit dose administration. Illiterate participants are allowed to enroll in the study and are exempt from completing ePROs (refer to Section 8.2.3). |
| ECOG Performance Status | X | X | | X | | X | | X | | X | | X | | Within 7 days prior to Cycle 1, Day 1; prior to dosing on Day 1 in subsequent cycles. |

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Treatment Administration** | | | | | | | | | | | | | | |
| Pembrolizumab | | X | | X | | X | | X | | X | | X | | Participants should not be dosed after Week 18 scan (see Section 8.2.2.2.1) during induction. |
| Gemcitabine | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Carboplatin | | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Tumor Tissue Collection** | | | | | | | | | | | | | | |
| Recently or Newly Obtained Tumor Tissue Collection | X | | | | | | | | | | | | | Screening Window does not apply. |
| **Efficacy Procedures** | | | | | | | | | | | | | | |
| Tumor Scans –[a] - Chest, Abdomen, and Pelvis | X* | | | | | X | | | | X | | | X | * Tumor scans for screening should be done within 28 days before Cycle 1, Day 1. Tumor scans should be performed at Week 6 (42+7 days), Week 12 (84±7 days), and Week 18 (126-7 days) during induction. Timing of on-study tumor scans is relative to Cycle 1, Day 1 during induction, should follow calendar days, and not be adjusted for any dose modifications. The same scan technique and consistent use of contrast should be used throughout the study to optimize assessment of existing and new tumor burden. See the SIM for details. |

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| Brain Scan | X* | | | | | X* | | | | X* | | | X* | *Brain scans (MRI is preferred) are required at screening and during induction (at the same schedule as other tumor scans for evaluation of disease status) ONLY for participants with known brain metastases and those with worsening and/or new neurological symptoms. Brain imaging CT scans will be acceptable if MRI is medically contraindicated. See the SIM for details. |
| Bone Scan | X* | ←---------- If clinically indicated----------→ | | | | | | | | | | | | *Bone scans are required at screening, ONLY if a participant has a history of bone metastases and/or has new bone pain or other symptoms/signs suggestive of bone metastases and if the bone scan is negative, a plain X-ray is also required. During the study, a bone scan (and plain X-ray, if participant has signs/symptoms of bone metastases and bone scan is negative) will be performed if clinically indicated for evaluation of known, worsening and/or new bone pain or other symptoms/signs suggestive of bone metastases OR if the site believes a participant has attained a CR. See the SIM for details. |
| **Safety Procedures** | | | | | | | | | | | | | | |
| Full Physical Examination | X | | | | | | | | | | | | | |
| Directed Physical Examination | | | X | X | X | X | X | X | X | X | X | X | X | |

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| 12-lead Electrocardiogram | X | | | | | | | | | | | | | |
| Vital Signs/Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | Vital signs/weight should be measured within 3 days before each dosing day. |
| AEs / SAEs | | <---------- | | | | | | | | | | | -> | |
| **Laboratory Assessments – Analysis performed by local laboratories** | | | | | | | | | | | | | | |
| Urine Pregnancy Test (WOCBP only) [b] | X | <---------- | | | | | | | | | | | -> | Pregnancy testing should be completed at screening and then monthly or if clinically indicated in WOCBP. |
| Serum FSH and Estradiol (WOCBP only) [b] | X | | | | | | | | | | | | | Will be measured only if clinically indicated for determination of menopausal status |
| HIV, and Hepatitis B and C screen [c] | X | | | | | | | | | | | | | Performed only if mandated by local health authority. |
| CBC with Differential [c] | X | X* | X | X | X | X | X | X | X | X | X | X | X | *If screening is performed within 10 days of Cycle 1, Day 1, there is no need to repeat on Cycle 1, Day 1. |
| Chemistry [c] | X | X* | | X | | X | | X | | X | | X | | |
| Urinalysis [c] | X | | | | | | | | | | | | | |
| PT/INR and aPTT/PTT [c] | X | | | | | | | | | | | | | Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy. |
| Vitamin D (serum) | X | | | | | | | | | | | | | Perform at screening and as clinically indicated. |
| T3 (or Free T3), Free T4, and TSH [c] | X | | | X | | | | X | | | | X | | |

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| Other Tumor Markers CA 15-3, CEA, CA 27.29 | X* | | | | | X | | | | X | | | X | Should be collected during screening and then according to the tumor scan schedule ie, Week 6 (+7 days), Week 12 (±7 days), and Week 18 (-7 days) (can be conducted at corresponding study visit) until study treatment discontinuation.<br>* Blood collection is required before Cycle 1 Day 1, but results are not required before dosing. |
| **Laboratory Assessments (Tissue Samples) – Analysis performed by central laboratory** | | | | | | | | | | | | | | |
| TNBC Tumor Markers (ER, PGR, HER2) | X | | | | | | | | | | | | | TNBC and PD-L1 status must be centrally confirmed prior to enrollment in the study. |
| PD-L1 Tumor Marker | X | | | | | | | | | | | | | |
| Other Tumor Markers (BRCA) | X | | | | | | | | | | | | | BRCA results must be available prior to randomization in post-induction (Section 1.3.2). |
| **Laboratory Assessments (Blood Samples) – Analysis performed by central laboratory** | | | | | | | | | | | | | | |
| Blood for Genetic Analysis | | X | | | | | | | | | | | | Drawn pre-dose. |
| Blood for ctDNA analyses | | X | | | | X | | | | | | | | |

| **Study Period:** | **Induction (21-Day Cycles)** | | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | Scree-ning | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | |
| **Scheduled Day:** | -28 to -1 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Screening days are relative to Cycle 1, Day 1 of induction. |
| **Scheduling Window (Days):** | | NA | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BRCA=breast cancer susceptibility gene; CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CR=complete response; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire 30; EORTC QLQ-BR23=European Organization for the Research and Treatment of Cancer Breast Cancer Specific Quality of Life Questionnaire; EQ-5D-5L=EuroQoL-5 dimensions-5 levels; ePRO=electronic patient-reported outcomes; ER=estrogen receptor; FBR=future biomedical research; FSH=follicle-stimulating hormone; HER2=human epidermal growth factor receptor-2; HIV=human immunodeficiency virus; INR=international normalized ratio; MRI=magnetic resonance imaging; PD-L1=programmed cell death-ligand 1; PGR=progesterone receptor; PR=partial response; PT=prothrombin time; PTT=partial thromboplastin time; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SD=stable disease; TNBC=triple negative breast cancer; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

a. A participant with a tumor response at Week 18 (-7 days) of CR, PR, or SD, according to RECIST 1.1 as determined by BICR expedited review, is eligible regarding tumor response for randomization to post-induction treatment. Participants with centrally verified disease progression based on tumor scans at any time point will be discontinued from study treatment.
b. For WOCBP, a urine or serum pregnancy test should be performed within 24 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
c. Screening laboratory tests must be performed within 10 days prior to the start of study treatment. Thereafter, laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment.

### 1.3.2 Post-induction

*Note:* Participants who are randomized to Arm 1 (olaparib + pembrolizumab) in post-induction will not require the Day 8 scheduled assessments.

*Note*: As of Amendment 03, participants who are still receiving study intervention in post-induction may have the option of continuing with study treatment if they are deriving clinical benefit. If continuing on study treatment, participants will no longer have tumor response assessments by BICR, but local tumor imaging assessments should continue per SOC schedule. In addition, ePRO assessments (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L) will no longer be performed and biomarker samples (blood for ctDNA analysis) will no longer be collected.

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Administrative Procedures** | | | | | | | | | | | | | | |
| Post-induction Inclusion / Exclusion Criteria | X | | | | | | | | | | | | | |
| Prior/Concomitant Medication | X | <---------- | | | | | | | | | | | ----------> | |
| Randomization 1:1 to Post-Induction | X | | | | | | | | | | | | | Randomization is performed after participant has met post-induction eligibility criteria and no more than 3 days before Cycle 1, Day 1. |
| Informed Consent Addendum (If Required) | | <---------- | | | | | | | | | | | ----------> | If the investigator plans to continue post-induction study intervention beyond BICR-verified disease progression, Sponsor communication with documented SCF and an informed consent addendum are required. |

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Quality of Life and Physical Performance Measures** | | | | | | | | | | | | | | |
| ePROs<br>EORTC QLQ-C30<br>EORTC QLQ-BR23<br>EQ-5D-5L™ | | X | | X | | X | | X | | X | | X | | Day 1 of the first 8 cycles, then every second cycle in Year 1 of post-induction and then every fourth cycle (every 12 weeks) starting in Year 2 of post-induction until end of treatment, disease progression as determined by BICR, or death (whichever occurs first). Should be completed in the order listed and within 3 days prior to visit dose administration.<br>Illiterate participants are exempt from completing ePROs (refer to Section 8.2.3). |
| ECOG Performance Status | X | X | | X | | X | | X | | X | | X | | Within 7 days prior to Cycle 1, Day 1; <u>prior to</u> dosing on Day 1 in subsequent cycles. |
| **Treatment Administration – Arm 1** | | | | | | | | | | | | | | |
| Olaparib | | <---------- | | | | | | | | | | | ----------> | Self-administered |
| Pembrolizumab | | X | | X | | X | | X | | X | | X | | |
| **Treatment Administration – Arm 2** | | | | | | | | | | | | | | |
| Carboplatin | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Gemcitabine | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Pembrolizumab | | X | | X | | X | | X | | X | | X | | |

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Efficacy Procedures** | | | | | | | | | | | | | | |
| Tumor Scans - Chest, Abdomen, and Pelvis | | | | | | X | | | | X | | | | Tumor scans should be performed at Week 6 (42+7 days), then every 6 weeks (±7 days) for the first year. In the second year post-induction, tumor scans move to every 12 weeks (±7 days). Timing of tumor scans is relative to randomization date of post-induction. Tumor scans should follow calendar days and not be adjusted for any dose modifications. The same scan technique and consistent use of contrast should be used throughout the study to optimize assessment of existing and new tumor burden. See the SIM for details. |
| Brain Scans | | | | | | X* | | | | X* | | | | *Brain scans (MRI is preferred) are required during post-induction (at the same schedule as other tumor scans for evaluation of disease status) ONLY for participants with known brain metastases and those with worsening and/or new neurological symptoms. Brain imaging CT scans will be acceptable if MRI is medically contraindicated. See the SIM for details. |

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| Bone Scans | | ←----------If clinically indicated----------→ | | | | | | | | | | | | During the study, a bone scan (and plain X-ray, if participant has signs/symptoms of bone metastases and bone scan is negative) will be performed ONLY if clinically indicated for evaluation of known, worsening and/or new bone pain or other symptoms/signs suggestive of bone metastases OR if the site believes a participant has attained a CR. See the SIM for details. |
| **Safety Procedures** | | | | | | | | | | | | | | |
| Full Physical Examination | X | | | | | | | | | | | | | |
| Directed Physical Examination | | | X | X | X | X | X | X | X | X | X | X | X | |
| 12-lead Electrocardiogram | X | | | | | | | | | | | | | |
| Vital Signs and Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | Vital signs/weight should be measured within 3 days before each dosing day. |
| AEs / SAEs | X | <---------- | | | | | | | | | | | ----------> | |
| **Laboratory Assessments – Analysis performed by local laboratories** | | | | | | | | | | | | | | |
| Urine Pregnancy Test (WOCBP only) [a] | X | <---------- | | | | | | | | | | | ----------> | Pregnancy testing should be completed monthly or if clinically indicated in WOCBP. |
| CBC with Differential [b] | X | X[c] | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry [b] | X | X[c] | | X | | X | | X | | X | | X | | |

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| T3 (or Free T3), Free T4, and TSH [b] | | | | | | X | | | | X | | | | Can be assayed based on local guidelines and practices. To be repeated every 2 cycles after Cycle 5, or as clinically indicated. The thyroid functions collected at the end of induction will be the Baseline for safety analyses. |
| Other Tumor Markers (CA 15-3, CEA, CA 27.29) | | | | | | X | | | | X | | | | Should be collected according to the tumor scan schedule ie, Week 6 (42+7 days), then every 6 weeks (±7 days) for the first year, and every 12 weeks (±7 days) in the second year post-induction (can be conducted at corresponding study visit, but must be collected within the same window specified for imaging) until study treatment discontinuation. |

| **Study Period:** | **Pre-randomization Visit** | **Post-induction (21-Day Cycles)** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | Cycle 1, Day 1 may occur on the same day as randomization or at most 3 days post randomization. |
| **Scheduling Window (Days):** | -14 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Laboratory Assessments (Blood Samples) – Analysis performed by central laboratory** | | | | | | | | | | | | | | |
| Blood for ctDNA analyses* | | X | | X | | | | | | X | | | | *Blood for ctDNA analyses to be collected pre-dose at C1D1, C2D1, C5D1 of Post-induction. After C5D1, collect blood for ctDNA every 6 weeks during Year 1 of Post-induction, and every 12 weeks from Year 2 until the end of Year 5, or until discontinuation of study treatment, whichever is earlier. ctDNA collections post-induction should be aligned with clinic visit closest to tumor scan visits. If a clinic visit is not feasible, blood for ctDNA collection will not be collected. |

Abbreviations: AE=adverse event; C=cycle; CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; D=day; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire 30; EORTC QLQ-BR23=European Organization for the Research and Treatment of Cancer Breast Cancer Specific Quality of Life Questionnaire; EQ-5D-5L=EuroQoL-5 dimensions-5 levels; MRI=magnetic resonance imaging; SAE=serious adverse event; SCF=Sponsor Consultation Form; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

a. For WOCBP, a urine or serum pregnancy test should be performed within 24 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

b. Laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment.

c. Laboratory samples do not have to be repeated if done within 72 hours of Cycle 1, Day 1.

### 1.3.3 End-of-Treatment and Follow-up After Treatment Discontinuation

*Note*: As of Amendment 03, participants who discontinue from study treatment should complete the End-of-Treatment and Safety Follow-up visits. Disease Status Follow-up and Survival Follow-up visits will no longer be conducted. In addition, ePRO assessments (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L) will no longer be performed and biomarker samples (blood for ctDNA analysis) will no longer be collected.

| | **End-of-Treatment** | **Follow-up After Treatment Discontinuation** | | | Notes |
|---|---|---|---|---|---|
| | **Last Dose, Disease Progression, or Other Reasons** | **Safety Follow-up [a]** | **Disease Status Follow-up [b]** | **Survival Follow-up [c]** | |
| **Treatment Cycle/Title:** | **At Treatment Discontinuation** | **30 Days After Last Dose** | **Every 6 or 12 Weeks After Last Dose** | **Every 12 Weeks** | |
| **Scheduling Window (Days):** | **NA** | **±3** | **±7** | **±7** | |
| **Administrative Procedures** | | | | | |
| Prior/Concomitant Medication | X | X | | | |
| Disease Status | | | X | X | Record other therapies administered for disease under study and outcomes. Refer to Section 8.12.4.2 for details. |
| Survival (Vital) Status | <---------- | | | > | X | Survival (vital) status may be requested by the Sponsor at any time during the study. Telephonic every 12 weeks (or more often as needed) until death, withdrawal of consent, or the end of the study. |
| **Quality of Life and Physical Performance Measures** | | | | | |
| ePROs<br>EORTC QLQ-C30<br>EORTC QLQ-BR23<br>EQ-5D-5L™ | X | X | | | Should be completed in the order listed. ePROs are not performed during Second Course Retreatment follow-up. Illiterate participants are exempt from completing ePROs (refer to Section 8.2.3). |
| ECOG Performance Status | X | X | | | |

| | End-of-Treatment | Follow-up After Treatment Discontinuation | | | Notes |
|---|---|---|---|---|---|
| | **Last Dose, Disease Progression, or Other Reasons** | **Safety Follow-up [a]** | **Disease Status Follow-up [b]** | **Survival Follow-up [c]** | |
| **Treatment Cycle/Title:** | **At Treatment Discontinuation** | **30 Days After Last Dose** | **Every 6 or 12 Weeks After Last Dose** | **Every 12 Weeks** | |
| **Scheduling Window (Days):** | **NA** | **±3** | **±7** | **±7** | |
| **Tumor Tissue Collection** | | | | | |
| Optional Tumor Tissue Collection | X* | | | | *If possible, collect tumor tissue at the end of treatment (ie, either induction or post-induction).<br>Participant must provide optional biopsy consent. |
| **Efficacy Procedures** | | | | | |
| Tumor Scans – Chest, Abdomen, and Pelvis | | | X | | Assessed according to the already followed tumor scan schedule during disease status follow-up for participants who discontinue study intervention during post-induction (ie, every 6 weeks [+7 days] for the first year and every 12 weeks [±7 days] in the second year post-induction, relative to randomization date of post-induction), see Section 8.12.4.2.<br>The same scan technique and consistent use of contrast should be used throughout the study to optimize assessment of existing and new tumor burden. |
| **Safety Procedures** | | | | | |
| Full Physical Examination | X | | | | |
| Vital Signs and Weight | X | X | | | |
| 12-lead Electrocardiogram | X | | | | |

| | End-of-Treatment | Follow-up After Treatment Discontinuation | | | Notes |
|---|---|---|---|---|---|
| | **Last Dose, Disease Progression, or Other Reasons** | **Safety Follow-up [a]** | **Disease Status Follow-up [b]** | **Survival Follow-up [c]** | |
| **Treatment Cycle/Title:** | **At Treatment Discontinuation** | **30 Days After Last Dose** | **Every 6 or 12 Weeks After Last Dose** | **Every 12 Weeks** | |
| **Scheduling Window (Days):** | **NA** | **±3** | **±7** | **±7** | |
| AEs / SAEs | X | X | | | AEs that occur within 30 days of the end of treatment should be recorded. SAEs that occur within 90 days following the last dose of study intervention (or 30 days following the last dose if participant initiates a new anticancer therapy) should be reported, followed, and recorded. |
| **Laboratory Assessments – Analysis performed by local laboratories** | | | | | |
| Urine Pregnancy Test (WOCBP only) | X | X | (X) | (X) | Pregnancy testing in WOCBP should be performed at treatment discontinuation, at the 30-day safety follow-up, and as required locally or if clinically indicated. Pregnancy testing should continue in posttreatment until 120 days after the last dose of pembrolizumab and 180 days after last dose of olaparib or chemotherapy. Refer to Appendix 7 for country-specific requirements. |
| CBC with Differential | X | X | | | |
| Chemistry | X | X | | | |
| T3 (or Free T3), Free T4, and TSH | X | | | | |

| | End-of-Treatment | Follow-up After Treatment Discontinuation | | | Notes |
|---|---|---|---|---|---|
| | **Last Dose, Disease Progression, or Other Reasons** | **Safety Follow-up [a]** | **Disease Status Follow-up [b]** | **Survival Follow-up [c]** | |
| **Treatment Cycle/Title:** | **At Treatment Discontinuation** | **30 Days After Last Dose** | **Every 6 or 12 Weeks After Last Dose** | **Every 12 Weeks** | |
| **Scheduling Window (Days):** | **NA** | **±3** | **±7** | **±7** | |
| Other Tumor Markers (CA 15-3, CEA, CA 27.29) | | | X | | Should be collected during disease status follow-up according to the tumor scan schedule (ie, every 6 weeks [+7 days] for the first year and every 12 weeks [±7 days] in the second year post-induction). Must be collected within the same window specified for imaging. |
| **Laboratory Assessments – Analysis performed by central laboratory** | | | | | |
| Blood for ctDNA Analysis | X | | | | |

Abbreviations: AE=adverse event; CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; ctDNA=circulating tumor deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire 30; EORTC QLQ-BR23=European Organization for the Research and Treatment of Cancer Breast Cancer Specific Quality of Life Questionnaire; ePRO=electronic patient-reported outcomes; EQ-5D-5L=EuroQoL-5 dimensions-5 levels; SAE=serious adverse event; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

a. Participants enter the 30-day safety follow-up after discontinuation of all study interventions for any reason during induction or post-induction. If the End of Treatment Visit occurs ≥30 days from last dose of study treatment, a separate Safety Follow-up visit is not required.
b. Participants who discontinue all study interventions for any reason during induction and are not randomized to the post-induction phase will not enter disease status follow-up. Participants enter disease status follow-up after discontinuation of all study interventions for reasons other than centrally verified disease progression during post-induction.
c. Participants who discontinue all study interventions for any reason during induction and are not randomized to the post-induction phase will not enter survival follow-up. Participants enter survival follow-up after discontinuation of all study interventions due to centrally verified disease progression during post-induction or after starting a new anticancer therapy, whichever occurs first.

### 1.3.4 Second Course Retreatment

The Schedule of Activities (SoA) for Second Course Retreatment is provided in this section for eligible participants. Complete details regarding Second Course Retreatment are provided in Section 8.12.6.

*Note:* As of Amendment 03, the study will be discontinued based on the recommendation of the internal DMC, and Second Course Retreatment is no longer an option for participants.

Participants who are already receiving Second Course Retreatment and deriving clinical benefit may continue Second Course Retreatment, and local tumor imaging assessments should continue per SOC schedule, until radiographic disease progression per RECIST 1.1 as determined by the investigator/site/local radiology review. No treatment beyond progression will be authorized.

*Note:* Participants who receive olaparib + pembrolizumab during Second Course Retreatment will not require the Day 8 scheduled assessments.

| **Study Period:** | **Second Course Retreatment (21-Day Cycles) Combination Treatment** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Administrative Procedures** | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | Assess before starting second course retreatment. |
| Additional Informed Consent | X | | | | | | | | | | | | Sponsor consultation with documented SCF, followed by reconsent to main study ICF, is required before starting second course retreatment. |
| Prior/Concomitant Medication | <---------- | | | | | | | | | | | ----------> | |
| **Quality of Life and Physical Performance Measures** | | | | | | | | | | | | | |
| ECOG Performance Status | X | | X | | X | | X | | X | | X | | Within 7 days prior to Cycle 1, Day 1; prior to dosing on Day 1 in subsequent cycles. |
| **Treatment Administration – Arm 1** | | | | | | | | | | | | | |
| Olaparib | <---------- | | | | | | | | | | | ----------> | Self-administered if applicable to retreatment. |
| Pembrolizumab | X | | X | | X | | X | | X | | X | | |
| **Treatment Administration – Arm 2** | | | | | | | | | | | | | |
| Pembrolizumab | X | | X | | X | | X | | X | | X | | |
| Gemcitabine | X | X | X | X | X | X | X | X | X | X | X | X | |
| Carboplatin | X | X | X | X | X | X | X | X | X | X | X | X | If applicable to retreatment. |

| **Study Period:** | **Second Course Retreatment (21-Day Cycles) Combination Treatment** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| **Efficacy Procedures** | | | | | | | | | | | | | |
| Tumor Scans – Chest, abdomen, and pelvis | X* | | | | | X | | | | | | X | *Tumor scans must be or must have been performed within 28 days prior to Cycle 1, Day 1 of Second Course Retreatment.<br>Subsequent tumor scans every 9 weeks (±7 days); timing of tumor scans is relative to Cycle 1, Day 1 of Second Course Retreatment, should follow calendar days, and not be adjusted for any dose modifications.<br>See the SIM for details. |
| Brain Scans | X* | | | | | X* | | | | | | X* | *Brain scans (MRI is preferred) are required during Second Course Retreatment (at the same schedule as other tumor scans for evaluation of disease status) ONLY for participants with known brain metastases and those with worsening and/or new neurological symptoms. Brain imaging CT scans will be acceptable if MRI is medically contraindicated.<br>See the SIM for details. |

| **Study Period:** | **Second Course Retreatment (21-Day Cycles) Combination Treatment** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| Bone Scans | ←----------If clinically indicated----------→ | | | | | | | | | | | | During Second Course Retreatment, a bone scan (and plain X-ray, if participant has signs/symptoms of bone metastases and bone scan is negative) will be performed ONLY if clinically indicated for evaluation of known, worsening and/or new bone pain or other symptoms/signs suggestive of bone metastases OR if the site believes a participant has attained a CR. See the SIM for details. |
| **Safety Procedures** | | | | | | | | | | | | | |
| Full Physical Examination | X | | | | | | | | | | | | Assess before starting second course retreatment. |
| Directed Physical Examination | | X | X | X | X | X | X | X | X | X | X | X | |
| 12-lead Electrocardiogram | X | | | | | | | | | | | | Assess before starting second course retreatment. |
| Vital Signs and Weight | X | X | X | X | X | X | X | X | X | X | X | X | Vital signs/weight should be measured within 3 days before each dosing day. |
| AEs / SAEs | <----------> | | | | | | | | | | | | |
| **Laboratory Assessments – Analysis performed by local laboratories** | | | | | | | | | | | | | |
| Urine Pregnancy Test (WOCBP only) [a] | X | <----------> | | | | | | | | | | | Pregnancy testing should be performed within 24 hours prior to receiving the first retreatment dose and monthly thereafter or if clinically indicated in WOCBP. |
| CBC with Differential [b] | X [c] | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry [b] | X [c] | | X | | X | | X | | X | | X | | |
| Urinalysis [b] | X | | | | | | | | | | | | |

| **Study Period:** | **Second Course Retreatment (21-Day Cycles) Combination Treatment** | | | | | | | | | | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment Cycle/Title:** | 1 | | 2 | | 3 | | 4 | | 5 | | 6+ | | |
| **Scheduled Day:** | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 8 | |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | Different windows are applicable for tumor scans. |
| PT/INR and aPTT/PTT [b] | X | | | | | | | | | | | | Coagulation tests should be conducted as clinically indicated for participants taking anticoagulation therapy |
| T3 (or Free T3), Free T4, and TSH [b] | X | | | | X | | | | X | | | | Can be assayed based on local guidelines and practices. To be repeated every 2 cycles after Cycle 5. |
| Other Tumor Markers (CA 15-3, CEA, CA 27.29) | X | | | X | | | | X | | | | X | Should be collected within 28 days prior to Cycle 1, Day 1 of second course retreatment and then according to the tumor scan schedule (can be conducted at corresponding study visit, but must be collected within the same window specified for imaging) until study treatment discontinuation. |

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CA=cancer antigen; CBC=complete blood count; CEA=carcinoembryonic antigen; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; INR=international normalized ratio; MRI=magnetic resonance imaging; PT=prothrombin time; PTT=partial thromboplastin time; SAE=serious adverse event; SCF=Sponsor Consultation Form; SIM=Site Imaging Manual; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential.

a. For WOCBP, a urine or serum pregnancy test should be performed within 24 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

b. Laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment.

c. CBC and chemistry laboratory tests should be performed within 10 days prior to the first retreatment dose of pembrolizumab to determine eligibility, but do not need to be repeated on Cycle 1, Day 1 if obtained within 10 days prior to the first retreatment dose. However, they will be performed within 72 hours prior to dosing on Day 1 of each subsequent cycle.

# 2 INTRODUCTION

This clinical study will evaluate the combination of olaparib plus pembrolizumab versus chemotherapy (carboplatin + gemcitabine) plus pembrolizumab after 4 to 6 cycles of induction therapy with 1L chemotherapy (carboplatin + gemcitabine) plus pembrolizumab that demonstrates clinical benefit (CR, PR, or SD per RECIST 1.1 as determined by BICR) in participants with locally recurrent inoperable or metastatic TNBC.

## 2.1 Study Rationale

Immunotherapy plus chemotherapy combinations for the first-line (1L) treatment of participants with metastatic TNBC (mTNBC) have been explored in several Phase 3 clinical studies.

The Phase 3 IMpassion 130 trial enrolled 902 patients with mTNBC who had not received prior treatment for metastatic disease. Patients were randomly allocated to standard chemotherapy (nab-paclitaxel) plus atezolizumab, an antibody targeting the protein PD-L1, or to standard chemotherapy plus placebo. The 2 main objectives were to determine if the drug combination would improve PFS and prolong OS in all patients and in those with tumors expressing PD-L1. The median follow-up was 12.9 months. The combination therapy reduced the risk of disease worsening or death by 20% in all patients and 38% in the subgroup expressing PD-L1. In the entire study population, the median PFS was 7.2 months with the combination and 5.5 months with chemotherapy alone; the PFS hazard ratio (HR) was 0.80 (95% confidence interval [CI]: 0.69, 0.92; $p$=0.002). In the PD-L1 positive group, the median PFS was 7.5 months with the combination and 5.0 months with chemotherapy alone; the PFS HR was 0.62 (95% CI: 0.49, 0.78, $p$<0.0001). More than half of patients were alive at the time of analysis, so this was an interim assessment of OS. In the entire population, the median OS was 21.3 months with the combination versus 17.6 months with chemotherapy alone; the OS HR was 0.84 (95% CI: 0.69 to 1.02; $p$=0.08). In patients with PD-L1 positive tumors, the median OS was 25.0 months with the combination compared to 15.5 months with standard chemotherapy alone; the OS HR was 0.62 (95% CI: 0.45, 0.86). The proportion of patients responding to treatment (objective response rate [ORR]) was higher with the combination compared to chemotherapy alone for all patients (56.0% vs 45.9%) and those with PD-L1 positive tumors (58.9% vs 42.6%) [Schmid, P., et al 2018]. Given the benefit demonstrated in the treatment subgroup with PD-L1 positive tumors in the IMpassion 130 trial, the study population for this study will be stratified at randomization by PD-L1 tumor status. Recently, as atezolizumab plus nab-paclitaxel did not demonstrate a significant improvement in OS in IMpassion 130 and atezolizumab plus paclitaxel did not improve OS in IMpassion 131 [Miles, D. W., et al 2020], this combination was removed from the NCCN treatment guidelines as a preferred 1L treatment option for patients with mTNBC whose tumors express PD-L1 [National Comprehensive Cancer Network 2021].

Improved outcomes have been demonstrated for pembrolizumab plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) versus placebo plus chemotherapy in 1L mTNBC in study KEYNOTE-355. After median follow-up of 26 months, median PFS was 9.7 months with pembrolizumab-chemotherapy and 5.6 months with placebo-

chemotherapy (HR: 0.65, 95% CI 0.49-0.86, *p*=0.012) in patients with CPS ≥10, 7.6 and 5.6 months (HR: 0.74, 95% CI: 0.61-0.90, *p*=0.0014) in patients with CPS ≥1, and 7.5 and 5.6 months (HR: 0.82, 95% CI: 0.69-0.97, not tested) among the ITT population [Cortes, J., et al 2020]. At the final analysis (after median follow-up of 44 months), the benefit of pembrolizumab + chemotherapy on PFS was consistent with the prior results. Median OS was 23.0 months with pembrolizumab-chemotherapy and 16.1 months with placebo-chemotherapy (HR: 0.73, 95% CI 0.55-0.95, *p*=0.0093) in patients with CPS ≥10, 17.6 and 16.0 months (HR: 0.86, 95% CI: 0.72-1.04, *p*=0.0563) in patients with CPS ≥1, and 17.2 and 15.5 months (HR: 0.89, 95% CI: 0.76-1.05, not tested) among the ITT population. In summary, pembrolizumab + chemotherapy showed a statistically significant and clinically meaningful improvement in PFS and OS versus chemotherapy alone in patients with PD-L1 positive tumors (CPS ≥10) [Cortes, J., et al 2021]. The FDA granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) in NOV-2020, with conversion to full approval in JUL-2021.

The MK-7339-009 study seeks to investigate if olaparib plus pembrolizumab will maintain the clinical benefit achieved after induction therapy with a platinum-based regimen (carboplatin + gemcitabine) plus pembrolizumab and may predict and/or increase sensitivity to a polyadenosine 5′ diphosphoribose (polyADP ribose) polymerization (PARP) inhibitor (PARPi). There is a strong rationale for treating TNBC with DNA-damaging agents because of the similarities in the gene-expression profiles of breast cancer susceptibility gene 1 (BRCA1)-deficient and sporadic TNBCs. Approximately 70% of BRCA1-mutated breast cancers are triple negative, and these tumors appear to be particularly sensitive to the cytotoxic effects of DNA interstrand cross-linking agents such as cisplatin and carboplatin [Rottenberg, S., et al 2007]. Some metastatic TNBCs are also responsive to platinum-based chemotherapies [Isakoff, S. J., et al 2012] [Chia, J. W., et al 2007] [Koshy, N., et al 2010] [Baselga, J., et al 2013]. The carboplatin-plus-gemcitabine combination has been shown to be more potent against TNBC cells compared with non-TNBC cells [Hastak, K., et al 2010], and the regimen has been demonstrated to have clinical activity in metastatic breast cancer, with response rates of 26% to 34% [Chew, H. K., et al 2009] [Loesch, D., et al 2008] [Yardley, D. A., et al 2008].

An optimal duration of induction chemotherapy in TNBC has not been established. In other tumor types, such as advanced nonsquamous non-small cell lung cancer (NSCLC), current treatment guidelines recommend 4 to 6 cycles of platinum-based doublet as first-line or induction treatment [National Comprehensive Cancer Network 2016] [Novello, S., et al 2016] [Park, J. O., et al 2007] [Rossi, A., et al 2014]. More than 6 cycles of treatment in this population demonstrated prolonged PFS, added no benefit in OS, and increased toxicities [Park, J. O., et al 2007] [Rossi, A., et al 2014]. Given these results in NSCLC, 6 cycles of carboplatin and gemcitabine were considered optimal for the duration of induction in this study. Pembrolizumab as background immunotherapy is planned for up to 35 administrations.

Olaparib is now established as maintenance therapy for platinum-sensitive populations regardless of BRCA status in the setting of other tumor types. However, there is no current

regimen that uses a maintenance agent(s) in the metastatic TNBC setting. Furthermore, preclinical and clinical data indicates that an olaparib and pembrolizumab combination have an improved therapeutic effect, showing synergistic benefits [Karzai, F., et al 2017] [Vinayak, S., et al 2018]. Therefore, adding olaparib to pembrolizumab after induction treatment with a platinum-based regimen plus pembrolizumab will change and expand the treatment paradigm in this disease, particularly for those patients with platinum-sensitive TNBC tumors. Olaparib plus pembrolizumab has the potential for further treatment benefit in a chemo-sparing regimen.

## 2.2 Background

### 2.2.1 Olaparib

Olaparib (AZD2281, KU-0059436, LYNPARZA®) is a potent PARPi (PARP1, 2, and 3) that is being developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anticancer agents, including novel agents and immunotherapy.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumors with HRR deficiency (HRD), such as ovarian cancers in patients with breast cancer susceptibility gene 1/2 (BRCA1/2) mutations (BRCAm), 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 ataxia-telangiectasia mutated (ATM) 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.

The Phase 3 OlympiAD trial enrolled 302 patients with germline BRCAm (gBRCAm) human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer who had received no more than 2 lines of prior chemotherapy. Patients were randomly assigned (2:1 ratio) to receive olaparib or physician's choice of single-agent chemotherapy. Median PFS was longer in the 205 patients who received olaparib than in the 97 patients who received the chemotherapy regimen (7.0 months vs 4.2 months). The HR for disease progression or death was 0.58 (95% CI: 0.43 to 0.80; $p<0.001$). The response rate in the olaparib group was 59.9% versus 28.8% in the chemotherapy group. In addition, the rate of Grade 3 or higher AEs was lower in the olaparib group (36.6% vs 50.5%) as was the rate of treatment discontinuations (4.9% vs 7.7%, respectively) [Robson, M., et al 2017]. Olaparib is currently approved for use in the United States (US) in previously treated patients with deleterious or suspected deleterious gBRCAm HER2-negative metastatic breast cancer and

as adjuvant treatment for patients with gBRCAm HER2-negative high-risk early breast cancer. In the population with metastatic TNBC being studied in this MK-7339-009 study, the PFS in participants randomly assigned to receive olaparib or chemotherapy will be evaluated as a secondary objective in a subset of participants with BRCAm tumors.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on olaparib.

### 2.2.2 Pembrolizumab

Pembrolizumab (MK-3475, KEYTRUDA®) is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies and is indicated for the treatment of patients across a number of indications.

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

### 2.2.3 Pharmaceutical and Therapeutic Background

#### 2.2.3.1 Inhibition of PARP as a Target for Cancer Therapy

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 base excision repair (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 [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 [Fong, Peter C., et al 2009] such as HRR. Cells unable to perform HRR (eg, due to inactivation of genes required for HR, such as BRCA1 or BRCA2) are more likely to use the error-prone non-homologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair these DSBs and risk accumulating multiple lesions or loss of heterozygosity (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 BRCAm [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.

#### 2.2.3.2 Inhibition of PD-1 as a Target for Cancer Therapy

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation 8 (CD8)+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes (TILs) can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as cluster of differentiation 3 (CD3) zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001][Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004][Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in TNBC.

### 2.2.4 Disease Background

#### 2.2.4.1 Triple Negative Breast Cancer

Breast cancer is the most commonly diagnosed malignancy in women, excluding basal cell and squamous cell skin cancers, accounting for 30% of all new cancers. It is also the second

leading cause of cancer death (after lung cancer) among women. About 268,000 new cases of breast cancer and approximately 41,000 deaths due to breast cancer are expected in women in the US in 2019 [Siegel, R. L., et al 2019]. Breast cancer is the leading cause of cancer-related death among females worldwide with an estimated 1.2 million cases and 521,900 deaths reported in 2012. The highest mortality rates are found in Western Europe, the US, and Israel (which has some of the highest rates), and the lowest rates are found in Africa and Asia [Torre, L. A., et al 2016].

TNBC is phenotypically defined by a lack of estrogen receptor and progesterone receptor (ER/PGR) expression and the absence of HER2 overexpression and/or amplification [Dent, R., et al 2007]. TNBC represents 15% to 20% of all breast cancers [Bauer, K. R., et al 2007] and is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics [Badve, S., et al 2011] [Sorlie, T., et al 2001].

TNBC is a molecularly heterogeneous disease and includes tumor subsets with different prognoses. Recent gene expression profiling has identified up to 6 distinct TNBC subtypes (2 basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor [AR] subtype) [Lehmann, B. D., et al 2011].

TNBC is associated with younger age at diagnosis, premenopausal status, African American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer, BRCA1 mutations, and more aggressive behavior than other breast cancer subtypes [Bauer, K. R., et al 2007]. As reported in a seminal study on TNBC, 34% of all participants with TNBC experience distant recurrence with a median distant recurrence-free survival (DRFS) of 2.6 years, compared to a distant recurrence rate of 20% and a median DRFS of 5 years in other breast cancer subtypes; the peak of recurrence for TNBC is within 1 to 3 years after initial diagnosis, and decreases significantly thereafter; participants with TNBC also have shorter median overall survival (OS) compared with participants with non-TNBC (4.2 vs 6.0 years, respectively) [Dent, R., et al 2007]. Finally, participants with TNBC tend to relapse with distant metastases rather than local recurrences and are more likely to develop visceral metastases, including central nervous system (CNS) involvement [Lin, N. U., et al 2008].

Treatment of TNBC is challenging and represents an area of unmet medical need, as these tumors lack therapeutic targets, such as ER and HER2, and become rapidly resistant to chemotherapy upon local recurrence and/or metastasis (even though they are often sensitive to cytotoxic drugs at initial presentation) [Arnedos, M., et al 2012]. The majority of participants with metastatic TNBC have experienced relapse after neoadjuvant/adjuvant therapy for early or locally advanced disease. In a frequently referenced study, the median OS of all (at any line of therapy) participants with mTNBC was 13.3 months [Kassam, F., et al 2009]. Additionally, locally recurrent inoperable breast cancer is considered clinically similar to previously untreated metastatic disease [Cardoso, F., et al 2014], and thus the MK-7339-009 study population includes participants with “early” advanced disease, requiring 1L treatment for locally recurrent inoperable or metastatic TNBC.

With the exception of those patients with metastatic PD-L1 positive TNBC, no specific chemotherapy regimen is currently established as a standard-of-care for the treatment for TNBC in any setting. Similar to any advanced breast cancer, the recommended initial treatment for participants with locally recurrent inoperable or metastatic TNBC includes anthracyclines and taxanes. For participants previously treated with an anthracycline, or for whom anthracyclines are contraindicated or not considered the best treatment option, taxanes are most commonly used as a 1L treatment, when the time interval between completion of taxane-based neoadjuvant/adjuvant therapy and recurrence is at least 12 months [Andre, F. 2012]. Participants with earlier (<12 months) local or distant disease recurrence are treated with chemotherapies not previously used in the neoadjuvant/adjuvant setting; in the case of aggressive disease and/or visceral crisis, combination, rather than single agent, chemotherapy is thus indicated and may include any one of different regimens, such as gemcitabine/carboplatin, capecitabine/vinorelbine, gemcitabine/cisplatin, etc. The PARP inhibitors, olaparib and talazoparib, are indicated for the treatment of patients with deleterious or suspected deleterious gBRCAm HER2-negative metastatic breast cancer. PARP inhibitors are a reasonable treatment option for patients with gBRCA mutations previously treated with an anthracycline and/or a taxane and provide improvements in PFS and QoL with an acceptable toxicity profile [National Comprehensive Cancer Network 2019] [Cardoso, F., et al 2018].

### 2.2.5 Rationale for Combination Therapy

#### 2.2.5.1 Chemotherapy in Combination With Pembrolizumab

The rationale behind combining chemotherapy with pembrolizumab is based on the immunomodulatory effects of the former [Zitvogel, L., et al 2008], which may in turn increase the antitumor activity of PD-1 pathway inhibition. Even though cytotoxic drugs, including taxanes and gemcitabine/carboplatin, have historically been considered immunosuppressive, they can also have immunopotentiating roles by 1) depleting immunosuppressive cells, such as regulatory T-cells and myeloid-derived suppressor cells, to enhance a latent antitumor immune response, 2) inducing an immunogenic cell death, 3) enhancing tumor antigen presentation by upregulating the expression of tumor antigens themselves, or of the major histocompatibility complex (MHC) class I molecules to which the antigens bind, 4) upregulating co-stimulatory molecules (B7-1) or down regulating co-inhibitory molecules (PD-L1/B7-H1 or B7-H4) expressed on the tumor cell surface, thus enhancing the strength of effector T-cell activity, and 5) rendering tumor cells more sensitive to T-cell–mediated lysis through fas-, perforin-, and granzyme B–dependent mechanisms [Emens, L. A. and Middleton, G. 2015].

#### 2.2.5.2 Olaparib in Combination With Pembrolizumab

PARP inhibition has both the immune-activating and immune-suppressive effects on cancer cells [Mouw, K. W. 2018]. Several reports demonstrated that PARPis may trigger an immune-activating interferon secretion via the cGAS-STING pathway activation in BRCA mutant and breast cancer susceptibility gene wildtype (BRCAwt) cells [Shen, J., et al 2019] [Ding, L., et al 2018] [Wang, Z., et al 2019]. In addition, it has been demonstrated that the PARP inhibitor niraparib potentiates anti-PD-1 antibody efficacy through interferon

activation, resulting in synergistic effects and tumor shrinkage in animal models [Wang, Z., et al 2019]. Some recent studies demonstrated that PARP inhibition can trigger immune-suppressive effects by increasing PD-L1 expression in cancer cells [Sato, H., et al 2017] [Jiao, S., et al 2017]. Continuous treatment with olaparib results in increased PD-L1 expression in BRCA2-depleted cancer cells [Sato, H., et al 2017]. This enhanced PD-L1 expression driven by olaparib is suggested to be dependent on the ATM/CHK1 axis. The effect of olaparib on PD-L2 expression seems to be independent of BRCA status. It has been demonstrated that olaparib can upregulate PD-L1 in both BRCA-proficient and BRCA-deficient breast cancer cells [Jiao, S., et al 2017].

Mechanistically, PARPis inactivated glycogen synthase kinase-3 beta (GSK3β), which in turn enhanced PARPis-mediated PD-L1 upregulation. PARPis attenuated anticancer immunity via upregulation of PD-L1, and blockade of PD-L1 re-sensitized PARPis-treated cancer cells to T-cell killing. The combination of PARPis and anti-PD-L1 therapy compared with each agent alone significantly increased the therapeutic efficacy. The cross-talk between PARPis and tumor-associated immunosuppression provides evidence to support the combination of PARPis and PD-L1 or PD-1 immune checkpoint blockade as a potential therapeutic approach in the treatment of breast cancer [Jiao, S., et al 2017].

Strickland et al demonstrated that ovarian cancers that have a higher neoantigen load were associated with improved OS and higher expression of immune genes associated with tumor cytotoxicity, such as genes of the T-cell receptor (TCR), the interferon-gamma (IFNγ), and the tumor necrosis factor receptor (TNFR) pathways. Furthermore, immunohistochemistry (IHC) studies demonstrated that BRCA1/2-mutated tumors exhibited significantly increased CD3+ and CD8+ TILs, as well as elevated expression of PD-1 and PD-L1 in tumor-associated immune cells compared to HR-proficient tumors. Survival analysis showed that both BRCA1/2-mutation status and number of TILs were independently associated with outcome [Strickland, K. C., et al 2016].

In a Phase 1 dose escalation study, Lee et al tested durvalumab in combination with the PARPi olaparib or the vascular endothelial growth factor (VEGF) receptor 1-3 inhibitor cediranib in women's cancers (NCT02484404). The recommended Phase 2 dose (RP2D) was reached with durvalumab at 1500 mg every 4 weeks in combination with olaparib 300 mg BID or cediranib 20 mg (5 days on/2 days off). No dose-limiting toxicity was recorded with durvalumab plus olaparib. The most common treatment-emergent AE with durvalumab plus olaparib was hematologic toxicity, which was observed in frequencies greater than that reported for single agent olaparib. Two PRs (≥15 months and ≥11 months; ORR 17%) and 8 SDs ≥4 months (median 8 months [range 4 to 14.5 months]) were seen in 12 patients (10 ovarian and 2 TNBC; 11 germline BRCA wildtype (gBRCAwt) and 1 gBRCA-unknown with SD for 3 months) who received durvalumab plus olaparib, yielding an 83% disease control rate (DCR). A trend toward association of response with degree of PD-L1–positive TIL infiltration was observed [Lee, J. M., et al 2017].

In a Phase 2 study, Karzai et al combined the anti-PD-L1 antibody durvalumab with olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior treatment with enzalutamide and/or abiraterone (NCT02484404). Since 25% to 30% of sporadic mCRPCs have defects in DNA repair pathways that may confer sensitivity to PARP

inhibition, immune checkpoint blockade is a promising avenue in mCRPC treatment. Durvalumab was administered at 1500 mg IV every 28 days in combination with olaparib at 300 mg orally every 12 hours to 25 patients (the study is still open and active). Seven (of 16) patients (44%) on-study >2 months have had prostate-specific antigen (PSA) declines >50%. Six-month and 9-month PFS rates were 86.7% and 57.8%. Median PFS has not yet been reached. Grade 3/4 AEs included anemia (3/14, 21%), thrombocytopenia, lymphopenia, leukopenia, neutropenia, nausea, vomiting, hypertension, syncope, fatigue, urinary tract infection (UTI), and lung infection. Preliminary data show tolerability and synergistic activity in mCRPC patients without a gBRCAm [Karzai, F., et al 2018].

In an ongoing Phase 2 study in which patients with TNBC received the PARPi niraparib 200 mg orally once daily (QD) plus pembrolizumab 200 mg Q3W, Vinayak et al reported interim results for 45 evaluable patients. Twenty-two (41%) had received prior platinum in the metastatic setting and 39 (72%) had received prior neoadjuvant/adjuvant therapy. Thirteen patients had received >6 months of treatment with the combination (6 BRCAm, 5 BRCAwildtype(wt), and 2 BRCA status unknown). As of this reported analysis, the ORR was 29%, including 3 CRs (7%), 10 PRs (22%), 9 SDs (20%); the DCR was 49%. Of the 45 evaluable patients, 12 had BRCAm tumors with 1 CR, 7 PRs, 1 SD, and 3 with progressive disease (PD) reported in this subpopulation. Median PFS in this BRCAm group was 8.1 months (95% CI 0.2-Not evaluable). The ORR for patients regardless of BRCA status was 33% in PD-L1 positive (combined positive score [CPS] ≥1) versus 15% in PD-L1 negative patients. Responses were durable regardless of BRCA or PD-L1 status or prior platinum therapy. Adverse events of Grade 3 or higher occurred in 27 patients (50%), with thrombocytopenia (13%) and anemia (11%) most commonly reported. No new safety signals emerged as of this preliminary analysis [Vinayak, S., et al 2018].

### 2.2.6 Preclinical and Clinical Studies

For a summary of preclinical and clinical study data for olaparib and for pembrolizumab, refer to their respective IBs.

### 2.2.7 Ongoing Clinical Studies

For a summary of ongoing clinical study data for olaparib and pembrolizumab, refer to the respective IBs.

### 2.2.8 Information on Other Study-related Therapy

For additional information on carboplatin and gemcitabine, refer to the respective approved product labels.

## 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 rapid resistance to chemotherapy that develops upon local recurrence and/or metastasis [Arnedos, M., et al 2012] yields an unmet medical need for an effective and tolerable maintenance treatment regimen after tumor response is observed following initial treatment. Early phase studies conducted with combinations of olaparib and the PD-L1 inhibitor durvalumab showed tumor responses and no new safety signals for the combination (Section 2.2.5.2). In the ongoing KEYNOTE-162 study, the combination of pembrolizumab and a PARPi has shown preliminary efficacy and tolerability in previously treated participants with metastatic TNBC [Vinayak, S., et al 2018]. Given the early results from these studies, the combination of the PD-1 inhibitor pembrolizumab and the PARPi olaparib in participants with previously untreated locally recurrent inoperable or metastatic TNBC who demonstrate a tumor response following induction with carboplatin and gemcitabine plus pembrolizumab is expected in this study to demonstrate a favorable benefit/risk profile. It is also expected that participants randomly assigned to receive olaparib plus pembrolizumab in Arm 1 of the study will have fewer side effects than those participants receiving carboplatin and gemcitabine plus pembrolizumab in Arm 2 of the study, as carboplatin and gemcitabine will have been discontinued after induction in participants randomized to Arm 1, resulting in essentially a de-escalation to a chemo-sparing regimen.

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

# 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The Phase 2/3 2-in-1 adaptive design will not be pursued and the study is now a stand-alone Phase 2 study.

In males and females at least 18 years of age with locally recurrent inoperable or metastatic TNBC after induction of clinical benefit (objective response or stable disease [SD]) with first-line (1L) chemotherapy plus pembrolizumab:

Throughout this protocol, the term Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

| Objectives | Endpoints |
|---|---|
| Primary | |
| • Objective: To compare olaparib plus pembrolizumab to chemotherapy plus pembrolizumab with regards to progression-free survival (PFS) according to RECIST 1.1 by blinded independent central review (BICR).<br>Hypothesis (H1): Olaparib plus pembrolizumab is superior to chemotherapy plus pembrolizumab with respect to PFS according to RECIST 1.1 by BICR. | • PFS, the time from randomization until either the earliest date of documented disease progression or death due to any cause, whichever occurs first |
| • Objective: To compare olaparib plus pembrolizumab to chemotherapy plus pembrolizumab with regards to overall survival (OS).<br>Hypothesis (H2): Olaparib plus pembrolizumab is superior to chemotherapy plus pembrolizumab with respect to OS. | • OS, the time from randomization to death due to any cause |
| Secondary | |
| • Objective: To evaluate OS, and PFS according to RECIST 1.1 by BICR, in participants with PD-L1 positive tumors (CPS ≥10) following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • OS<br>• PFS |
| • Objective: To evaluate OS, and PFS according to RECIST 1.1 by BICR, in participants with BRCAm tumors following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • OS<br>• PFS |

| Objectives | Endpoints |
|---|---|
| • Objective: To evaluate health-related quality-of-life (HRQoL) and time to deterioration (TTD) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the breast cancer module (EORTC QLQ-BR23) in participants with BRCAm tumors and irrespective of BRCAm status following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • HRQoL, a change from baseline in Patient-Reported Outcomes (PRO) scores obtained in post-induction<br>• Time to Deterioration (TTD), the time from baseline to the first onset of a confirmed* ≥10-point deterioration from baseline in PRO scores<br>For the following domains:<br>– EORTC QLQ-C30 global health status/QoL (Items 29 and 30)<br>– EORTC QLQ-C30 physical functioning (Items 1-5)<br>– EORTC QLQ-C30 emotional functioning (Items 21-24), and<br>– EORTC QLQ-BR23 systemic therapy side effects (Items 1-4, 6, 7, and 8)<br>*confirmed by a ≥10-point deterioration from baseline in the subsequent PRO score |
| • Objective: To evaluate visual analogue scale (VAS) using the EuroQoL 5-dimension, 5-level questionnaire (EQ-5D-5L) in participants with BRCAm tumors and irrespective of BRCAm status following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • Visual analogue scale (VAS), a change from baseline in EQ-5D-5L VAS score obtained in post-induction |
| • Objective: To evaluate the safety and tolerability of olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • Adverse events (AEs)<br>• Study treatment discontinuation due to AEs |

| Objectives | Endpoints |
|---|---|
| Tertiary/Exploratory | |
| • Objective: To evaluate the objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) according to RECIST 1.1 by BICR, in all-comers and in participants with PD-L1 positive tumors (CPS ≥10) following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • Objective response: complete response (CR) or partial response (PR)<br>• DOR, the time from first documented evidence of CR or PR after randomization until disease progression or death due to any cause, whichever occurs first<br>• Disease control, CR or PR after randomization; or stable disease (SD) after randomization and for at least 24 weeks prior to any evidence of progression |
| • Objective: To evaluate the ORR, DOR, and DCR according to RECIST 1.1 by BICR in participants with BRCAm tumors following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • ORR<br>• DOR<br>• DCR |
| • Objective: To evaluate PFS after next line treatment (PFS2) according to the local standard of clinical practice as determined by the investigator, in all-comers, in participants with PD-L1 positive tumors (CPS ≥10), and in participants with BRCAm tumors following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • PFS2, the time from randomization until disease progression on next-line treatment or death due to any cause, whichever occurs first |

| Objectives | Endpoints |
|---|---|
| • Objective: To evaluate the time to first subsequent treatment (TFST), the time to second subsequent treatment (TSST), and the time until discontinuation of study treatment or death (TDT), in all-comers, in participants with PD-L1 positive tumors (CPS ≥10), and in participants with BRCAm tumors following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • TFST, the time from randomization until initiation of first subsequent anticancer therapy or death due to any cause, whichever occurs first<br>• TSST, the time from randomization until initiation of second subsequent anticancer therapy or death due to any cause, whichever occurs first<br>• TDT, the time from randomization to discontinuation of study treatment or death due to any cause, whichever occurs first |
| • Objective: To evaluate HRQoL and TTD using the EORTC QLQ-C30 and the EORTC QLQ-BR23 in participants with PD-L1 positive tumors (CPS ≥10) following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • HRQoL, a change from baseline in PRO scores obtained in post-induction<br>• TTD, the time from baseline to the first onset of a confirmed* ≥10-point deterioration from baseline in PRO scores<br>For the following domains:<br>– EORTC QLQ-C30 global health status/QoL (Items 29 and 30)<br>– EORTC QLQ-C30 physical functioning (Items 1-5)<br>– EORTC QLQ-C30 emotional functioning (Items 21-24), and<br>– EORTC QLQ-BR23 systemic therapy side effects (Items 1-4, 6, 7, and 8)<br>*confirmed by a ≥10-point deterioration from baseline in the subsequent PRO score |
| • Objective: To evaluate VAS using the EQ-5D-5L in participants with PD-L1 positive tumors (CPS ≥10) following treatment with olaparib plus pembrolizumab or chemotherapy plus pembrolizumab. | • VAS, a change from baseline in EQ-5D-5L VAS score obtained in post-induction |

| Objectives | Endpoints |
|---|---|
| • 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 study drug and other treatments. | • Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue |

# 4 STUDY DESIGN

## 4.1 Overall Design

*Note:* Based on the data from a prespecified interim safety and efficacy analysis for KEYLYNK-009 (data cutoff 15-DEC-2022), the internal DMC recommended discontinuing the study. The combination of pembrolizumab plus olaparib did not show an improvement in PFS compared with the combination of chemotherapy plus pembrolizumab. Participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) may have the option to continue on study treatment if they are deriving clinical benefit, until criteria for discontinuation are met.

As of Amendment 03, participants who discontinue study treatment for any reason will complete the End-of-Treatment and Safety Follow-up visits, but no further data will be collected. If continuing on study treatment, participants will no longer have tumor response assessments by BICR, but local tumor imaging assessments should continue per SOC schedule. For all participants, ePRO assessments will no longer be performed, biomarker samples will no longer be collected, and Disease Status Follow-up and Survival Follow-up visits will no longer be conducted. The section below is retained for reference.

This is a Phase 2, multicenter, worldwide, randomized, open-label study in participants with previously untreated **locally** recurrent inoperable or metastatic TNBC who achieve CR, PR, or SD per RECIST 1.1 as determined by BICR after 4 to 6 cycles of induction therapy with carboplatin and gemcitabine plus pembrolizumab.

Prior treatment with chemotherapy in the neoadjuvant/adjuvant setting is allowed. For such participants, the period between completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence must be ≥6 months. Participants who received platinum-based chemotherapy or gemcitabine in the neoadjuvant/adjuvant setting may be treated with carboplatin and gemcitabine in this study if ≥12 months have elapsed between completion of treatment with curative intent and the first documented local or distant disease recurrence. Participants presenting with de novo metastatic TNBC are eligible for the study if anthracycline and/or a taxane is contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.

This study will be conducted in 2 periods, an induction period and a post-induction period.

### 4.1.1 Induction

Approximately 460 eligible participants will be enrolled in the induction portion of the study to receive both carboplatin (AUC 2) with gemcitabine (1000 mg/m$^2$) on Days 1 and 8 of each 21-day cycle in addition to pembrolizumab (200 mg) Q3W for a maximum of up to 6 cycles but not less than 4 cycles of treatment.

If either or both chemotherapy agents are withheld for toxicities, pembrolizumab may be continued until the chemotherapy toxicities resolve. Participants must receive up to 6 but not less than 4 cycles of one or both chemotherapy agents plus pembrolizumab to be eligible for post-induction. During induction, dose reductions of both carboplatin and/or gemcitabine are allowed. One of the 2 chemotherapeutic agents may be discontinued for toxicity; however, if both carboplatin and gemcitabine are discontinued due to toxicity, the participant must be discontinued from all study interventions. If the participant needs to be discontinued from pembrolizumab due to toxicity during induction, the participant must be discontinued from all study interventions. Participants who discontinue from all study interventions for any reason during induction, and are therefore not eligible to be randomized to receive post-induction treatment, will enter the 30-day safety follow-up.

Tumor assessments and response during induction will be evaluated by tumor scans at Week 6 (+7 days), Week 12 (±7 days), and Week 18 (-7 days) (see Section 8.2.2.2.1). A participant with a tumor response at Week 18 (-7 days) of CR, PR, or SD, according to RECIST 1.1 as determined by BICR expedited review, is eligible for randomization to post-induction treatment if all other eligibility criteria are met. Participants with disease progression as determined by BICR at any timepoint during induction will be discontinued from study intervention. The Week 18 (-7 days) evaluation will determine eligibility for randomization to the Post-induction period (see Section 8.2.2.2.2) (see Sections 5.1 and 5.2 for full eligibility criteria for post-induction). If there is an increase in the size of target lesion(s) and/or a worsening of non-target lesions at the Week 18 (-7 days) induction scan, but these changes do not meet the RECIST 1.1 guidelines for PD [Eisenhauer, E. A., et al 2009], the participant may be discontinued from study intervention at the discretion of the investigator. Participants with dose interruption for toxicity resolution cannot be randomized into post-induction until after the Week 18 (-7 days) scan tumor response is confirmed by BICR.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) will not be used to determine tumor response during induction. If PD seen by the site during induction is not verified by BICR, disease assessments should still be performed by the site/investigator using RECIST 1.1 if the participant is stable and continues treatment at treating physician's discretion.

### 4.1.2 Post-induction

Participants will be assessed during pre-randomization to ensure eligibility and should be randomized into and begin post-induction within approximately 14 to 21 days after the

Week 18 (-7 days) scan. This scan will also establish the baseline for post-induction tumor response assessments. An additional up to 3 weeks will be allowed for recovery from toxicities related to induction therapy (ie, the interval between the last dose of induction and first dose of post-induction should be no more than 6 weeks). The Eastern Cooperative Oncology Group (ECOG) performance status, safety, and laboratory studies conducted during pre-randomization and the electronic patient-reported outcomes (ePROs) conducted just before the Cycle 1, Day 1 dose of study medication will establish a baseline for each of these respective assessments.

During randomization, participants will be stratified by (1) best overall response to induction therapy (CR or PR vs SD) at Week 18 (-7 days) as assessed by BICR; (2) PD-L1(+) versus PD-L1(-); and (3) genomic tumor status (BRCAm vs BRCAwt). For the purpose of stratification, PD-L1 positive (+) is defined as a combined positive score (CPS) ≥1, and PD-L1 negative (-) is defined as a CPS <1.

The Sponsor, investigators, participants, and other study site staff will be blinded to participant PD-L1 and BRCA tumor results.

Approximately 260 participants will be randomly assigned in the post-induction portion of the study in a 1:1 ratio to Arm 1 or Arm 2 of treatment.

Participants in Arm 1 will continue to receive pembrolizumab 200 mg Q3W and will begin a concurrent regimen of olaparib 300 mg orally BID.

Participants in Arm 2 will continue to receive carboplatin and/or gemcitabine at the same dose and schedule administered at the last dose of the induction period plus pembrolizumab 200 mg Q3W. Participants must be able to receive at least 1 dose of single-agent chemotherapy plus 1 dose of pembrolizumab at Cycle 1, Day 1 of post-induction. In addition, the same chemotherapy agent or agents that were administered as the last dose in induction must also be administered at the Cycle 1, Day 1 dose in post-induction.

Participants who complete 35 cycles of pembrolizumab (this includes induction cycles) and continue to demonstrate clinical benefit during post-induction may continue to receive olaparib or carboplatin and/or gemcitabine. Crossover of participants between treatment arms will not be permitted.

Tumor assessments and response during post-induction will be evaluated by tumor scans every 6 weeks (±7 days, except for the first Week 6 scan after randomization, which should be 6 weeks +7 days) for the first year and every 12 weeks (±7 days) thereafter, independent of any dose modifications. All tumor scans performed post-induction will be assessed by BICR as described in Section 8.2.2.5.

Tumor response assessed per iRECIST may be performed during post-induction only.

Safety will be monitored according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Safety and efficacy data will be reviewed by an internal DMC (see Section 10.1.4.2).

### 4.1.3 End-of-Treatment

Participants will continue with study treatment until any of the following occurs during induction or post-induction: verified disease progression as determined by BICR according to RECIST 1.1 (after implementation of Amendment 03, this will be until disease progression according to RECIST 1.1 as determined by investigator/site/local radiology review); unacceptable toxicity; intercurrent illness that necessitates discontinuation of study treatment; investigator's decision to withdraw the participant; pregnancy; participant noncompliance with study treatment or procedure requirements; a documented complete withdrawal of consent from all further study treatment; death; end of the study; or other administrative reasons requiring cessation of study treatment (Section 7.1).

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.

### 4.1.4 Planned Analyses

Two IAs (IA1 and IA2) and a final analysis (FA) may be performed.

*Note:* IA1 was skipped to proceed to IA2 (see Section 9.1 for details).

As of Amendment 03, the prespecified final analysis of the study described in the SAP will not be performed.

Details of the planned analyses are provided in Section 9.7.

## 4.2 Scientific Rationale for Study Design

### 4.2.1 Rationale for Endpoints

#### 4.2.1.1 Efficacy Endpoints

This study will use PFS and OS as dual-primary endpoints based on RECIST 1.1 criteria, as outlined in Section 3. Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions overall and a maximum of 5 target lesions per organ.

Progression-free survival is an acceptable measure 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 PFS is typically considered acceptable by regulatory authorities. Images will be assessed by BICR according to RECIST 1.1 to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression, as assessed by BICR, will be communicated to the site.

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

#### 4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are safety endpoints including, but not limited to, the incidence, causality, and outcome of AEs/serious adverse events (SAE)s; and changes in vital sign measurements and laboratory values. Adverse events will be assessed, as defined by NCI CTCAE v5.0.

#### 4.2.1.3 Patient-Reported Outcomes

Improvement in patient-reported outcomes is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new treatment.

The EORTC QLQ-C30 was developed to assess the HRQoL 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 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. 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 a global health status/QoL score derived from 2 items that use 7-point scale scoring with anchors (1=very poor and 7=excellent).

The EORTC QLQ-BR23 is a breast cancer-specific quality-of-life questionnaire developed to assess the extent of symptoms or problems in subjects receiving treatment for breast cancer. The tool is used to supplement the EORTC QLQ-C30 and follows the same 4-point scale described above. The tool consists of 23 questions containing 4 functioning scales (body image, sexual functioning, sexual enjoyment, future perspective) and 4 symptom scales (arm symptoms, breast symptoms, systemic therapy side effects, upset by hair loss). It has been translated and validated in over 70 languages.

The European Quality of Life 5-dimension 5-level (EQ-5D-5L) questionnaire 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. The 5 health state dimensions in this instrument include the following: mobility, self -care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the patient rates his or her general state of health at the time of the assessment. The EQ-5D-5L will always be completed by patients after completing the EORTC QLQ-C30. The EQ-5D-5L is available in more than 130 languages, has been used extensively in cancer studies, and published results from these studies support its validity and reliability.

#### 4.2.1.4 Planned Exploratory Biomarker Research

PARP inhibitors and cancer immunotherapies represent important classes of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely

understood and much remains to be learned regarding how best to leverage these drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer therapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy. To identify novel biomarkers, biospecimens (ie, blood components, tumor material, tissue material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations of biomarkers that correlate with response or resistance to treatment may include but are not limited to:

*Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)*

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. In addition to studying variation across the human genome, mutations in DNA damage repair genes including, but not limited to *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L* as well as genome scars including LOH may be investigated. Based on data from participants in several olaparib studies in multiple cancer types, known or suspected deleterious mutations in these genes and LOH may be predictive of a response to the combination of olaparib and pembrolizumab. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer).

*Genetic (DNA) analyses from tumor*

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

*Tumor and/or blood RNA analyses*

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that

correlate to clinical response to treatment. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

*Proteomics and immunohistochemistry (IHC) using blood or tumor*

Tumor, tissue, and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to olaparib and pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for olaparib (MK-7339) and pembrolizumab (MK-3475) therapy.

*Other biomarkers*

In addition to expression on the tumor tissue, other tumor derived cells, proteins and DNA/RNA can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) that measure proteins and assays that measure cell-free DNA/RNA (cfDNA/cfRNA) may also be evaluated from blood samples. Correlation of these biomarkers with response to treatments may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

In addition to studying variation across the human genome, PD-L1 and BRCA gene variants will specifically be investigated for the relationship to tumor response.

#### 4.2.1.5 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for

future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

### 4.2.2 Rationale for the Use of Comparator

Carboplatin and gemcitabine have been shown to be an effective treatment option for 1L treatment of metastatic TNBC [O'Shaughnessy, J., et al 2014].

## 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 recommended dose in the current prescribing information.

### 4.3.2 Rationale for Chemotherapy Dosing Regimens

The planned starting dose of carboplatin in this study is AUC 2 on Days 1 and 8 of each 21-day cycle. The dose and timing of carboplatin administration is based on the most common clinical practice.

The planned starting dose of gemcitabine in this study is 1000 mg/m$^2$ on Days 1 and 8 of each 21-day cycle. The dose and timing of gemcitabine administration is based on the most common clinical practice.

### 4.3.3 Rationale for Pembrolizumab Dosing Regimen

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5-fold exposure range (refer to IB, Section 5.2.2)

- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

### 4.3.4 Maximum Dose/Exposure for This Study

There is no maximum duration of exposure for olaparib. Olaparib administration will continue until disease progression or until discontinuation from treatment for any reason.

The maximum duration of exposure for pembrolizumab is 35 total administrations (~2 years), inclusive of induction and post-induction administrations. Participants may be eligible for an additional 17 administrations (~1 year), as outlined in Section 8.12.6.

Carboplatin and gemcitabine will continue until disease progression or until discontinuation from treatment for any reason.

## 4.4 Beginning and End of Study Definition

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 (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory 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 FSR in any Member State.

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

### 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, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

In the event of Sponsor decision to no longer supply study interventions, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

*Note:* Based on the data from a prespecified interim safety and efficacy analysis for KEYLYNK-009 (data cutoff 15-DEC-2022), the internal DMC recommended discontinuing

the study. The combination of pembrolizumab plus olaparib did not show an improvement in PFS compared with the combination of chemotherapy plus pembrolizumab.

# 5 STUDY POPULATION

Male and female participants ≥18 years of age with locally recurrent inoperable or metastatic TNBC who are eligible for 1L therapy in the metastatic TNBC setting and are willing to participate in the study will be enrolled.

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

## 5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

**INDUCTION PERIOD**

**Type of Participant and Disease Characteristics**

1. Have locally recurrent inoperable centrally confirmed TNBC that has not previously been treated with chemotherapy in the metastatic setting and that cannot be treated with curative intent.

   OR

   Have metastatic TNBC that has not been previously treated with chemotherapy.

   *Note:* Participants with a history of locally recurrent TNBC that was treated with curative intent may be eligible. Local or distant disease recurrence must be ≥6 months from the completion of the most recent treatment with curative intent either in the neo-adjuvant or adjuvant setting.

   *Note:* Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6 month interval requirement described above.

   *Note:* First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.

   *Note:* Participants who received platinum agents or gemcitabine in the neoadjuvant/adjuvant setting are eligible for this study if ≥12 months have elapsed between completion of most recent treatment with curative intent and the first documented local or distant disease recurrence.

2. Have been treated with anthracycline and/or a taxane in the neoadjuvant/adjuvant setting, if they received systemic treatment in the neoadjuvant/adjuvant setting, unless

anthracycline and/or taxane was contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.

*Note:* Participants presenting with de novo metastatic TNBC are eligible for the study if anthracycline and/or a taxane is contraindicated or not considered the best treatment option for the participant, in the opinion of the treating physician.

3. Have measurable disease based on RECIST 1.1, as determined by local radiology review.

   *Note:* Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   *Note:* Chest wall recurrence can be used as a target lesion only if a radiologically measurable lesion is identified by quality imaging modality (digital photography alone is not adequate).

4. Have provided a recently obtained or archival (no more than 3 years old) core or excisional biopsy of a tumor lesion not previously irradiated for central determination of TNBC, PD-L1, and BRCA status.

   *Note:* TNBC and PD-L1 status must be centrally confirmed prior to enrollment in the study.

   *Note:* Adequacy of a biopsy specimen (fine needle aspiration is not adequate) for the above analyses must be confirmed by the central laboratory. Submission of another tumor specimen may be required if adequate tumor tissue was not provided the first time.

   *Note:* An archival tumor specimen obtained before the diagnosis of locally recurrent inoperable or metastatic TNBC that is more than 3 years old may be submitted after consultation with the Sponsor with documented SCF, if neither a recently nor a newly obtained biopsy from a locally recurrent inoperable or a metastatic site is available.

   *Note:* Participants initially diagnosed with hormone receptor-positive (HR+) or HER2-positive breast cancer in the neoadjuvant/adjuvant setting must have central confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.

   *Note:* Newly obtained tissue may be obtained at any time prior to the administration of systemic cytotoxic treatment for the treatment of metastatic TNBC. Formalin-fixed paraffin-embedded (FFPE) tumor blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).

## Demographics

5. Be a male or female at least 18 years of age on the day of signing the informed consent.

6. Have an ECOG performance status of 0 or 1 as assessed within 7 days prior to the start of induction study treatment.

7. Have a life expectancy ≥27 weeks from the day of first study treatment.

8. Demonstrate adequate organ function within 10 days prior to the start of study treatment as defined in the following table (Table 1).

Table 1 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | ≥1500 cells/µL |
| Platelets | ≥100 000 cells/µL |
| Hemoglobin | ≥9.0 g/dL or ≥5.6 mmol/L[1] |
| Renal | |
| Estimated creatinine clearance using the Cockcroft-Gault equation[2] | ≥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)/partial thromboplastin time (PTT) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT/PTT 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 within the last 14 days and without packed red blood cell (pRBC) transfusions within last 28 days.
2. Estimated creatinine clearance using Cockcroft-Gault:

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

*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.

**Male Participants**

9. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Olaparib: 95 days
    - Pembrolizumab: no contraception requirement
    - Chemotherapy: 95 days

    - Refrain from donating sperm

      PLUS either:

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

      OR

    - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

    - Agree to 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. 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-vaginal penetration.

    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

    Refer to Appendix 7 for country-specific requirements.

**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:

    - Is not a WOCBP

    OR

- Is a WOCBP and using 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
  - Pembrolizumab: 120 days
  - Chemotherapy: 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.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours 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 in Appendix 5.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

  Refer to Appendix 7 for country-specific requirements.

**Informed Consent**

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

## POST-INDUCTION PERIOD

### Types of Participant and Disease Characteristics

12. Have received up to 6 cycles but not less than 4 cycles of induction therapy without permanently discontinuing from pembrolizumab or both carboplatin and gemcitabine.

13. Have achieved CR, PR, or SD based on RECIST 1.1, as determined by BICR at the Week 18 evaluation. Radiographic eligibility will be determined solely based upon the Week 18 evaluation.

14. Should be able to complete during post-induction at least the Cycle 1, Day 1 doses of olaparib and pembrolizumab (Arm 1) or the Cycle 1, Day 1 doses of at least one of the chemotherapy agents being administered at the end of induction (carboplatin and/or gemcitabine in addition to pembrolizumab [Arm 2]).

### Demographics

15. Have an ECOG performance status of 0 or 1, as assessed within 7 days prior to the start of post-induction study treatment.

16. Have no higher than Grade 1 toxicities related to induction therapy (excluding alopecia) prior to randomization.

    *Note:* Hemoglobin (Hb) levels ≥9.0 g/dL or ≥5.6 mmol/L will be allowed.

    *Note:* Grade 2 hyperthyroidism or Grade 2 hypothyroidism will be allowed.

    *Note:* Grade 2 hyperglycemia will be allowed.

    *Note:* Recovery from toxicities related to induction therapy will be allowed for up to 3 weeks prior to randomization.

## 5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

## INDUCTION PERIOD

### Medical Conditions

1. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

    *Note:* Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

2. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

3. Has an active autoimmune disease that has required systemic treatment in the past 2 years (eg, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

4. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat scan (note that the repeat scan should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

5. Has myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or has features suggestive of MDS/AML.

6. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease.

7. Has active, or a history of, interstitial lung disease.

8. Has a known history of active tuberculosis.

9. Has an active infection requiring systemic therapy.

10. Has a known history of human immunodeficiency virus (HIV) infection.

    *Note:* No HIV testing is required unless mandated by local health authority.

11. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    *Note:* No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

12. Has a history of class II-IV congestive heart failure or myocardial infarction within 6 months of first study treatment.

13. Has neuropathy ≥Grade 2.

14. Has not recovered (eg, to ≤Grade 1 or to baseline) from AEs due to a previously administered therapy.

    *Note:* Alopecia of any grade is an exception to this criterion.

*Note:* Prior to first study treatment, the participant must have recovered adequately from any toxicity and/or complications associated with any recent procedure.

15. Has a known history of hypersensitivity or allergy to pembrolizumab, olaparib and any of its components, and/or to any of the study chemotherapies (eg, carboplatin or gemcitabine) and any of their components.

16. Has severe hypersensitivity (≥Grade 3) to the study treatments and/or any of their excipients.

17. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

18. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 180 days (or longer as specified by local institutional guidelines) after the last dose of study treatment.

19. Is a WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization or treatment allocation (Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    *Note:* In the event that 24 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study medication.

**Prior/Concomitant Therapy**

20. Has received prior therapy with either olaparib or any other PARP inhibitor.

21. Has received prior radiotherapy within 2 weeks of start of study treatment. 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.

22. Has received colony-stimulating factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment.

23. Has had an allogenic tissue/solid organ transplant.

24. Has received previous allogenic bone marrow transplant or double umbilical cord transplantation (dUCBT).

25. Had major surgery within 2 weeks of starting study intervention or has not recovered from any effects of any major surgery.

26. Has received a live or live-attenuated vaccine within 30 days prior to first study treatment. Administration of killed vaccines are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.

27. Is receiving any medication prohibited in combination with study chemotherapies as described in the respective product labels unless medication was stopped within 7 days prior to first study treatment.

**Prior/Concurrent Clinical Study Experience**

28. Has received prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (such as CTLA-4, OX-40, CD137) or has previously participated in a study evaluating pembrolizumab regardless of treatment received.

29. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    *Note:* Participants who have entered the follow-up of a clinical study may participate as long as 4 weeks have elapsed since the last dose of the investigational agent and/or removal of the device.

**Diagnostic Assessments**

30. Has presence of uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances), or participant has congenital long QT syndrome.

31. 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.

**Other Exclusions**

32. Is either unable to swallow orally administered medication or has a gastrointestinal disorder affecting absorption (eg, gastrectomy, partial bowel obstruction, malabsorption).

33. Is, in the judgement of the investigator, unlikely to comply with the study procedures, restrictions, and requirements of the study.

## POST-INDUCTION PERIOD

### Medical Conditions

34. Has severe hypersensitivity (≥Grade 3) to the study treatments and/or any of their excipients.

35. Has permanently discontinued from both carboplatin and gemcitabine during induction due to toxicity.

36. Has permanently discontinued from pembrolizumab during induction due to toxicity.

37. Has received less than 4 cycles of chemotherapy plus pembrolizumab during induction.

### Prior/Concomitant Therapy

38. 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 FDA-approved strong/moderate inhibitors of cytochrome P450 (3A4) (CYP3A4) can be found at the following website. This list is not all-inclusive. Any inhibitors not approved in the US will not appear in the list. The investigator should also refer to local approved product labels and use their best medical judgment.

    https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

39. 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 FDA-approved strong/moderate inducers of CYP3A4 can be found at the following website. This list is not all-inclusive. Any inducers not approved in the US will not appear in the list. The investigator should also refer to local approved product labels and use their best medical judgment.

    https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions

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

### 5.3.2 Contraception

Olaparib, pembrolizumab, carboplatin, and gemcitabine may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants should be informed that taking the study treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study treatment initiation (or 14 days prior to the initiation of study treatment for oral contraception) throughout the study period up to the time frame for participant contraception specified in Section 5.1. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

### 5.3.3 Pregnancy

If a participant inadvertently becomes pregnant during the study, the participant will be immediately discontinued from study treatment and will have an assessment of disease status by radiographic imaging. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

### 5.3.4 Use in Nursing Women

It is unknown whether any of the study medications are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

### 5.3.5 Practical Considerations

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.

### 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently entered 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.

Participants who fail screening may be re-screened for eligibility following consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

### 5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study 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 as described in Table 2 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

As of Amendment 03, the study is being discontinued based on the recommendation of the internal DMC. However, participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) may have the option of continuing with study treatment if they are deriving clinical benefit, until radiographic disease progression per RECIST 1.1 as determined by investigator/site/local radiology review or other discontinuation criteria are met. No treatment beyond progression will be authorized.

Participants who have experienced first disease progression by RECIST 1.1 in post-induction, who are continuing study treatment due to deriving clinical benefit and are being followed using the iRECIST criteria at the time of Amendment 03, may continue to receive study treatment only until the next confirmed disease progression (iCPD) by investigator/site/local radiology review. No treatment beyond iCPD as determined by investigator/site/local radiology review will be authorized.

The study intervention(s) to be used in this study are outlined in Table 2, and will be administered during induction and post-induction.

During induction, up to 6 cycles but not less than 4 cycles of DNA-damaging background chemotherapy (carboplatin and gemcitabine) in combination with the PD-1 inhibitor pembrolizumab will be administered to establish a tumor sensitizing effect.

Participants who achieve CR or PR or maintain SD at their Week 18 (-7 days) scan during induction, and who are otherwise eligible, will be randomized into 1 of 2 study arms to begin post-induction.

During post-induction, participants randomized to Arm 1 will continue to receive pembrolizumab and will begin olaparib; participants in Arm 2 will continue to receive at least one of the background chemotherapy agents (carboplatin and/or gemcitabine) plus pembrolizumab.

Refer to Appendix 7 for country-specific requirements.

Table 2 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Induction (all participants) | Experimental | Pembrolizumab | Drug | Solution for Infusion | 100 mg (25 mg/mL × 4 mL) | 200 mg | IV Infusion | On Day 1 of each 21-day cycle, 6 cycles | Test Product | IMP | Central |
| Induction (all participants) | Experimental | Carboplatin | Drug | Solution for Infusion | 600 mg (10 mg/mL × 60 mL) | AUC 2 | IV Infusion | On Days 1 and 8 of each 21-day cycle, 6 cycles | Test Product | IMP | Central or Local |
| Induction (all participants) | Experimental | Gemcitabine | Drug | Lyophilized Powder | 1000 mg | 1000 mg/m² | IV Infusion | On Days 1 and 8 of each 21-day cycle, 6 cycles | Test Product | IMP | Central or Local |
| Post-induction Arm 1 | Experimental | Pembrolizumab | Drug | Solution for Infusion | 100 mg (25 mg/mL × 4 mL) | 200 mg | IV Infusion | On Day 1 of each 21-day cycle, for up to 35 administrations (inclusive of induction administrations) | Test Product | IMP | Central |
| Post-induction Arm 1 | Experimental | Olaparib | Drug | Tablet | 150 mg 100 mg | 300 mg | Oral | BID until disease progression or prohibitive toxicity | Test Product | IMP | Central |
| Post-induction Arm 2 | Experimental | Pembrolizumab | Drug | Solution for Infusion | 100 mg (25 mg/mL × 4 mL) | 200 mg | IV Infusion | On Day 1 of each 21-day cycle, for up to 35 administrations (inclusive of induction administrations) | Test Product | IMP | Central |

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Post-induction Arm 2 | Experimental | Carboplatin | Drug | Solution for Infusion | 600 mg (10 mg/mL × 60 mL) | AUC 2 | IV Infusion | On Days 1 and 8 of each 21-day cycle until disease progression or prohibitive toxicity | Test Product | IMP | Central or Local |
| Post-induction Arm 2 | Experimental | Gemcitabine | Drug | Lyophilized Powder | 1000 mg | 1000 mg/m² | IV Infusion | On Days 1 and 8 of each 21-day cycle until disease progression or prohibitive toxicity | Test Product | IMP | Central or Local |

Abbreviations: AUC = area under the concentration-time curve; AxMP = auxiliary medicinal product; BID = twice daily; EEA = European Economic Area; IMP = investigational medicinal product; IV = intravenous; NIMP = non investigational 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/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study).

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

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Dose Preparation

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

Olaparib is a tablet for oral administration; no preparation is required. Olaparib will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

Carboplatin and gemcitabine should be prepared per local and institutional guidelines according to the approved product labels.

### 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

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to olaparib plus pembrolizumab study intervention (Arm 1) or carboplatin and gemcitabine plus pembrolizumab study intervention (Arm 2).

### 6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

1. Response (CR or PR vs SD) at Week 18 (-7 days) as assessed by BICR
2. PD-L1 positive (CPS ≥1) versus PD-L1 negative (CPS <1)
3. Genomic tumor status (BRCAm vs BRCAwt)

For the purpose of stratification, PD-L1 positive tumors are defined as those with a CPS of ≥1 [Kulangara, K., et al 2018].

Participants with a BRCA status that is considered not-determined due to a test failure or insufficient tumor tissue will be stratified as BRCAwt.

Participants with tumor scan result of non CR/non PD per BICR will be stratified as the same category of SD, and participants with tumor scan result of no evidence of disease per BICR will be stratified as the same category of CR or PR.

### 6.3.3 Tumor Marker Status Blinding

Participant-level tumor PD-L1 results and BRCA biomarker status will be masked in the database to the Sponsor (including clinical, statistical, statistical programming, and data management personnel), investigator, study site staff, and the participant throughout the study.

Access to the PD-L1 results and BRCA participant-level biomarker results will be limited to a designated team at the Sponsor who will be responsible for data review to ensure validity of results but who will have no other responsibilities associated with the study.

Unblinded BRCA participant-level biomarker results will be released to the investigator only after a request by the investigator and after consultation with the Sponsor with documented SCF if a participant is not eligible for randomization to post-induction therapy or following discontinuation from post-induction.

### 6.3.4 Study Intervention Blinding

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

## 6.4 Study Intervention Compliance

### 6.4.1 Olaparib Compliance

Participants will take their dose of olaparib BID without regard to food. Participants will self-administer olaparib except on Day 1 of each cycle, when the morning dose will be given at the study site clinic prior to the infusion of pembrolizumab. When Day 1 visits cannot be performed in the morning, participants should take their morning dose of olaparib at home prior to the clinic visit.

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. Olaparib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. All participants will be instructed to return their bottle 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.

Interruptions from the protocol-specified olaparib treatment plan for >28 consecutive days require consultation between the investigator and the Sponsor with documented SCF and written documentation of the collaborative decision on participant management.

### 6.4.2 Pembrolizumab, Carboplatin, and Gemcitabine Compliance

Administration of IV pembrolizumab, carboplatin, and gemcitabine will be performed by the investigator and/or study staff. Pembrolizumab and chemotherapy will be administered on an outpatient basis.

Interruptions from either the protocol-specified pembrolizumab or carboplatin/gemcitabine treatment plan require consultation between the investigator and the Sponsor with documented SCF and written documentation of the collaborative decision on participant management.

## 6.5 Concomitant Therapy

### 6.5.1 Acceptable Concomitant Medications

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 medications will be recorded on the electronic case report form (eCRF), including all prescription, over-the-counter (OTC), 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.

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 FDA-approved substrates can be found at the following website. This list is not all-inclusive. Any inducers or inhibitors not approved in the US will not appear in the list. The investigator should also refer to local approved product labels and use their best medical judgment.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

All concomitant medications received within 30 days before the first dose of induction study medication, while on study treatment, and up to 30 days after the last dose of study treatment should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

### 6.5.2 Prohibited Concomitant Medications

Medications specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during the ongoing study (ie, during screening, induction, and post-induction). If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. If discontinuation of study intervention is required, then the participant should continue in the study for assessment of disease status and survival. The investigator is to discuss prohibited medication/vaccination with the Sponsor. 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.

Additionally, the following restrictions apply to concomitant therapies. These therapies are not permitted during the study (exceptions are noted):

1. Antineoplastic systemic chemotherapy or biological therapy

2. Immunotherapy not specified in this protocol

3. Investigational agents other than those under study in this trial

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

   *Note:* Hormone replacement therapy is allowed.

5. Radiation therapy within 2 weeks prior to the start of study treatment for disease control

   *Note:* Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor with documented SCF (except during screening).

6. Herbal supplements

7. Live vaccines within 30 days prior to randomization, while participating in the study, and within 30 days of the last dose of study medication. Refer to Appendix 7 for country-specific requirements.

   - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, herpes zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccines.

   - Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines, and are not allowed.

   - *Note:* Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

8. Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology or as premedication for chemotherapy.

   *Note:* Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone (or equivalent) may be used during the study. Inhaled steroids for the management of asthma and prophylactic corticosteroids to avoid allergic reactions may be used during the study.

9. Prophylactic cytokines (eg, G-CSF or GM-CSF) should not be administered within 2 weeks prior to the first dose of induction study intervention or during the first cycle of induction but may be administered in subsequent cycles according to country-specific guidelines or local standard of care.

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

    *Note:* A current list of FDA-approved strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website. This list is not all-inclusive. Any inducers or inhibitors not approved in the US will not appear in the list. The investigator should also refer to local approved product labels and use their best medical judgment.

    https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

11. Any medication prohibited in combination with chemotherapy as described in the respective product labels for olaparib and pembrolizumab, and according to country-specific guidelines for gemcitabine and carboplatin.

There are no prohibited therapies during safety, disease status, or survival follow-up.

### 6.5.3 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.

> *Note*: If, after evaluation, the event is determined not to be related to olaparib or pembrolizumab, the investigator does not need to follow the treatment guidance.

Sponsor consultation with documented SCF is required prior to any planned surgical procedures.

#### 6.5.3.1 Rescue Medication and Supportive Care for Olaparib

Suggested supportive care measures for the management of AEs related to olaparib are outlined along with the dose modification guidelines in Section 6.6.1.

#### 6.5.3.2 Rescue Medication and Supportive Care for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.2, Table 8. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Refer to Table 8 in Section 6.6.2 for guidelines regarding dose modification and supportive care.

#### 6.5.3.3 Rescue Medication and Supportive Care for Chemotherapy (Carboplatin and Gemcitabine)

Suggested supportive care measures for the management of AEs related to carboplatin and gemcitabine are outlined along with the dose modification guidelines in Section 6.6.4.

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

The NCI CTCAE v5.0 must be used to grade the severity of AEs. If appropriate, the investigator may attribute each toxicity event to olaparib, pembrolizumab, carboplatin, or gemcitabine. Dose modifications for individual study treatment(s) must be based on the maximum toxicity experienced during the previous treatment cycle. Dose reductions for olaparib (Table 3, Table 6, and Table 7), and carboplatin or gemcitabine (Table 10) must be performed in a stepwise manner. Dose reductions for pembrolizumab are not allowed.

Dose modifications for the overlapping toxicities of pneumonitis and renal impairment for olaparib and pembrolizumab are described in Section 6.6.3.

If any of the study medications are reduced, interrupted, or discontinued, the other study medications may be continued as scheduled.

The reason for any dose reduction, interruption, discontinuation (including missed doses) should be captured on the appropriate eCRF.

### 6.6.1 Olaparib Dosing Modifications

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 olaparib should be discontinued. Once the dose has been reduced due to toxicity or tolerability issues, escalation is not permitted.

Table 3 Dose Modification Guidelines for Olaparib

| Study Treatment | Dose level 0 | Dose level -1 | Dose level -2 | Dose level -3 |
|---|---|---|---|---|
| Olaparib | 300 mg/BID | 250 mg/BID | 200 mg/BID | Discontinue |

#### 6.6.1.1 Management of Hematological Toxicities

Any olaparib-related hematological toxicity observed during post-induction could be managed by a brief interruption of study intervention or a dose reduction of olaparib (Table 4 and Table 5). Repeated interruptions, not exceeding 3 weeks (21 days) duration, are allowed as required. If the interruption is any longer, the Sponsor must be informed.

Table 4 Management of Olaparib-related Anemia

| Toxicity | NCI CTCAE Grade | Action Taken |
|---|---|---|
| Hemoglobin (Hb) | Grade 2 (<9.0 but ≥8 g/dL) | **First Occurrence:**<br>Give appropriate supportive treatment and investigate causality.<br>• Investigator judgement to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 3 weeks (21 days). Treatment can be restarted if Hb has recovered to >9.0 g/dL.<br>**Subsequent Recurrence:**<br>• **Hb <9.0 but ≥8 g/dL**: Investigator judgement to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for maximum of 3 weeks (21 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 3 weeks (21 days) until Hb improves to >9.0 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 (<8 g/dL) | Give appropriate supportive treatment (eg, transfusion) and investigate causality.<br>• Interrupt olaparib for a maximum of 3 weeks (21 days) until Hb improves to ≥9.0 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.

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 5 Management of Olaparib-related Neutropenia, Leukopenia, and Thrombocytopenia

| **Toxicity** | **NCI CTCAE Grade** | **Action Taken** |
|---|---|---|
| Neutropenia, Leukopenia, or Thrombocytopenia | Grades 1 or 2 | Investigator judgement to either continue olaparib or interrupt dosing for a maximum of 3 weeks (21 days). Give appropriate supportive treatment and investigate causality. |
| | Grades 3 or 4 | • Interrupt olaparib for a maximum of 3 weeks (21 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. |
| • 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.<br>• 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 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.<br>• Platelet transfusions, if indicated, should be done according to local guidelines.<br>• 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 related to olaparib, such as:

- ≥2 week interruption/delay in olaparib due to NCI CTCAE Grade 3 or worse anemia and/or the development of blood transfusion dependence
- ≥2 week interruption/delay in olaparib due to NCI CTCAE Grade 3 or worse neutropenia (absolute neutrophil count $<1 \times 10^9$/L)
- ≥2 week interruption/delay in olaparib 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 dose of olaparib has been interrupted for ≥3 weeks (≥21 days), the participant should be referred to a hematologist for further investigation. Bone marrow analysis and/or blood cytogenetic analysis should be considered according to local regulation and/or standard institutional

hematological practice. Olaparib should be discontinued if blood counts do not recover to NCI CTCAE Grade 1 or better within 3 weeks (21 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 of olaparib, not exceeding 3 weeks (21 days) duration, are allowed as required. If toxicity reoccurs following rechallenge with olaparib, and 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 olaparib.

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

##### 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 olaparib dosing is recommended and further diagnostic workup (including a high resolution computed tomography [CT] scan) should be performed to exclude pneumonitis.

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

Please refer to Table 8 as well, which outlines the Toxicity Management Guidelines for pembrolizumab as it can also cause pneumonitis.

##### 6.6.1.3.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib. 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 olaparib; 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 the first dose of olaparib, 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 6).

Please refer to Table 8, as well, which outlines the Toxicity Management Guidelines for pembrolizumab as it can also cause nephritis.

Table 6 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 51 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 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 olaparib within 4 weeks (28 days) due to intercurrent conditions not related to disease progression or toxicity, the investigator and the Sponsor should discuss the case, and the collaborative decision on participant management appropriately documented.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions, per drug accountability and participant feedback reconciliation, 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. Olaparib interruption is not required 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.

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

Strong or moderate CYP3A4 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 7. 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 7 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. | | |

### 6.6.2 Pembrolizumab Dosing Modifications

Pembrolizumab may be interrupted or discontinued. Dose reductions of pembrolizumab are not permitted.

#### 6.6.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

**Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab**

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 8.

If pembrolizumab is discontinued during the induction period, all study treatment must be discontinued. If pembrolizumab is discontinued during post-induction, dosing with either olaparib or chemotherapy (carboplatin and gemcitabine) may continue if the criteria outlined in Section 6.6.1 and Section 6.6.4 have not been met.

Table 8 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper<br>• Add prophylactic antibiotics for opportunistic infections | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment |
| | Recurrent Grade 2, Grade 3 or 4 | Permanently discontinue | | |
| Diarrhea/Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)<br>• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| AST or ALT Elevation or Increased Bilirubin | Grade 2 [a] | Withhold | • Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable) |
| | Grade 3 [b] or 4 [c] | Permanently discontinue | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | |
| T1DM or Hyperglycemia | New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold [d] | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer antihyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Hypothyroidism | Grade 2, 3 or 4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care | • Monitor for signs and symptoms of thyroid disorders |
| Nephritis: grading according to increased creatinine or acute kidney injury | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Neurological Toxicities | Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0) | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 2, 3 or 4 | Permanently discontinue | | |
| Exfoliative Dermatologic Conditions | Suspected SJS, TEN, or DRESS | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| All Other irAEs | Persistent Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the event [e] | | |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

**Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.**

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

#### 6.6.2.2 Management of Infusion Reactions

Pembrolizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reactions are provided in Table 9.

Table 9 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.** | Participant may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab with:<br>diphenhydramine 50 mg orally (PO) (or equivalent dose of antihistamine).<br>acetaminophen 500-1000 mg PO (or equivalent dose of analgesic). |

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Participant is permanently discontinued from further study drug treatment.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov | | |

#### 6.6.2.3 Interruptions for Intercurrent Non-Toxicity-related Events

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

### 6.6.3 Management of Overlapping Toxicities of Olaparib and Pembrolizumab

Both olaparib and pembrolizumab treatment may be associated with the development of pneumonitis and renal toxicity.

Treatment with olaparib must be held for **any grade** of pneumonitis. Treatment with pembrolizumab must be held for pneumonitis ≥Grade 2 (Table 8). When the pneumonitis resolves to <Grade 2, then pembrolizumab may be resumed as per the guidelines in Table 8. Olaparib may be restarted after pneumonitis has **completely** resolved. Pembrolizumab must be discontinued for recurrent Grade 2 pneumonitis (Section 7.1).

For renal dysfunction, follow the dose modification guidelines provided in Table 6 (olaparib) and Table 8 (pembrolizumab). A kidney biopsy is strongly recommended to help to determine etiology of renal dysfunction.

### 6.6.4 Chemotherapy (Carboplatin and Gemcitabine) Dosing Modifications

Carboplatin and gemcitabine may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels and local regulations. Missed doses of carboplatin and gemcitabine should be skipped if not given within the allowed window of ±3 days.

Carboplatin should be interrupted in participants who experience a hypersensitivity reaction. Participants may be desensitized to carboplatin per country guidelines and then restarted on carboplatin at the discretion of the investigator. Other study interventions may continue while the participant undergoes carboplatin desensitization.

Suggested dose modifications for chemotherapy (carboplatin and gemcitabine) are detailed in Table 10.

Table 10 Dose Modification Guidelines for Chemotherapy (Carboplatin and Gemcitabine)

| Study Treatment | Dose level 0 | Dose level - 1 | Dose level - 2 | Dose level - 3 |
|---|---|---|---|---|
| Gemcitabine | 1000 mg/m$^2$ | ~20% reduction | ~20% reduction | Discontinue |
| Carboplatin | AUC 2 | AUC 1.5 | AUC 1 | Discontinue |

### 6.6.5 Management of Overlapping Toxicities of Gemcitabine and Pembrolizumab

Both gemcitabine and pembrolizumab treatment may be associated with the development of pneumonitis.

Gemcitabine may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels and local regulations (Table 10). Treatment with pembrolizumab must be held for pneumonitis ≥Grade 2 (Table 8). When the pneumonitis resolves to <Grade 2, then pembrolizumab may be resumed as per the guidelines in Table 8. Pembrolizumab must be discontinued for recurrent Grade 2 pneumonitis (Table 8).

## 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 (name, strength, or potency) 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 of controlled substances. 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.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

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 be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.12.3. unless the participant has withdrawn from the study (Section 7.2).

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 and Section 8.12.3.

A participant must be discontinued from all study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- Radiographic disease progression per RECIST 1.1 as verified by BICR.

  *Note:* As of Amendment 03, central tumor response assessments will no longer be performed. However, participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) and deriving clinical benefit who are continuing to receive study treatment, will be assessed by investigator/site/local radiology review for disease progression per SOC schedule.

  *Note:* During post-induction, an exception to continue study treatment beyond any confirmed PD per iRECIST (iCPD) may be considered after Sponsor communication with documented SCF and obtaining informed consent addendum (Section 8.2.2.6).

  As of Amendment 03, the note above regarding iRECIST is no longer applicable but retained for reference. Treatment beyond progression by iRECIST will no longer be authorized. Participants who have experienced first disease progression by RECIST 1.1 in post-induction, who are continuing study treatment due to deriving clinical benefit and are being followed using the iRECIST criteria at the time of Amendment 03, may continue to receive study treatment only until the next confirmed disease progression (iCPD) by investigator/site/local radiology review. No treatment beyond iCPD as determined by investigator/site/local radiology review will be authorized.

- Active systemic treatment is required for any progression or recurrence of any malignancy (excluding the cancer under treatment) or for any occurrence of another malignancy.

- 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 serum pregnancy test.

- Bone marrow findings consistent with MDS or AML.

- The participant is permanently discontinued from both carboplatin and gemcitabine during induction due to toxicity.

- The participant is permanently discontinued from pembrolizumab during induction due to toxicity.

- The participant misses more than 6 consecutive weeks of study interventions due to toxicity or any other cause before Cycle 1 Day 1 of post-induction.

Participants should discontinue specific study interventions when any of the following occurs:

- Unacceptable AEs related to the specific study intervention.

- Pembrolizumab must be discontinued for any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.2.

- The participant interrupts olaparib for more than 28 consecutive days without Sponsor consultation with documented SCF.

  *Note:* Participants may remain on study intervention other than olaparib if appropriate (ie, pembrolizumab).

- The participant interrupts pembrolizumab administration for more than 12 consecutive weeks for an AE/toxicity or for more than 3 weeks for administrative reasons without Sponsor consultation with documented SCF.

  *Note:* Participants may remain on study intervention other than pembrolizumab if appropriate (ie, olaparib, carboplatin, gemcitabine).

- The participant interrupts chemotherapy (carboplatin or gemcitabine) for more than 6 consecutive weeks without Sponsor consultation with documented SCF.

  *Note:* Participants may remain on study intervention other than carboplatin (ie, pembrolizumab or gemcitabine) or other than gemcitabine (ie, pembrolizumab or carboplatin).

- Completion of 35 administrations (approximately 2 years) of pembrolizumab, inclusive of induction and post-induction administrations. Participants may stay on study intervention other than pembrolizumab if appropriate (ie, olaparib, carboplatin, gemcitabine).

  Participants may be eligible for an additional 17 administrations (approximately 1 year) as outlined in Section 8.12.6. As of Amendment 03, Second Course Retreatment is no longer an option for participants.

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

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

## 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 intervention 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. Participants who wish to withdraw from treatment and/or imaging may retain consent specifically for the non-invasive survival follow-up portion of the study. All participants are encouraged to be followed for survival (vital) status until death or the closure of the study, if they consent to do so. 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

- Study procedures and their timing are summarized in the SoA.

- 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 Trial 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.

The maximum amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual.

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. Refer to Appendix 7 for country-specific requirements.

#### 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 informed consent form 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 Institutional Review Board/Independent Ethics Committee's (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.

Specifics about the study and the study population are to be included in the study informed consent form.

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 future biomedical research 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 future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

### 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 treatment/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

Demographic information and 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. Any autoimmune disorders should be recorded regardless of the onset date.

Details regarding the disease under treatment in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of Screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention during screening.

#### 8.1.4.1 Breast Cancer History

The investigator or qualified designee will obtain prior and current details regarding the participant's TNBC, including investigator-determined tumor size per RECIST 1.1.

#### 8.1.4.2 Prior Treatments for Breast Cancer

The investigator or qualified designee will review all prior treatment for the participant's breast cancer diagnosis, including neoadjuvant/adjuvant treatments, other systemic treatments, radiation, and surgeries.

#### 8.1.4.3 Childbearing Potential

A participant's childbearing potential must be assessed, and the appropriate types and use of contraception should be discussed, as detailed in Appendix 5.

### 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 30 days before the first dose of induction study medication.

Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

#### 8.1.5.2 Concomitant Medications

The investigator or qualified designee will review and record at each study visit all concomitant medication used during the study, including medications taken throughout induction, pre-randomization, and post-induction, and at treatment discontinuation and the 30-day safety follow-up.

All treatments administered for AEs, reportable SAEs, and events of clinical interest (ECI)s (Section 8.4) should be recorded.

Washout requirements for CYP3A4 inhibitors/inducers taken during induction should be completed before the first dose of post-induction treatment (Section 5.2).

#### 8.1.5.3 Subsequent Anticancer Therapy

Details of subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected during disease status and survival follow-up (Sections 8.12.4.2 and 8.12.4.3). Reasons for starting subsequent anticancer therapies, including access to other PD-1/PD-L1 inhibitors, PARP inhibitors, or investigational drugs will be collected.

> *Note:* The mandatory Safety Follow-up visit should be conducted approximately 30 days after the last dose of study treatment or before the first dose of any new anticancer therapy, whichever comes first. Once a new anticancer therapy has been initiated, the participant will move into survival follow-up.

### 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 first 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 8.12.1. “Re-screening” in this protocol refers to a participant who could not complete screening tests within the specified 28-day period.

### 8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization 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/randomization number.

Only those participants who have completed induction and meet the eligibility requirements for post-induction, as detailed in Section 5, will be randomly assigned to either Arm 1 or Arm 2 of treatment, as shown in the study schema in Section 1.2.

The randomization number will be assigned during pre-randomization after the participant's eligibility to enter post-induction has been determined. Administration of Cycle 1, Day 1 of post-induction study treatment may occur on the same day as randomization or no more than 3 days after randomization.

### 8.1.8 Study Intervention Administration

Study treatment will be administered in 21-day cycles. Pembrolizumab will be administered by the investigator and/or study staff according to the specifications in the Pharmacy Manual. Carboplatin and gemcitabine will be administered per the approved product labels and institutional guidelines. Participants will self-administer olaparib according to instructions provided by the investigator and/or study staff.

#### 8.1.8.1 Timing of Dose Administration

On Day 1 and Day 8 of each 21-day cycle, study treatment will be administered by qualified study staff after all procedures and assessments have been completed. Study treatment can be administered within ±3 days of the targeted Day 1 or Day 8 of each cycle. Treatment doses of olaparib, carboplatin, or gemcitabine may be reduced, as detailed in Section 6.6. Dose reductions of pembrolizumab are not allowed.

##### 8.1.8.1.1 Induction

Participants will receive pembrolizumab + gemcitabine + carboplatin for six, 21-day cycles as follows:

<u>Day 1</u>

Pembrolizumab 200 mg + Gemcitabine 1000 mg/m$^2$ + Carboplatin AUC 2

<u>Day 8</u>

Gemcitabine 1000 mg/m$^2$ + Carboplatin AUC 2

Depending on which individual components of the regimen are being administered during any given cycle, study treatment should be administered during induction in the following order:

1) Pembrolizumab

2) Gemcitabine

3) Carboplatin

*Note:* participants should not be dosed after Week 18 (-7 days) scan (see Section 8.2.2.2.1) during induction.

#### 8.1.8.1.1.1 Pembrolizumab

Pembrolizumab will be administered during induction as a 30-minute IV infusion on Day 1 of each 21-day cycle prior to gemcitabine and carboplatin. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 minutes/+10 minutes).

Dose modifications allowed for pembrolizumab are provided in Section 6.6.2.

#### 8.1.8.1.1.2 Gemcitabine

Gemcitabine will be administered during induction as an IV infusion over 30 minutes on Day 1 and Day 8 of each 21-day cycle after pembrolizumab and prior to carboplatin.

Dose modifications allowed for gemcitabine are provided in Section 6.6.4.

#### 8.1.8.1.1.3 Carboplatin

Carboplatin will be administered during induction as an IV infusion given over no less than 15 minutes on Day 1 and Day 8 of each 21-day cycle after gemcitabine. The dose of carboplatin should be calculated using the Calvert formula as shown below or per country or local/institutional guidelines:

Calvert Formula:

$$\text{Total Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25)$$

Dose modifications allowed for carboplatin are provided in Section 6.6.4.

Participants must receive up to 6 cycles but not less than 4 cycles of induction treatment and meet the eligibility requirements as described in Section 5 to be eligible for randomization into post-induction.

#### 8.1.8.1.2 Post-induction

Participants who meet the eligibility requirements for post-induction will be randomized on a 1:1 basis to 1 of 2 treatment arms to receive continued pembrolizumab with either olaparib as a continuous daily dose or continued carboplatin and gemcitabine. The first dose of post-induction study treatment should be administered within 3 days of randomization. All doses of post-induction study treatment should be administered in 21-day cycles as follows:

**Arm 1**

Day 1

Olaparib 300 mg BID orally + Pembrolizumab 200 mg

Days 2 though 21

Olaparib 300 mg BID orally daily

**Note:** Participants who are randomized to Arm 1 (olaparib + pembrolizumab) of post-induction will not need to visit the study site at Day 8 of each cycle.

**Arm 2**

Day 1

Pembrolizumab 200 mg + Gemcitabine 1000 mg/$m^2$ + Carboplatin AUC 2

Day 8

Gemcitabine 1000 mg/$m^2$ + Carboplatin AUC 2

Depending on which individual components of the regimen are being administered during any given cycle, study treatment should be administered in the following order:

**Arm 1**

1) Olaparib
2) Pembrolizumab

**Arm 2**

1) Pembrolizumab
2) Gemcitabine
3) Carboplatin

#### 8.1.8.1.2.1 Olaparib

Participants in Arm 1 will self-administer, under observation by qualified study site staff, the planned dose of olaparib on Day 1 of each 21-day cycle prior to administration of pembrolizumab. The subsequent daily doses of olaparib will be self-administered on the remaining days of each respective cycle. When Day 1 visits cannot be performed in the morning, participants should take their morning dose of olaparib at home prior to the clinic visit.

Participants should be given clear instructions on how and when to take their study treatment. 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 the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for any reason (eg, 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.

The 300-mg dose of olaparib should be made up of 2 × 150 mg tablets. 100 mg tablets are provided for dose reduction. Dose modifications allowed for olaparib are provided in Section 6.6.1.

#### 8.1.8.1.2.2 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle after olaparib is administered to participants in Arm 1 and prior to gemcitabine and carboplatin to participants in Arm 2. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 minutes/+10 minutes).

Dose modifications allowed for pembrolizumab are provided in Section 6.6.2.

#### 8.1.8.1.2.3 Gemcitabine

Gemcitabine will be administered as an IV infusion over 30 minutes on Day 1 and Day 8 of each 21-day cycle after pembrolizumab and prior to carboplatin in participants in Arm 2.

Dose modifications allowed for gemcitabine are provided in Section 6.6.4.

#### 8.1.8.1.2.4 Carboplatin

Carboplatin will be administered as an IV infusion given over no less than 15 minutes on Day 1 and Day 8 of each 21-day cycle after gemcitabine in participants. The dose of

carboplatin should be calculated using the Calvert formula as shown below or per country or local/institutional guidelines:

Calvert Formula:

$$\text{Total Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25)$$

Dose modifications allowed for carboplatin are provided in Section 6.6.4.

### 8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the post-induction treatment period should be encouraged to continue to be followed for all remaining study visits . Participants who discontinue study intervention prior to completion of induction should be followed for safety. Additional details regarding procedures to be followed after discontinuation from study treatment are outlined in Section 1.3 and in Section 8.12.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit 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 Blinding of Study Intervention

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

### 8.1.11 Blinding of Tumor Marker Status

Participant-level tumor PD-L1 results and BRCA biomarker status will be blinded in the database to the Sponsor (including clinical, statistical, statistical programming, and data management personnel), investigator, study site staff, and the participant throughout the study.

Access to the PD-L1 results and BRCA participant-level biomarker results will be limited to a designated team at the Sponsor (as further detailed in Section 9.2) who will be responsible for data review to ensure validity of results but who will have no other responsibilities associated with the study.

If requested by the investigator and after consultation with the Sponsor with documented SCF, unblinded BRCA participant-level biomarker results will be provided if a participant is not eligible for randomization to post-induction therapy or following discontinuation from post-induction treatment.

### 8.1.12 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.

### 8.1.13 Tumor Tissue Collection

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

During screening, participants are required to provide recently or newly obtained tumor tissue from an excisional or core biopsy (fine needle aspiration is not adequate) of a locally recurrent inoperable or metastatic tumor lesion. The tumor tissue will be used for central determination of TNBC, PD-L1, and BRCA status. Archival tissue samples (more than 3 years old) will be allowed after consultation with the Sponsor with documented SCF. Tumor tissue samples must not be obtained from bone sites. Brain tissue is acceptable for TNBC and PD-L1, but not for BRCA testing.

The results of central testing to assess BRCA status will yield information about other genes and will support exploratory translational science objectives.

> *Note:* Newly obtained tissue may be obtained at any time prior to the administration of systemic cytotoxic treatment for the treatment of metastatic TNBC tumors. Formalin-fixed paraffin-embedded (FFPE) tumor blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date the

slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual). More than one tissue sample may be submitted after Sponsor communication, as needed.

An optional tumor biopsy sample may be collected at the end of treatment (ie, either induction or post-induction) in participants who provide optional biopsy consent (this consent may be obtained at any time during the study).

## 8.2 Efficacy Assessments

### 8.2.1 Tumor Markers

Tumor markers for confirmation of TNBC, and determination of PD-L1 and BRCA status will be performed by a central vendor using commercially validated assays on tumor tissue collected prior to study enrollment (Section 8.1.13).

- ER, PGR, and HER2 to confirm TNBC will be determined according to the most recent American Society of Clinical Oncologists (ASCO)/College of American Pathologists (CAP) guidelines [Hammond, M. E., et al 2010][Wolff, A. C., et al 2018].

- PD-L1 testing will confirm PD-L1 positive tumors as defined by CPS ≥1 and CPS ≥10.

- Myriad Genetics Inc.'s myChoice® CDx Plus assay (BRCA1/BRCA2) testing will confirm BRCAm and BRCAwt status for stratification before randomization.

- The myChoice® CDx Plus assay will simultaneously interrogate other genomic alterations (such as HRR, HRD, TMB, MSI), which will be analyzed and reported retrospectively (HRR testing will confirm HRD status) for exploratory purposes.

Tumor biomarkers cancer antigen (CA) 15-3, carcinoembryonic antigen (CEA), and CA 27.29 will be determined by the local laboratory, or central vendor if locally not available (see Laboratory Manual) using commercially validated assays on blood samples obtained during screening and at each scheduled tumor scan (or corresponding study visit) during induction, post-induction, and disease status follow-up.

### 8.2.2 Tumor Scans and Assessment of Disease

**As of Amendment 03:** Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The subsections below are retained for reference.

However, for participants who are still receiving study intervention (in post-induction or Second Course Retreatment phase) and deriving clinical benefit who are continuing on study treatment until criteria for discontinuation are met, local tumor imaging should continue per SOC schedule.

Throughout this section, the term "scan" refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as computed tomography [CT] or magnetic resonance imaging [MRI]), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. For each participant, the same scan technique and consistent use of contrast should be used throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans. For scans of the chest, abdomen, and pelvis, CT with IV contrast is strongly preferred. For scans of the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated and/or when mandated by local practice.

Brain scans (MRI is preferred) are required at screening and during the study (at the same schedule as other scans for evaluation of disease status) for participants with known brain metastases and those with worsening and/or new neurological symptoms. Brain imaging CT scans will be acceptable if MRI is medically contraindicated.

At screening, if a participant has a history of bone metastases and/or has new bone pain or other symptoms/signs suggestive of bone metastases, a bone scan is required, and if the bone scan is negative, a plain X-ray is also required. During the study, a bone scan (and plain X-ray, if participant has signs/symptoms of bone metastases and bone scan is negative) will be performed if clinically indicated for evaluation of known, worsening and/or new bone pain or other symptoms/signs suggestive of bone metastases OR if the site believes a participant has attained a CR. Any supplemental scans done to support a positive or negative bone scan should be submitted for BICR.

Guidance and preference for imaging modalities as well as the process for scan collection and transmission for BICR can be found in the Site Imaging Manual (SIM).

Measurable disease for participant eligibility will be determined based on RECIST 1.1 (Section 8.2.2.5), as assessed by site/local radiology review. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol follows a maximum of 10 target lesions in total and 5 per organ. While on study, scheduled scans should be submitted for BICR. While on study, any unscheduled scans obtained for assessment of disease progression or other reasons, but capturing radiologic progression or used in response assessments, should also be submitted for BICR.

#### 8.2.2.1 Tumor Scans During Screening

##### 8.2.2.1.1 Scans of Target Lesions

Baseline tumor scans must be performed during the 28-day screening window to confirm measurable disease based on RECIST 1.1, as assessed by site/local radiology review. Baseline tumor scans should be submitted for retrospective BICR.

Scans performed as part of routine clinical management are acceptable for use as screening tumor scans, if they are of diagnostic quality, were performed within 28 days prior to Cycle 1 Day 1 of induction, and were submitted for retrospective BICR.

#### 8.2.2.1.2 Scans of Brain Metastases

Participants with previously treated brain metastasis(es) may be eligible for study participation provided metastatic disease to the brain is radiographically stable, ie, without site/investigator-assessed radiologic evidence of progression for at least 4 weeks prior to the screening brain scan. A brain scan must be obtained during screening (ie, within 28 days of Cycle 1, Day 1 of induction) and must be >4 weeks after the previous post-treatment brain scan. Any neurologic symptoms must have returned to baseline and steroids must not have been used for management of symptoms related to brain metastases for at least 14 days prior to the first dose of induction study intervention. Participants with carcinomatous meningitis are excluded regardless of clinical stability.

### 8.2.2.2 Tumor Scans During Induction

#### 8.2.2.2.1 Timing of Tumor Scans

Tumor scans, including brain scans if required, conducted during induction should be performed every 6 weeks; ie, at Week 6 (42+7 days), Week 12 (84±7 days), and Week 18 (126-7 days). Timing of on-study tumor scans is relative to Cycle 1, Day 1 during induction. Scan timing should follow **calendar days** from Cycle 1, Day 1 and should not be adjusted for any dose modifications.

#### 8.2.2.2.2 Response Evaluation

Participants with tumor responses during induction of CR, PR, or SD at Week 18 (-7 days), according to RECIST 1.1 as determined by expedited BICR, are eligible regarding tumor response for randomization to post-induction. The site and Sponsor will be notified of the CR, PR, or SD response via e-mail, and randomization into 1 of the 2 arms of study treatment will be performed no more than 3 days prior to Cycle 1, Day 1 of post-induction.

The last induction scan at Week 18 (-7 days) will also be the baseline for assessment of post-induction tumor responses. A new assessment for any target or non-target lesions should be made using these images. Presence of measurable disease per RECIST 1.1 is not required at post-induction baseline.

#### 8.2.2.2.3 Determination of Radiographic Progression

Participants with radiographically documented disease progression as determined by BICR at any time point during induction will be discontinued from study intervention (Section 8.2.2.4).

Tumor response assessments by iRECIST criteria will not be used during induction. If PD seen by the site during induction is not verified by BICR, disease assessments should still be

performed by the site/investigator using RECIST 1.1 if the participant is stable and continues treatment at treating physician's discretion.

#### 8.2.2.3 Tumor Scans During Post-induction

##### 8.2.2.3.1 Timing of Tumor Scans

After eligible participants are randomly assigned to and begin post-induction study interventions, subsequent tumor scans will be performed at Week 6 (42+7 days), and then every 6 weeks (±7 days) for the first year. In the second year of post-induction, scans move to every 12 weeks (±7 days). Timing of tumor scans is relative to randomization date of post-induction. Scan timing should follow **calendar days** from the randomization date and should not be adjusted for any dose modifications.

##### 8.2.2.3.2 Response Evaluation

Study treatment may be continued into post-induction for participants with centrally verified stable disease or objective response (CR or PR) according to RECIST 1.1 during induction.

> *Note:* During the post-induction treatment, response does not need to be verified in an expedited manner by BICR, but will be assessed locally. Only disease progression, as assessed by the site/local radiology review, is verified in an expedited manner by BICR during post-induction.

##### 8.2.2.3.3 Determination of Radiographic Progression

**As of Amendment 03:** Central tumor response assessments will be discontinued. Participants with radiographically documented disease progression during post-induction as assessed by investigator/site/local radiology review according to RECIST 1.1 will be discontinued from study intervention. The section below is retained for reference.

Those participants with radiographically documented disease progression during post-induction, as assessed by site/local radiology review according to RECIST 1.1, and verified by expedited BICR, will be discontinued from study intervention (Section 8.2.2.4).

If the investigator considers the participant has disease progression per RECIST 1.1 criteria, but elects to implement iRECIST, study intervention may continue in clinically stable participants, and the investigator will assess for confirmation of progression by iRECIST at subsequent time points (Section 8.2.2.6 and Figure 3). Scans should continue to be submitted to the iCRO for potential retrospective review. If the investigator plans to continue study intervention beyond BICR-verified disease progression, Sponsor communication with documented SCF and an informed consent addendum are required.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status

- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Participants being assessed under iRECIST during post-induction who have confirmed progression or unconfirmed progression with clinical instability will discontinue study interventions as described in Section 8.2.2.4.

#### 8.2.2.4 Discontinuation and Follow-up Tumor Scans

In participants who discontinue all study interventions after verification of disease progression per expedited BICR during induction or post-induction, no further tumor scans are required, and the participant will enter safety follow-up as described in Section 8.12.4.1 and then survival follow-up as described in Section 8.12.4.3. It is preferred that disease progression is verified by BICR before discontinuation of study intervention.

In participants who discontinue all study interventions during post-induction for reasons other than radiographic disease progression, the participants will enter safety follow-up (Section 8.12.4.1), and every effort should be made to continue monitoring of disease status (Section 8.12.4.2). Scans should be performed at the same schedule as before treatment discontinuation depending on time elapsed since the start of study treatment and be submitted for BICR until (1) the start of new anticancer therapy, (2) disease progression as verified by BICR based on RECIST 1.1, (3) pregnancy, (4) death, (5) complete documented withdrawal of consent to study participation, or (6) the end of the study, whichever occurs first.

Participants who are clinically stable and treated past radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

#### 8.2.2.5 RECIST 1.1 Assessment of Disease During Induction and Post-induction

Participant eligibility to the induction phase will be assessed by site/local radiology review based on RECIST 1.1. Participant eligibility to the post-induction phase and assessment of efficacy measures (other than OS), as described in the primary and secondary study objectives, will be performed by BICR based on RECIST 1.1. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

**During the induction phase**, the site and Sponsor will be notified by the iCRO of first radiologic evidence of disease progression as determined by expedited BICR based on RECIST 1.1.

**During the post-induction phase**, upon site/local radiology-assessed disease progression, the indicative scans are to be submitted immediately to the iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If, during post-induction, site/local radiology-assessed **disease progression is not verified by BICR**, the process continues as follows:

- If participant is **clinically stable**, continue study intervention per protocol
  - Continue scans per protocol schedule
  - Send scans to iCRO
  - Continue local assessment by iRECIST
  - Do not change investigator assessment of progression
  - If subsequent scan(s) indicate progression, request verification from iCRO
- If the participant is **not clinically stable**, best medical practice is to be applied. Communication with the Sponsor with documented SCF are strongly recommended to document clinical status instability.

**Before stopping study intervention or imaging or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor with documented SCF is required.**

If, during post-induction, site/local radiology-assessed **disease progression is verified by BICR**, the process continues as follows:

- Investigator judgement will determine action.
- If the participant is clinically stable and study intervention is to continue, communication with the Sponsor with documented SCF and an informed consent addendum are required.
- Obtain scans locally per original protocol schedule and continue local assessment by iRECIST
- Continue to send scans to iCRO for potential retrospective review until one of the criteria for discontinuing imaging listed in Section 8.2.2.4 are met

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - Unacceptable toxicity
  - Clinical signs or symptoms indicating clinically significant disease progression
  - Decline in performance status

- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

#### 8.2.2.6 iRECIST Assessment of Disease During Post-induction

**As of Amendment 03: iRECIST assessment of disease is no longer applicable for participants who have an initial PD evaluated by RECIST 1:1.** Participants who are currently being assessed by iRECIST may continue to be assessed per iRECIST until iCPD is determined by investigator/site/local radiology review. The section below is retained for reference.

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator during post-induction to assess tumor response and progression and to make treatment decisions [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 9. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. These data will be captured in the clinical database.

- If participant is clinically stable (refer to Section 8.2.2.5), continue study intervention per protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST
  - Continue to send scans to iCRO for potential retrospective review
- If the participant is not clinically stable, best medical practice is to be applied.

Any participant being assessed under iRECIST who is clinically unstable should be discontinued from study treatment and is not required to have repeat tumor scans for confirmation of progression by iRECIST.

#### 8.2.2.7 Tumor Scan Flow for Determination of Disease Progression

Figure 2 and Figure 3 illustrate the tumor scan flow algorithm for RECIST 1.1 and iRECIST, respectively, for determination and verification of disease progression during post-induction in clinically stable participants.

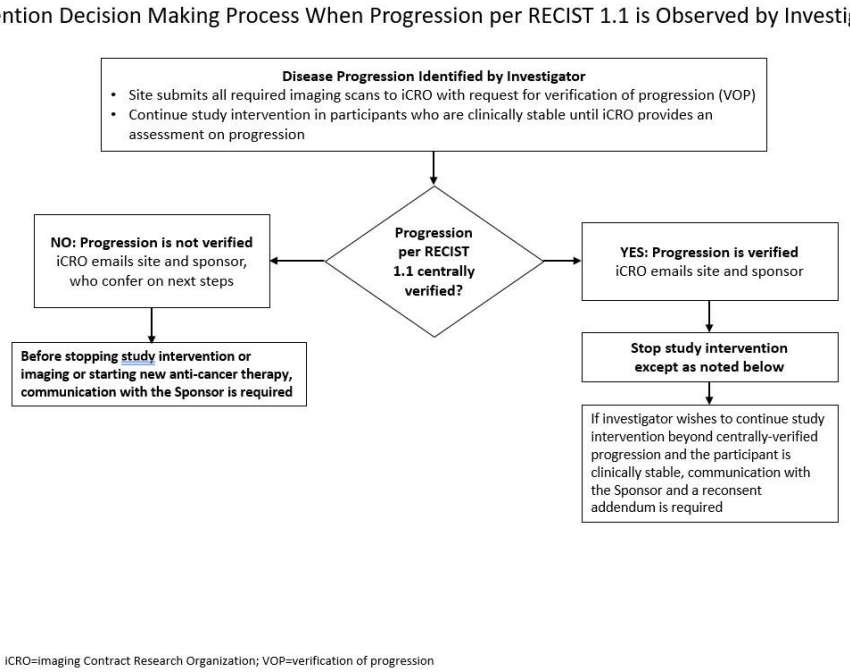


Figure 2 RECIST 1.1 Assessment During Post-induction for Clinically Stable Participants After First Radiologic Evidence of Disease Progression as Assessed by the Investigator

*Note:* Centrally verified refers to BICR.

*Note:* Documented Sponsor Consultation Form is required as part of Sponsor communication.

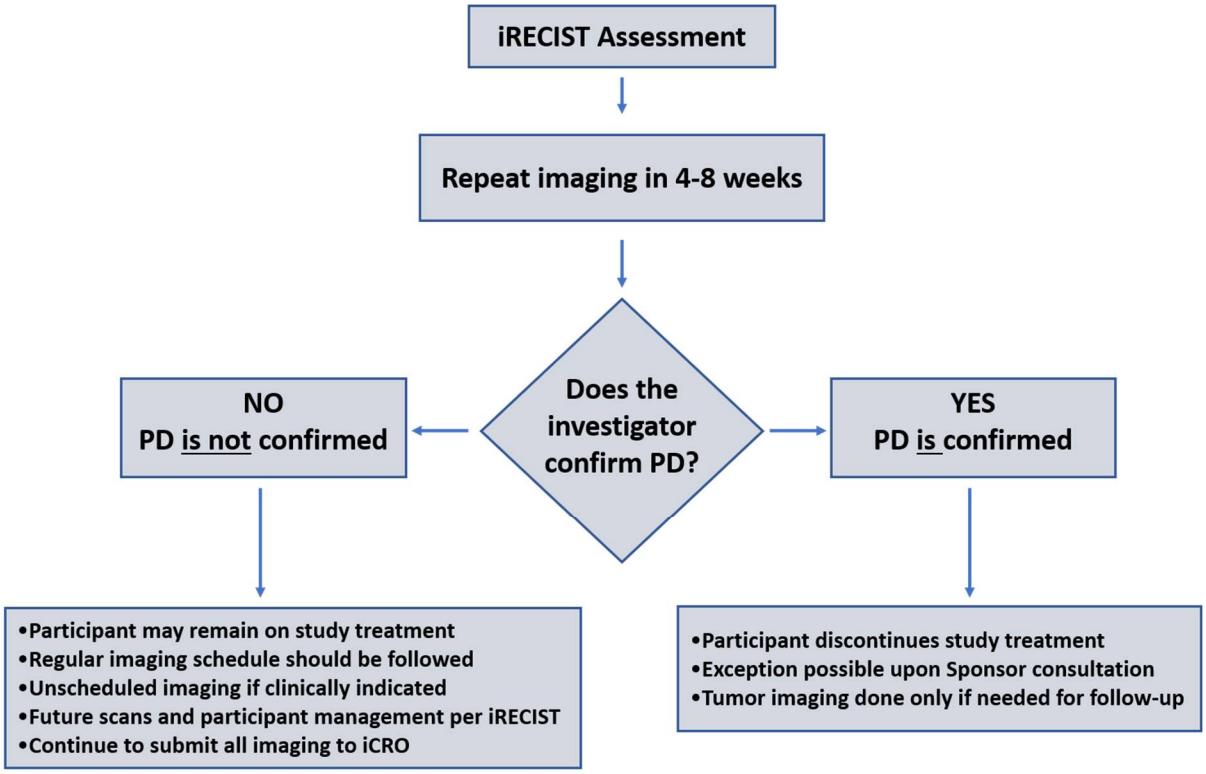


Figure 3 iRECIST Assessment During Post-induction for Clinically Stable Participants

### 8.2.3 Patient-Reported Outcomes

**As of Amendment 03: PROs and Quality of Life assessments will be discontinued.** The subsections below are retained for reference.

The PROs questionnaires performed is this study are the EORTC QLQ-C30, the breast cancer module EORTC QLQ-BR23, and the EQ-5D-5L™, and will be administered by trained study site personnel and completed electronically by the participants themselves.

PROs should be completed within 3 days prior to visit dose administration. It is strongly recommended that PROs are administered prior to AE evaluations and any discussions of disease status with the participant. The PROs are completed in the following order: EORTC QLQ-C30, then the EORTC QLQ-BR23, and then last the EQ-5D-5L at the time points specified in the SoAs (Section 1.3) and as briefly summarized in Section 8.2.3.1 and Section 8.2.3.2.

Site staff must not read, administer, or complete the PRO questionnaires on behalf of the participant. If the participant is unable to read the questionnaire (eg, is blind or illiterate), that participant may still participate in the study, but is exempt from completing PRO questionnaires. Participants exempt in this regard should be flagged appropriately by the site staff.

#### 8.2.3.1 Timing During Induction

The PROs are assessed during induction prior to AE evaluations, the administration of study treatments, and any discussions of disease status with the participant as follows:

- On Day 1 of Cycles 1, 4, 5, and 6
- At the Treatment Discontinuation Visit [a]
- At the 30-day Safety Follow-up Visit [a]

[a] If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, PROs do not need to be repeated at the time of the mandatory Safety Follow-up Visit.

#### 8.2.3.2 Timing During Post-induction

The PROs are assessed during post-induction prior to AE evaluations, the administration of study treatments, and any discussions of disease status with the participant as follows:

- On Day 1 of each of the first 8 cycles
- After the first 8 cycles,
  - During Year 1 of post-induction, every second cycle (every 6 weeks) until end of treatment, disease progression as determined by BICR, or death, whichever occurs first (Cycles 10, 12, 14, 16)
  - Starting in Year 2 of post-induction, every fourth cycle (every 12 weeks) until end of treatment, disease progression as determined by BICR, or death, whichever occurs first (Cycles 18, 22, 26, 30, etc)
- At the Treatment Discontinuation Visit [a]
- At 30-day Safety Follow-up Visit [a]

[a] If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, PROs do not need to be repeated at the time of the mandatory Safety Follow-up Visit.

### 8.2.4 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (Appendix 8) at screening and at pre-randomization; within 7 days prior to the administration of Cycle 1, Day 1 study treatment of induction and post-induction; prior to administration of study treatment on Day 1 of each subsequent treatment cycle during induction and post-induction; and at treatment discontinuation and the safety follow-up, as specified in Section 1.3.

## 8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided throughout Section 8.3. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual. Planned time points for all safety assessments are provided in the SoA.

### 8.3.1 Physical Examinations

A complete physical examination that includes a neurologic examination will be conducted during screening, pre-randomization, and at treatment discontinuation by an investigator or a medically qualified designee (consistent with local requirements), as per institutional standards.

A brief directed physical examination that includes a neurologic examination will be conducted before study treatment administration at all on-treatment study visits by an investigator or a medically qualified designee (consistent with local requirements) per institutional standards.

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

### 8.3.2 Vital Signs

Vital signs will be performed by the investigator or a medically qualified designee during screening and pre-randomization, at each study visit prior to any blood collection and the administration of each dose of study treatment, at treatment discontinuation, and at the safety follow-up.

- Vital signs will include temperature, systolic and diastolic blood pressures, pulse, and respiratory rate. Vital signs should be measured within 3 days before each dosing day.

- Height will be measured during screening only, and weight will be measured and recorded at screening and at all subsequent study visits through the safety follow-up. Weight should be measured within 3 days before each dosing day.

### 8.3.3 Electrocardiograms

A single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals and will be reviewed by an investigator or a medically qualified designee (consistent with local requirements) during screening (with clinically significant abnormal findings recorded as medical history), and at pre-randomization and treatment discontinuation. Additional ECG evaluations may be performed as 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 SoAs in Section 1.3.

- If laboratory values from nonprotocol 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.

## 8.4 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 events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

The investigator remains 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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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.

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

All AEs meeting serious criteria, from the time of intervention allocation/randomization 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, must be reported by the investigator.

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.

All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

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 related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs 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 he/she 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 11.

Table 11 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

| **Type of Event** | **Reporting Time Period: Consent to Randomization/ Allocation** | **Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period** | **Reporting Time Period: After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to Sponsor:** |
|---|---|---|---|---|
| Nonserious Adverse Event (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 |
| Serious Adverse Event (SAE) including Cancer and 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/vaccine related.<br>(Follow ongoing to outcome) | Within 24 hours of learning of event |
| Pregnancy/ Lactation Exposure | Report if:<br>- 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 – Follow to completion/ termination; report outcome | Within 24 hours of learning of event |
| Event of Clinical Interest (require regulatory reporting) | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- potential drug-induced liver injury (DILI)<br>- require regulatory reporting | Not required | Within 24 hours of learning of event |
| Event of Clinical Interest (do not require regulatory reporting) | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- non-DILI ECIs and those not requiring regulatory reporting | Not required | Within 5 calendar days of learning of 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 AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), 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. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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.

### 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.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

### 8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

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

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon 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).

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

## 8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for olaparib, and any dose approximately ≥20% above the prescribed dose for carboplatin and gemcitabine as specified in this protocol or per local/country guidelines and should be reported as such. Olaparib, carboplatin, and gemcitabine must be used only in accordance with the dosing recommendations in this protocol. For pembrolizumab, any dose of 1000 mg or greater should be reported as an overdose. No specific information is available on the treatment of overdose of olaparib, carboplatin, gemcitabine, or pembrolizumab. In the event of overdose, the specific study intervention should be withheld, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

## 8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

## 8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

## 8.8 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover tumor tissue
- Leftover plasma or derivative for circulating tumor DNA (ctDNA)

## 8.9 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

## 8.10 Biomarkers

**As of Amendment 03: Biomarker sample collections will be discontinued.** Biomarker samples already collected before implementation of Amendment 03 will be analyzed. The section below is retained for reference.

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

All specimens collected on a dosing day should be drawn pre-dose, unless the visit cannot be performed in the morning and the participant has taken their morning dose of olaparib at home before the visit.

- During screening
    - Tumor tissue
- During induction pre-dose on Cycle 1, Day 1, Cycle 3, Day 1
    - Blood for genetic analysis
    - Blood for ctDNA analysis
- During post-induction pre-dose on Cycle 1, Day 1; Cycle 2, Day 1; and Cycle 5, Day 1; and at treatment discontinuation
    - Blood for ctDNA analysis

After Cycle 5, Day 1, additional blood samples for ctDNA analysis will be collected every 6 weeks during Year 1 of post-induction, and every 12 weeks from Year 2 until the end of Year 5, or until discontinuation of study treatment, whichever is earlier. ctDNA collections post-induction should be aligned with clinic visit closest to tumor scan visits. If a clinic visit is not feasible, blood for ctDNA collection will not be collected.

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Laboratory Manual.

## 8.11 Medical Resource Utilization and Health Economics

**As of Amendment 03: Medical Resource Utilization and Health Economics data collection will be discontinued.** The section below is retained for reference.

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization 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. ER visits that are not considered SAEs should be reported through 30 days following cessation of study intervention.

## 8.12 Visit Requirements

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

### 8.12.1 Screening

Approximately 28 days before administration of study intervention on Cycle 1, Day 1 of induction, potential participants will be evaluated to determine that they fulfill the entry requirements as described in Section 5. Documented informed consent for the study must be obtained before any screening procedures (Section 8.1.1). Results of tests that were performed as part of routine clinical management before the participant provided documented informed consent are acceptable in lieu of a screening test if performed within the specified time frame. Consent for FBR is optional and can be provided before or after Cycle 1, Day 1.

Screening procedures as detailed in the SoA in Section 1.3.1 are to be completed within 28 days of the administration of the first dose of induction study treatment, except for the following:

- Laboratory tests are to be performed within 10 days before the start of induction study treatment.
- ECOG performance status is to be performed within 7 days before the start of induction study treatment.
- For WOCBP, a urine or serum pregnancy test will be performed within 24 hours before the participant receives the first dose of study treatment of induction. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Participants who initially did not meet the inclusion/exclusion criteria may repeat screening procedures after Sponsor communication, if needed. “Re-screening” in this protocol refers to a participants who could not complete screening tests within the specified 28-day period. Results from assessments performed 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 criterion is met.

### 8.12.2 Treatment Visits

**Timing of Study Assessments and Procedures**

The timing of the study assessments and procedures for this study are presented in the Schedule of Activities (SoAs) in Section 1.3 and throughout Section 8. Starting with Cycle 7

of induction and post-induction, the pattern of study treatment administration, assessments, and procedures performed at Cycle 6 will be repeated unless otherwise stated.

#### 8.12.2.1 Induction

Assessments/procedures should be performed during induction prior to administration of study intervention on Day 1 of each cycle unless otherwise specified in the SoA in Section 1.3.1.

Visit timing requirements during induction are as follows:

- Treatment cycles are 21 days (starting with Cycle 1, Day 1 of induction).
- The window for each visit is ±3 days unless otherwise specified.

Study interventions administered during induction are detailed in Section 8.1.8.

The full list of all visit assessments/procedures conducted during induction are provided in the SoA in Section 1.3.1. Specific procedures related to the efficacy assessments are detailed in Section 8.2 and those related to the safety assessments are detailed in Section 8.3.

#### 8.12.2.2 Pre-randomization

During the approximately 14-day period after the Cycle 6, Day 8 dose of induction study intervention, potential participants will be evaluated to determine that they fulfill the post-induction eligibility requirements as described in Section 5. Note: participants are not eligible to be treated in post-induction if they miss more than 6 consecutive weeks of study interventions due to toxicity or any other cause before Cycle 1 Day 1 of post-induction (Section 7.1). The minimum permitted interval between the last dose of pembrolizumab in induction and the first dose of pembrolizumab in post-induction is 21 days.

Pre-randomization procedures as detailed in the SoA in Section 1.3.2 are to be completed within this 14-day period, except for the following:

- For WOCBP, a urine or serum pregnancy test will be performed within 24 hours before the participant receives the first dose of study treatment of induction. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- ECOG performance status should be performed within 7 days of administration of the Cycle 1, Day 1 dose of study intervention.
- Participants with toxicities related to induction therapy may have up to 3 weeks for these events to recover to Grade 1 or less, or to achieve a Hb level of 9.0 g/dL.

#### 8.12.2.3 Post-induction

Assessments/procedures should be performed during post-induction before administration of study intervention on Day 1 of each cycle unless otherwise specified in the SoA in Section 1.3.2.

*Note:* Participants who are randomized to Arm 1 (olaparib + pembrolizumab) of post-induction will not need to visit the study site at Day 8 of each cycle.

Visit timing requirements during post-induction are as follows:

- Administration of Cycle 1, Day 1 post-induction study treatment must occur within 3 days after randomization.
- Treatment cycles are 21 days (starting with Cycle 1, Day 1 of post-induction).
- The window for each visit is ±3 days unless otherwise noted.
- Laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment and do not need repeated if obtained within 72 hours of Cycle 1, Day 1.

If both carboplatin and gemcitabine are permanently discontinued during post-induction (Section 7.1), the participant does not need to come to the clinic on Day 8 and will follow the treatment and procedure schedule for pembrolizumab.

Study interventions administered during post-induction are detailed in Section 8.1.8.

The full list of all visit assessments/procedures conducted during post-induction are provided in the SoA in Section 1.3.2. Specific procedures related to the efficacy assessments are detailed in Section 8.2 and to the safety assessments are detailed in Section 8.3.

### 8.12.3 Treatment Discontinuation

The End of Treatment Visit should occur at the time that study treatment is discontinued as detailed in Section 7.1. If the End of Treatment Visit occurs ≥30 days from last dose of study treatment, a separate Safety Follow-up Visit (Section 8.12.4.1) is not required.

For the full list of all visit assessments/procedures conducted at treatment discontinuation, please see the SoA in Section 1.3.3. Specific procedures related to the efficacy assessments are detailed in Section 8.2 and to the safety assessments are detailed in Section 8.3.

### 8.12.4 Post-treatment Follow-up

#### 8.12.4.1 Safety Follow-up

After all study interventions are permanently discontinued (Section 7.1) in either induction or post-induction, the mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer

therapy, whichever comes first. All AEs, SAEs, and other reportable events will be followed to resolution as described in Section 8.4.3.

The Safety Follow-up Visit is the last required visit for participants who discontinue all study interventions for any reason during induction.

#### 8.12.4.2 Disease Status Follow-up

**As of Amendment 03: Disease Status Follow-up Visits will be discontinued.** The section below is retained for reference.

Participants who complete the protocol-required cycles of study intervention or who discontinue all study interventions for a reason other than disease progression during post-induction will move into disease status follow-up and should be assessed according to the already followed tumor scan schedule (Section 8.2.2.2 and Section 8.2.2.3). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, centrally verified disease progression, pregnancy, death, or the end of study. Information regarding new treatment for the disease under study will be collected if applicable.

Participants who complete all disease status assessments and/or will not have further disease status assessments must enter the Survival Follow-up Phase.

#### 8.12.4.3 Survival Follow-up Contacts

**As of Amendment 03: Survival Follow-up visits will be discontinued. Those participants remaining on study treatment at the time of Amendment 03 should continue to be monitored in the study through the AE reporting period (Section 8.4).** The section below is retained for reference.

Participants will move into survival follow-up after centrally verified disease progression during post-induction or after starting a new anticancer therapy, whichever occurs first. During survival follow-up participants should be contacted by telephone approximately every 12 weeks to assess for subsequent anticancer therapy, disease status, and survival (vital) status until death, complete documented withdrawal of consent from the study, or the end of the study, whichever occurs first.

Investigators will ask during the regular survival follow up if the participant has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

*Note:* Survival (vital) status may be requested by the Sponsor at any time during the study.

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

- For participants who discontinue treatment intervention and who will not enter the disease status follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up visit (whichever is last).

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

### 8.12.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before, but not limited to, an internal DMC review, interim and/or FA. 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 vital status.

### 8.12.6 Second Course Retreatment

*Note:* As of Amendment 03, the study will be discontinued based on the recommendation of the internal DMC, and Second Course Retreatment is no longer an option for participants. The section below is retained for reference.

Participants who are already receiving Second Course Retreatment and deriving clinical benefit may continue Second Course Retreatment, and local tumor imaging assessments should continue per SOC schedule, until radiographic disease progression per RECIST 1.1 as determined by investigator/site/local radiology review. No treatment beyond progression will be authorized.

#### 8.12.6.1 Conditions of Second Course Retreatment

Participants who stop pembrolizumab during post-induction with SD or better may be eligible for up to 17 additional administrations of pembrolizumab if they progress after stopping pembrolizumab and only after consultation with the Sponsor with documented SCF, followed by reconsent to main study ICF. Retreatment with pembrolizumab is termed Second Course Retreatment and is available only if the study remains open, and the participant meets the following conditions:

**Either**

- Stopped post-induction treatment with pembrolizumab after attaining a confirmed CR based on RECIST 1.1 by site/local radiology assessment, and

- Was treated with at least 8 cycles of pembrolizumab (inclusive of induction and post-induction) before discontinuing study treatment, and

- Received at least 2 cycles of post-induction pembrolizumab beyond the date when the initial CR was declared,

**OR**

- Had SD, PR, or CR and stopped post-induction pembrolizumab treatment after 35 administrations for reasons other than disease progression or intolerability,

**AND**

- Experienced an investigator-determined and BICR-verified PD by RECIST 1.1 after stopping post-induction treatment with pembrolizumab, and
- No new anticancer therapy was administered since the last dose of post-induction pembrolizumab, and
- The participant meets the safety parameters listed in the post-induction inclusion/exclusion criteria, and
- The study is ongoing.

An objective response or disease progression that occurs for a participant during Second Course Retreatment will not be counted as an event in the primary efficacy analyses in this study.

#### 8.12.6.2 Treatment Requirements for Second Course Retreatment

Participants may resume pembrolizumab in combination with the same randomly assigned treatments received during post-induction, either olaparib (Arm 1) or gemcitabine and/or carboplatin (Arm 2), at the discretion of the investigator and after documented consultation with the Sponsor, with documented SCF. The use of study treatments in combination with pembrolizumab that are different from those received during post-induction are not permitted.

- If either carboplatin or gemcitabine (Arm 2) were discontinued during post-induction due to toxicity and the participant experiences BICR-verified PD on the continued single-agent chemotherapy, the participant may be eligible to continue the single-agent chemotherapy in combination with Second Course Retreatment with pembrolizumab after consultation with the Sponsor, with documented SCF.
- If olaparib (Arm 1) or both carboplatin and gemcitabine (Arm 2) were discontinued during post-induction due to toxicity, and the participant achieved or sustained an SD or better after completing 35 administrations of pembrolizumab monotherapy, and the participant then experiences BICR-verified PD, the participant may be eligible for Second Course Retreatment with pembrolizumab as monotherapy after consultation with the Sponsor, with documented SCF.

#### 8.12.6.3 Visit Requirements of Second Course Retreatment

Treatments, assessments, and procedures during Second Course Retreatment will be performed as specified in the SoAs in Section 1.3.4 for participants who are eligible to resume pembrolizumab in combination with olaparib (Arm 1) or pembrolizumab in

combination with gemcitabine and/or carboplatin (Arm 2); or for participants who are eligible to resume pembrolizumab monotherapy.

Study cycles will reset to Cycle 1 with the first dose of Second Course Retreatment. Treatment cycles are 3 weeks (starting with the first pembrolizumab retreatment) and visit windows are ±3 days unless otherwise noted. Starting with Cycle 7, the pattern of study treatment administration, assessments, and procedures performed at Cycle 6 will be repeated unless otherwise stated.

#### 8.12.6.4 Study Treatments During Second Course Retreatment

Participants who start retreatment should resume pembrolizumab at 200 mg IV Q3W. Participants who continue with olaparib (Arm 1), or gemcitabine and/or carboplatin (Arm 2) should receive the same dose level given at the last dose of post-induction and should follow the dose schedule as detailed in Section 8.1.8.1.2.

#### 8.12.6.5 Concomitant Medications During Second Course Retreatment

Enter new medications started during Second Course Retreatment through the safety follow-up. Record all medications taken for AEs as defined in Section 8.4.

#### 8.12.6.6 Laboratory Tests During Second Course Retreatment

Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose. See Section 8.3.4 for details regarding laboratory tests.

For WOCBP, a urine or serum pregnancy test should be performed within 24 hours prior to receiving the first retreatment dose. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the participant is on study, pregnancy testing should be conducted monthly and as per local regulations where applicable (see Section 10.5.3).

After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. T3 (or Free T3), Free T4, or TSH can be assayed based on local standards and should be repeated every 2 cycles after Cycle 5.

Coagulation factors should be monitored closely throughout the Second Course Retreatment for any participant receiving anticoagulant therapy (see Section 10.2).

Clinically significant abnormal laboratory test results that are drug-related AEs should be followed until return to within the normal range or baseline. Laboratory tests do not need to be repeated after the end of retreatment if values are within normal range.

Laboratory safety measurements will be graded per NCI CTCAE v5.0.

### 8.12.6.7 Vital Signs During Second Course Retreatment

Vital signs will include temperature, pulse, respiratory rate, weight, and blood pressure as detailed in Section 8.3.2. Height will not be measured in the Second Course Retreatment. Vital signs should be measured within 3 days before each dosing day.

### 8.12.6.8 Adverse Events During Second Course Retreatment

Adverse events will be assessed and recorded during Second Course Retreatment as detailed in Section 8.4.

### 8.12.6.9 Tumor Scans During Second Course Retreatment

**As of Amendment 03:** Central tumor response assessments will be discontinued. For participants who are already receiving Second Course Retreatment and deriving clinical benefit who are continuing on study treatment until criteria for discontinuation are met, local tumor imaging should continue per SOC schedule. Participants with radiographically documented disease progression during Second Course Retreatment as assessed by investigator/site/local radiology review according to RECIST 1.1 will be discontinued from study intervention. Participants who are currently being assessed by iRECIST during Second Course Retreatment may continue to be assessed per iRECIST until iCPD is determined by investigator/site/local radiology review. Treatment beyond RECIST 1.1 progression or iCPD will no longer be authorized after implementation of Amendment 03. The section below is retained for reference.

Tumor scans must be or must have been performed within 28 days prior to Cycle 1, Day 1 of Second Course Retreatment. Local readings (investigator assessment with site radiology readings) will be used to determine eligibility. Scans should not be submitted for BICR.

Tumor scans during Second Course Retreatment should begin 9 weeks (±7 days) after Cycle 1, Day 1 of Second Course Retreatment and should be assessed using RECIST 1.1 criteria. Subsequent tumor scans should be performed every 9 weeks (±7 days), or more frequently if clinically indicated.

Per iRECIST (Section 8.2.2.6), if tumor scans show initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing retreatment while awaiting radiologic confirmation of progression. Participants who obtain a confirmation scan do not need to undergo scheduled tumor scans if it is <4 weeks later and may wait until the next scheduled tumor scan time point if clinically stable.

Tumor scans should continue to be performed until disease progression, the start of new anticancer therapy, pregnancy, withdrawal of consent, or death, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor scan indicating PD in clinically stable participants. Should the investigator wish to continue a clinically stable participant after investigator assessed progression, communication with the Sponsor, with documented SCF approving continued treatment, is required. In such cases the treatment administered must remain unchanged.

In participants who discontinue retreatment, tumor scans should be performed at the time of retreatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In participants who discontinue retreatment due to confirmed disease progression, this is the final required tumor scan.

In participants who discontinue retreatment without further documented disease progression, every effort should be made to continue monitoring their disease status by radiologic scans every 9 weeks (±7 days) until (1) the start of new anticancer therapy, (2) disease progression, (3) pregnancy, (4) death, or (5) the end of the study, whichever occurs first.

#### 8.12.6.10 Discontinuation During Second Course Retreatment

Discontinuation of study retreatments should follow the criteria detailed in Section 7.1, and the participant will enter end of treatment and follow-up as detailed in Section 1.3.3. Participants must discontinue pembrolizumab after 17 administrations. Tumor scan requirements for these participants are described in Section 8.12.6.9.

## 9 STATISTICAL ANALYSIS PLAN

***Note*: As of Amendment 03, the Statistical Analysis Plan is amended as follows.**

Based on the data from a prespecified interim safety and efficacy analysis for KEYLYNK-009 (data cutoff 15-DEC-2022), the internal DMC recommended discontinuing the study because the combination of pembrolizumab plus olaparib did not show an improvement in PFS compared with the combination of chemotherapy plus pembrolizumab. Based upon these data and the recommendation of the internal DMC, the prespecified final analysis of the study described in the SAP will not be performed. Selected safety analyses will be performed at the end of the study.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to these hypotheses, then the protocol will be amended (consistent with International Conference on Harmonization [ICH] Guideline E9). Changes to the exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, 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. The PRO analysis plan will be included in the sSAP. A separate biomarker analysis plan may be provided as appropriate in the sSAP.

In this section, the number of participants refers to the number of randomized participants in post-induction.

## 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 through 9.12. As of Amendment 03, the prespecified final analysis of the study described in the SAP will not be performed. The SAP summary has been updated accordingly.

| | |
|---|---|
| **Study Design Overview** | An Open-label, Randomized, Phase 2 Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab in Participants With Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (TNBC) After Induction of Clinical Benefit With First-line Chemotherapy Plus Pembrolizumab |
| **Treatment Assignment** | Approximately **260** participants will be expected to be randomized post-induction in a 1:1 ratio between two treatment groups: (1) olaparib + pembrolizumab arm and (2) chemotherapy + pembrolizumab arm.<br>Stratification factors are as follows:<br>• Response to the induction therapy (CR or PR versus SD) at Week 18 (-7 days) as assessed by BICR<br>• PD-L1 positive (CPS ≥1) versus PD-L1 negative (CPS <1)<br>• BRCAm versus BRCAwt<br>This is an open-label study.<br>As of Amendment 03, all ongoing participants may have the option to continue receiving study treatment, until criteria for discontinuation are met, if they are deriving clinical benefit. |
| **Analysis Populations** | Efficacy: Intention-to-Treat (ITT)<br>Safety: All Participants as Treated (APaT) |
| **Primary Endpoints** | • Progression-free survival (PFS)<br>• Overall survival (OS) |
| **Secondary Endpoints** | • AEs and discontinuations due to AEs<br>• PRO assessment |
| **Statistical Methods for Key Efficacy Analyses** | The primary hypotheses comparing olaparib + pembrolizumab to chemotherapy + pembrolizumab with respect to PFS and OS will be evaluated using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. |
| **Statistical Methods for Key Safety Analyses** | The safety analysis will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There is no Tier 1 safety endpoint for this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-arm comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method. |

| | |
|---|---|
| **Interim Analyses** | As of Amendment 03, the prespecified final analysis of the study described in the SAP will not be performed.<br>CCI [redacted] |
| **Multiplicity** | As of Amendment 03, no final analysis of the study will be performed.<br>CCI [redacted] |
| **Sample Size and Power** | As of Amendment 03, no final analysis of the study will be performed.<br>CCI [redacted] |

## 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.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

Although the trial is an open-label study, analyses or summaries generated by randomized treatment assignment, actual treatment received, PD-L1 biomarker results and BRCA status will be limited and documented. The investigator, study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, study site staff, and the participant will be blinded to subject-level PD-L1 biomarker results and BRCA

status. A summary of PD-L1 and BRCA biomarker prevalence may be provided to the study team at the Sponsor by the unblinded designated Sponsor statistician. Further documentation will be provided in the sSAP. In addition, independent radiologist(s) will perform the central tumor scan review without knowledge of treatment assignments.

Planned IAs are described in Section 9.7. The treatment-level results of the IAs will not be shared with the investigator prior to completion of the study.

## 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.

### 9.4.1 Efficacy Endpoints

**Primary:**

**Progression-free survival (PFS) –** PFS is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first, based on RECIST 1.1 by BICR.

**Overall Survival (OS) -** OS is defined as the time from randomization to death due to any cause.

**Exploratory:**

**Objective Response Rate (ORR)**: **–** ORR is defined as the proportion of participants in the analysis population who have a best overall response of either confirmed CR or PR after the randomization, based on RECIST 1.1 as assessed by BICR.

**Duration of Response (DOR)**: – For participants who demonstrate confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR (that is subsequently confirmed) after the date of randomization until the first documented date of disease progression or death due to any cause, whichever occurs first, based on RECIST 1.1 by BICR.

**Disease Control Rate (DCR)**: **–** DCR is defined as the percentage of participants who have achieved CR or PR after the randomization or have demonstrated SD for at least 24 weeks after the randomization, based on RECIST 1.1 by BICR.

**PFS after next line treatment (PFS2): –** PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anticancer therapy as assessed by investigator according to the local standard of clinical practice, or death due to any cause, whichever occurs first.

**Time to First Subsequent Treatment (TFST)**: – TFST is defined as the time from the date of randomization until initiation of first subsequent anticancer therapy or death due to any cause, whichever occurs first.

**Time to Second Subsequent Treatment (TSST): –** TSST is defined as the time from the date of randomization until initiation of second subsequent anticancer therapy or death due to any cause, whichever occurs first.

**Time until Discontinuation of study treatment or Death (TDT): –** TDT is defined as the time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first.

### 9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2, including, but not limited to, the incidence of, causality of, and outcome of AEs/SAEs; and changes in vital sign measurements and laboratory values.

### 9.4.3 PRO Endpoints

The following secondary PRO endpoints will be evaluated as described in Section 4.2.1.3:

- Global Health Status/QoL scale (EORTC QLQ-C30 Items 29 and 30)
- Physical functioning (EORTC QLQ-C30 Items 1-5)
- Emotional functioning (EORTC QLQ-C30 Items 21-24)
- Systemic therapy side effects (EORTC QLQ-BR23 Items 1-4, 6, 7, and 8)
- Visual analogue scale (VAS) based the EuroQoL 5-dimension, 5-level questionnaire (EQ-5D-5L)
- Time to Deterioration (TTD), the time from baseline to the first onset of a confirmed*≥10-point deterioration from baseline in PRO scores for the following domains:

  - EORTC QLQ-C30 global health status/HRQoL (Items 29 and 30),

  - EORTC QLQ-C30 physical functioning (Items 1-5),

  - EORTC QLQ-C30 emotional functioning (Items 21-24), and

  - EORTC QLQ-BR23 systemic therapy side effects (Items 1-4, 6, 7, and 8)

  *confirmed by a ≥10-point deterioration after baseline in the subsequent PRO score

## 9.5 Analysis Populations

### 9.5.1 Efficacy Analysis Population

The intention-to-treat (ITT) population will serve as the population for primary efficacy analysis. All randomized participants will be included in this population. Participants will be included in the treatment arm to which they are randomized.

The analysis population for ORR consists of all randomized participants with measurable disease at the baseline for the post-induction.

### 9.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study treatment for one cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific 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 randomized participants who have at least one PRO assessment available and have received at least one dose of study treatment.

## 9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the induction phase or exploratory objectives will be described in the sSAP.

### 9.6.1 Statistical Methods for Efficacy Analyses

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity. The efficacy analyses for ORR, DOR, DCR, and PFS will include responses and documented progression events that occur prior to Second Course treatment. If there are a

small number of responses/events in one or more strata, for the purpose of analysis strata will be combined to ensure sufficient number of responses/events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of response counts by stratum.

#### 9.6.1.1 Progression-free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the interval between the last assessment when PD is not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Participants who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on the investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, one primary and two sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to the missed visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than CR to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 12.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of PFS

| Situation | Primary Analysis | Sensitivity Analysis 1 | Sensitivity Analysis 2 |
|---|---|---|---|
| PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any | Progressed at date of documented PD or death | Progressed at date of documented PD or death | 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 assessments and new anticancer therapy, if any | Progressed at date of documented PD or death | Progressed at date of documented PD or death |
| No PD and no death; new anticancer treatment is not initiated | Censored at last disease assessment | Censored at last disease assessment | Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if participant is still receiving study treatment or has completed study treatment |
| No PD and no death; new anticancer treatment is initiated | Censored at last disease assessment before new anticancer treatment | Censored at last disease assessment | Progressed at date of new anticancer treatment |
| Abbreviations: PD = progressive disease; PFS = progression-free survival | | | |

#### 9.6.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Participants without documented death at the time of analysis will be censored at the date of last known contact. Analysis using the Restricted Mean Survival Time method may be conducted for OS to account for the possible nonproportional hazards effect and to estimate the absolute benefit of experimental treatment.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP as needed.

### 9.6.1.3 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 13.

Table 13 Analysis Strategy for Key Efficacy Endpoints

| Endpoint/Variable | Statistical Method† | Analysis Population | Missing Data Approach |
|---|---|---|---|
| **Primary Hypothesis 1** | | | |
| PFS as assessed by BICR according to RECIST 1.1 in the overall population | Test: Stratified log-rank test<br>Estimation: Stratified Cox model with Efron's tie handling method | ITT | Primary censoring rule<br>• Sensitivity analysis 1<br>• Sensitivity analysis 2<br>(More details are in Table 12) |
| **Primary Hypothesis 2** | | | |
| OS in the overall population | Test: stratified log-rank test<br>Estimation: stratified Cox model with Efron's tie handling method | ITT | Censored at last known alive date |
| **Secondary Estimation** | | | |
| PFS as assessed by BICR according to RECIST 1.1 in participants with BRCAm tumors or with PD-L1 positive tumors (CPS ≥10) | Estimation: Stratified Cox model with Efron's tie handling method | ITT | Primary censoring rule<br>• Sensitivity analysis 1<br>• Sensitivity analysis 2<br>(More details are in Table 12) |
| OS in participants with BRCAm tumors or with PD-L1 positive tumors (CPS ≥10) | Estimation: Stratified Cox model with Efron's tie handling method | ITT | Censored at last known alive date |

Abbreviations: BRCAm = breast cancer susceptibility gene mutation; BICR = blinded independent central review; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.
† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

## 9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur prior to Second Course Treatment.

Safety and tolerability will be assessed by clinical review of all relevant parameters, including adverse experiences (AEs), laboratory tests, and vital signs after randomization.

The safety analysis will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either pre-specified as Tier-1 endpoints, or will be classified as belong to "Tier 2" or "Tier 3", based on the number of events observed.

## Tier 1 Events

Safety parameters or adverse events of special interest that are identified a priori constitute Tier 1 safety endpoints that will be participant to inferential testing for statistical significance.

AEs of special interest that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Finally, there are no known AEs associated with participants with breast cancer for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

## Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

## Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

## Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 14 Analysis Strategy for Safety Parameters

| Safety Tier | Safety Endpoint | 95% CI for Treatment Comparison | Descriptive Statistics |
|---|---|---|---|
| Tier 2 | AEs (incidence ≥10% of participants in one of the treatment groups) | X | X |
| | Serious AEs (incidence ≥5% of participants in one of the treatment groups) | X | X |
| | Grade 3 to 5 AEs (incidence ≥5% of participants in one of the treatment groups) | X | X |
| Tier 3 | Any AE | | X |
| | Any serious AE | | X |
| | Any Grade 3 to 5 AE | | X |
| | Any drug-related AE | | X |
| | Any serious and drug-related AE | | X |
| | Any Grade 3 to 5 and drug-related AE | | X |
| | Discontinuation due to AE | | X |
| | Death | | X |
| | Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups) | | X |
| | Change from baseline results (laboratory, vital signs) | | X |

Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class X = results will be provided.

Methods for safety analyses related to the induction phase will be described in the sSAP.

### 9.6.3 Statistical Methods for Patient-reported Outcomes (PRO) Analyses

Participants in the induction and post induction periods will be analyzed separately. The analysis methods regarding between treatment comparisons will only be applied to the post-induction period.

To assess the treatment effect on the PROs, for each continuous PRO endpoint, a constrained longitudinal data analysis (cLDA) model will be used as the primary analysis method, with the PRO score as the response variable, and treatment, time, treatment by timepoint interaction, and stratification factors (used for randomization and defined in Section 6.3.2) as covariates.

The treatment effect on PRO score change from baseline will be evaluated at the primary analysis time point, where the baseline PRO assessment is defined as the last PRO assessment that occurs prior to the first dose of post-induction. The between-group

comparison will be performed and the differences in the least-squares mean change from baseline at the primary analysis time point will be reported, together with 95% CI and nominal p-value. In addition, model-based least-squares mean score with corresponding 95% CI will be provided by treatment group at primary analysis time point.

TTD is defined as the time from baseline to the first onset of a ≥10 point deterioration from baseline in PRO score with confirmation at the subsequent visit of a ≥10 point deterioration from baseline. The Kaplan-Meier method will be used to estimate the TTD survival curves for global health status/QoL (QLQ-C30 Items 29 and 30), physical functioning (QLQ-C30 Items 1-5), emotional functioning (Items 21-24), and BR23 systemic therapy side effects (Items 1-4, 6, 7, and 8), separately, in each treatment arm. Stratified Cox proportional hazards models with Efron's method of tie handling will be used to assess the magnitude of the treatment difference for pembrolizumab plus olaparib compared to pembrolizumab plus carboplatin and gemcitabine. Stratification factors used for randomization will be used in the stratified Cox proportional hazards models. The HR, 95% CI, and nominal p-value will be reported.

Details of additional PRO analyses and methods related to the induction phase will be included in the sSAP.

### 9.6.4 Summaries of Baseline Characteristics and Demographic

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

## 9.7 Interim Analyses

*Note:* As of Amendment 03, the prespecified final analysis of the study described in the SAP will not be performed. The information related to FA is retained for reference.

The internal DMC will serve as the primary reviewer of the results of the interim analysis (analyses) of the study and will make recommendations for discontinuation of the study or protocol modifications. The limited Sponsor personnel will be unblinded to results at the treatment level. The extent to which individuals are unblinded IAs will be documented. Additional logistical details will be provided in the internal DMC Charter.

Treatment-level results from the interim analysis will be provided by the unblinded statistician to the internal DMC. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

### 9.7.1 Efficacy Interim Analyses

CCI

[redacted]

### 9.7.2 Safety Interim Analyses

The internal DMC will be responsible for periodic interim safety reviews, as specified in the DMC charter. Interim safety analysis will also be performed at the time of interim efficacy analysis.

## 9.8 Multiplicity

CCI

[redacted]

### 9.8.1 Progression-free Survival

CCI

[redacted]

### 9.8.2 Overall Survival

CCI

[redacted]

## 9.9 Sample Size and Power Calculations

CCI

[redacted]

CCI

[redacted]

## 9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of each subgroup. The following are examples of classification variables:

- Age category (<65 years vs ≥65 years)

- Race: white versus nonwhite
- Geographic region (Europe /North America vs Asia vs Rest of World)
- Ethnic origin (Hispanic vs Non-Hispanic)
- ECOG status (0 vs 1)
- Visceral disease (yes vs no)
- PD-L1 status (CPS ≥1 vs CPS <1; CPS ≥10 vs CPS <10)
- Response at randomization assessed by BICR (CR/PR vs SD)
- Genomic tumor status (BRCAmutant vs BRCA wild type)

  *Note:* Not-determined BRCA status due to the test failure will be put under the category of BRCA wild type.

- HRD status (HRD≥33 vs HRD<33)
- BRCA by HRD status (BRCAmutant and HRD≥33 vs BRCAmutant and HRD<33 vs BRCA wild type and HRD≥33 vs BRCA wild type and HRD<33)
- Menopausal status (for females only; pre- vs postmenopausal)

## 9.11 Compliance (Medication Adherence)

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

## 9.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate. 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**

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 local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) 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. Participants must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

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.

**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.

#### 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 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

As of Amendment 03, the Steering Committee and internal Data Monitoring Committee are no longer applicable.

#### 10.1.4.1 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee may be comprised of some or all of the following members:

- Sponsor personnel,
- Investigators participating in the study, and
- Consulting therapeutic-area experts and clinical trialists.

The Steering Committee will provide guidance on the operational aspects of the study and evaluate recommendations from the Data Monitoring Committee (DMC).

Specific details regarding responsibilities and governance of the Steering Committee will be described in a separate charter.

#### 10.1.4.2 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate internal DMC will monitor the interim data from this study. The internal DMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The internal DMC will monitor the study progress for evidence of any adverse effects of study intervention. The internal DMC will also make recommendations to the Sponsor study team regarding steps to ensure both participant safety and the continued ethical integrity of the study. Specific details are described in the internal DMC charter.

### 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 International Committee of Medical Journal Editors 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 trial Directive 2001/20/EC, 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 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 GCP); 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.

### 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. 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. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution 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

The tests detailed in Table 18 will be performed by the local laboratory.

- Following Cycle 1, Day 1 of induction and post-induction study intervention, collection of samples for pre-dose 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<br>(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) [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 (CO2 or bicarbonate) [3] | Chloride | Phosphorous |
| | Creatinine or creatinine clearance [4] | Sodium | Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT) | Total Protein |
| | Glucose (nonfasting) | Calcium | Alkaline phosphatase | Magnesium |
| | Thyroid-stimulating hormone (TSH) [5] | Triiodothyronine (T3) [5] | Free thyroxine [5] | Lactate dehydrogenase (LDH) |
| 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 | Serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP). Refer to Appendix 5 for additional testing requirements.<br>Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)<br>Serum Vitamin D<br>Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus 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) is required during screening to establish eligibility. Additional testing to be conducted as clinically indicated for participants taking anticoagulation therapy.<br>• Blood collection for CA 15-3, CEA, CA 27.29 is required before Cycle 1 Day 1, but results are not required before dosing. |
| 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 15-3, CEA, CA 27.29 according to the tumor scan schedule |

Abbreviations: aPTT = activated partial thromboplastin time; CA = cancer antigen; CEA = carcino-embryonic antigen; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell

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. Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function test results after dosing is acceptable.

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

The following laboratory results will be performed by the central laboratory:

- TNBC tumor markers (estrogen receptor [ER] and progesterone receptor [PGR] and human epidermal growth factor receptor-2 [HER2])

The following blinded laboratory results will be performed by the central laboratory:

- Breast cancer gene (BRCA)
- Programmed cell death-ligand 1 (PD-L1)

The BRCA status and PD-L1 results will be blinded to the investigator, participants, study site staff, and the Sponsor. These results will not be unblinded until the study is unblinded.

## 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, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), 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, 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 judgement 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.

### 10.3.4 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 time frame 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

### 10.3.5 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/toxicity**

- 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 5.0. 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 INIRB/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 his/her 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- 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 his/her 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.

### 10.3.6 Reporting of AEs, SAEs, 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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

## 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 (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  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 two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one 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

## Female Participants

| **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>• Intrauterine hormone-releasing system (IUS)[c,d]<br>• Intrauterine device (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 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 Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.<br>[c] Male condoms must be used in addition to the 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 lactational amenorrhea method (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). |

**Male Participants**

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 5.1:

- 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 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.

### 10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 24 hours before the first dose.

Following initiation of treatment, additional pregnancy testing will be performed at monthly intervals during the treatment period in WOCBP, at treatment discontinuation, at the 30-day safety follow-up, and as required locally.

Pregnancy testing (urine or serum as required by local regulations) should continue to be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:

- Olaparib: 180 days
- Pembrolizumab: 120 days
- Chemotherapy: 180 days

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Refer to Appendix 7 for country-specific requirements.

## 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 the 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 intervention 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 France

**5.1 Inclusion Criteria**

Inclusion Criterion No. 9: Male participants are required to continue using contraception for 4 months after chemotherapy discontinuation.

Inclusion Criterion No. 10: WOCBP are required to continue using contraception for 7 months after chemotherapy discontinuation.

**1.3.3 End-of-Treatment and Follow-up After Treatment Discontinuation; 10.5.3 Pregnancy Testing**

The length of time to require to continue pregnancy testing for each study intervention is 180 days following the last dose of olaparib, 120 days following the last dose of pembrolizumab, and 210 days following the last dose of chemotherapy.

### 10.7.2 Germany

**Sections 1.3 Schedule of Activities and 10.5 Appendix 5 Contraceptive Guidelines**

Pregnancy testing: Monthly urine pregnancy testing is required during study treatment as well as at the end of treatment/discontinuation visit.

**Sections 1.1, 4.4, 5.1, 7.1, 7.2, 8.1.1, 8.1.1.1, 8.1.1.2, and 8.4**

Legally Acceptable Representative: Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

**Section 5.2 Exclusion Criteria**

Exclusion Criterion 10: HIV testing is required at screening for participants.

Exclusion Criterion 11: hepatitis B and C testing is required at screening for participants.

**Section 6.5.2 Prohibited Concomitant Medications**

Live vaccines must not be administered for 90 days after the last dose of study intervention.

### 10.7.3 Japan

**Section 6.1 Study Intervention(s) Administered**

Table 2 Study Interventions

Carboplatin and Gemcitabine used in this study are categorized as “product(s) used in the clinical trial other than test product(s)” in Japan local regulation.

## 10.8 Appendix 8: Eastern Cooperative Oncology Group Performance Status

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

Source: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

http://ecog-acrin.org/resources/ecog-performance-status

## 10.9 Appendix 9: Description of the iRECIST Process for Assessment of Disease Progression During Post-induction

**As of Amendment 03: iRECIST assessment of disease is no longer applicable for participants who have an initial PD evaluated by RECIST 1:1.** Participants who are currently being assessed by iRECIST may continue to be assessed per iRECIST until iCPD is determined by the investigator/site/local radiology review. The appendix below is retained for reference.

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression during post-induction, and to guide decisions about changes in management.

*Assessment During Post-induction Prior to RECIST 1.1 Progression*

Until radiographic disease progression during post-induction based on RECIST 1.1 is verified by BICR in clinically stable participants, there is no distinct iRECIST assessment (see Figure 2).

*Assessment and Decision During Post-induction at RECIST 1.1 Progression*

For participants who show radiological PD during post-induction, based on RECIST 1.1 as verified by BICR, the investigator will decide whether to use iRECIST for participant management (see Figure 3). If the investigator elects to use iRECIST, the clinically stable participant may continue study treatment until repeat scan is obtained 4 to 8 weeks later.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at BICR-determined first radiologic evidence of PD and is not required to have repeat tumor scans for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Scans should continue to be sent into the imaging contract research organization (iCRO) for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed PD) and iCPD (confirmed PD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculate and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

*Assessment at the Confirmatory Scan*

On the confirmatory scan, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

*Confirmation of Progression*

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1

- For new lesions, worsening is any of these:
  - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
  - Visible growth of new non-target lesions
  - The appearance of additional new lesions

- Any new factor appears that would have triggered PD by RECIST 1.1

*Persistent iUPD*

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional scans for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

*Resolution of iUPD*

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

*Management Following the Confirmatory Scan*

If repeat scans do not confirm disease progression, and the participant continues to be clinically stable, study treatment is to continue. The regular scan schedule is to be followed. If disease progression is confirmed, participants may be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study treatment may be continued following communication with the Sponsor, with documented SCF. If study treatment is continued, tumor scans are to be performed following the intervals as outlined in Section 1.3 and submitted to the iCRO for potential retrospective review.

*Detection of Progression at Visits After Pseudo-progression Resolves*

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan, then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening cause of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

## 10.10 Appendix 10: Abbreviations

| Abbreviation | Expanded Term |
|---|---|
| 1L | first-line |
| ADL | activities of daily living |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| APaT | all participants as treated |
| aPTT | activated partial thromboplastin time |
| AR | androgen receptor |
| ASCO | American Society of Clinical Oncologists |
| AST | aspartate aminotransferase |
| ATM | ataxia-telangiectasia mutated |
| AUC | area under the concentration-time curve |
| AxMP | auxiliary medicinal product |
| BCG | bacillus Calmette–Guérin |
| BER | base excision repair |
| β-hCG | β-human chorionic gonadotropin |
| BICR | blinded independent central review |
| BID | twice daily |
| BRCA1 | breast cancer susceptibility gene 1 |
| BRCA1/2 | breast cancer susceptibility gene 1/2 |
| BRCAm | breast cancer susceptibility gene mutation |
| BRCAwt | breast cancer susceptibility gene wildtype |
| BUN | blood urea nitrogen |
| CA 15-3 | cancer antigen 15-3 |
| CA 27.29 | cancer antigen 27.29 |
| CAP | College of American Pathologists |
| CBC | complete blood count |
| CD3 | cluster of differentiation 3 |
| CD8 | cluster of differentiation 8 |
| CD28 | cluster of differentiation 28 |
| CD3ζ | CD3 zeta |
| CEA | carcinoembryonic antigen |
| cfDNA | cell-free deoxyribonucleic acid |
| cfRNA | cell-free ribonucleic acid |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| cLDA | constrained longitudinal data analysis |
| CNS | central nervous system |
| CONSORT | Consolidated Standards of Reporting Trials |
| COVID-19 | Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 |
| CPS | combined positive score |
| 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 DNA |
| CTFG | Clinical Trial Facilitation Group |

| Abbreviation | Expanded Term |
|---|---|
| CTLA-4 | cytotoxic T-lymphocyte-associated protein 4 |
| CTR | Clinical Trials Regulation |
| CYP3A4 | cytochrome P450 (3A4) |
| DCR | disease control rate |
| DILI | drug-induced liver injury |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| DRFS | distant recurrence-free survival |
| DSB | double strand breaks |
| dUCBT | double umbilical cord transplantation |
| ECG | electrocardiogram |
| ECI | event of clinical interest |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data collection |
| eDMC | external Data Monitoring Committee |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ELISA | enzyme-linked immunoassay |
| EORTC QLQ | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| EORTC QLQ-BR23 | European Organisation for Research and Treatment of Cancer Breast Cancer–Specific Quality of Life Questionnaire |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 |
| ePRO | electronic patient-reported outcomes |
| EQ-5D-5L | European Quality of Life 5-dimension, 5-level Questionnaire |
| ER | estrogen receptor |
| ESMO | European Society for Medical Oncology |
| EU | European Union |
| EU CTR | European Union Clinical Trials Regulation |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FA | final analysis |
| FAS | full analysis set |
| FBR | Future Biomedical Research |
| FDAAA | Food and Drug Administration Amendments Act |
| FFPE | formalin-fixed paraffin-embedded |
| FPR | first participant randomized |
| FSH | follicle stimulating hormone |
| FSR | First site ready |
| gBRCAm | germline breast cancer gene mutation |
| gBRCAwt | germline breast cancer gene wildtype |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony stimulating factor |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GM-CSF | granulocyte macrophage colony stimulating factor |
| GMP | Good Manufacturing Practice |
| GSK3β | glycogen synthase kinase-3 beta |
| H1, 2, 3 | hypothesis 1, 2, 3 |
| Hb | hemoglobin |

| Abbreviation | Expanded Term |
|---|---|
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor-2 |
| HIV | human immunodeficiency virus |
| HR | homologous recombination or hazard ratio |
| HR+ | hormone receptor-positive |
| HRD | homologous recombination repair deficiency |
| HRQoL | health-related quality-of-life |
| HRR | homologous recombination repair |
| HRT | hormone replacement therapy |
| IA1, 2, 3, 4 | interim analysis 1, 2, 3, 4 |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| iCPD | iRECIST confirmed progressive disease |
| iCR | iRECIST confirmed complete response |
| iCRO | imaging contract research organization |
| IEC | Independent Ethics Committee |
| IFNγ | interferon-gamma |
| Ig | immunoglobulin |
| IgG4 | immunoglobulin G4 |
| IgV-type | Ig-variable–type |
| IHC | immunohistochemistry |
| IMP | investigational medicinal product |
| IND | Investigational New Drug |
| INR | international normalized ratio |
| iPR | iRECIST partial response |
| irAE/s | immune-related adverse event/s |
| IRB | Institutional Review Board |
| iRECIST | Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics |
| IRT | interactive response technology |
| iSD | iRECIST confirmed stable disease |
| ITT | intention-to-treat |
| IUD | intrauterine device |
| iUPD | iRECIST unconfirmed progressive disease |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous/ly |
| IVD | in vitro diagnostic |
| LAM | lactational amenorrhea method |
| LDH | lactate dehydrogenase |
| LOH | loss of heterozygosity |
| mAb | monoclonal antibody |
| MATE | multidrug and toxic compound extrusion |
| MCH | mean corpuscular hemoglobin |
| mCRPC | metastatic castration-resistant prostate cancer |
| MCV | mean corpuscular volume |
| MDS | myelodysplastic syndrome |
| MHC | major histocompatibility complex |

| Abbreviation | Expanded Term |
|---|---|
| MRI | magnetic resonance imaging |
| mRNA | messenger ribonucleic acid |
| MSI | microsatellite instability |
| mTNBC | metastatic triple negative breast cancer |
| NCCN | National Comprehensive Cancer Network |
| NCI | National Cancer Institute |
| NHEJ | non-homologous end-joining |
| NI | non-inferiority |
| NIMP | non-investigational medicinal product |
| NSAE | nonserious adverse event |
| NSAID/s | nonsteroidal anti-inflammatory drug/s |
| NSCLC | non-small cell lung cancer |
| OATP | organic-anion-transporting polypeptide |
| OCT | organic cation transporter |
| ORR | objective response rate |
| OS | overall survival |
| OTC | over-the-counter |
| PARP | polyadenosine 5′ diphosphoribose (polyADP ribose) polymerization |
| PARPi | polyadenosine 5′ diphosphoribose (polyADP ribose) polymerization inhibitor |
| PD | progressive disease |
| PD-L1 | programmed cell death-ligand 1 |
| PD-L2 | programmed cell death-ligand 2 |
| PFS | progression-free survival |
| PFS2 | progression-free survival after next-line treatment |
| PGR | progesterone receptor |
| PK | pharmacokinetic(s) |
| PKCθ | protein kinase C-theta |
| PO | by mouth |
| PR | partial response |
| pRBC | packed red blood cell |
| PRO | patient-reported outcomes |
| PSA | prostate-specific antigen |
| PT | prothrombin time |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| QD | once daily |
| QoL | quality of life |
| RBC | red blood cell |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | ribonucleic acid |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| SCF | Sponsor Consultation Form |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SIM | Site Imaging Manual |
| SoA | schedule of activities |
| SOC | standard of care |
| sSAP | supplemental statistical analysis plan |
| SSBs | single strand breaks |
| SUSAR | suspected unexpected serious adverse reaction |

| Abbreviation | Expanded Term |
|---|---|
| T1DM | type 1 diabetes mellitus |
| T3 | triiodothyronine |
| T4 | thyroxine |
| TCR | T-cell receptor |
| TDT | time until discontinuation of study treatment or death |
| TFST | time to first subsequent treatment |
| TIL | tumor-infiltrating lymphocyte |
| TMDD | target-mediated drug disposition |
| TNBC | triple negative breast cancer |
| TNFR | tumor necrosis factor receptor |
| TSH | thyroid stimulating hormone |
| TSST | time to second subsequent treatment |
| TTD | time to deterioration |
| ULN | upper limit of normal |
| US | United States |
| UTI | urinary tract infection |
| VAS | visual analogue scale |
| VEGF | vascular endothelial growth factor |
| WBC | white blood cell |
| WOCBP | woman/women of childbearing potential |
| ZAP70 | zeta-chain-associated protein kinase |

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